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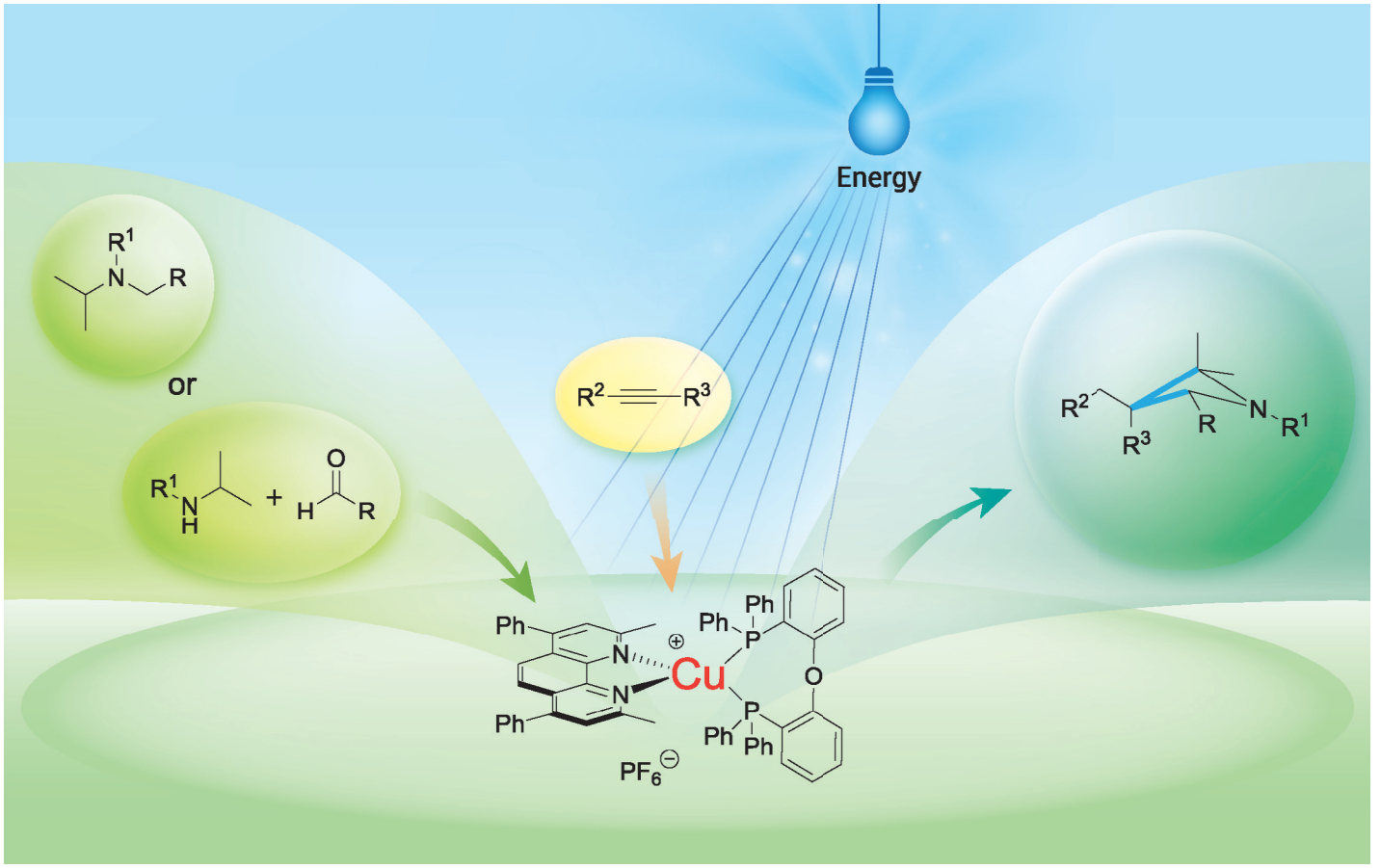
GRAPHICAL ABSTRACT



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

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Report

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

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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 alkynes to produce azetidines. This reaction occurred in a two- or three-component manner. The alkynes efficiently captured photogenerated α-aminoalkyl 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[1–6] (Figure 1A). Specifically, the incorporation of azetidine blocks has been shown to enable scaffold hopping,[5,6] which can result in improved pharmacokinetic properties and metabolic stability.[6] 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.[7–10] 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 through 4-*exo*-tet substitution. However, compared to other ring systems (three-, five-, and six-membered rings), the formation of four-membered rings is the most energetically unfavorable.[8,10–12] The photo-induced [2 + 2] aza-Paternò-Büchi reaction was advanced by Schindler,[13] Maruoka,[14] and Sivaguru et al.[15] in intra- and intermolecular manners, where a range of complex azetidine scaffolds was readily constructed with slight restrictions in the substrate requirements. In addition, [3 + 1] formal ring expansion reactions were developed to construct azetidine upon strain release of the azacyclopropanes (Figure 1B).[16–22] Despite these developments, the intrinsic ring strain and its sterically congested nature rendered atom-economical access to the highly substituted, densely functionalized azetidines a challenging task from simple starting materials. Thus, a new synthetic approach to access azetidine scaffolds with varied substitutions and stereochemistry is needed.

The [3 + 1] cyclization of simple alkyl amines with alkynes would offer another efficient and direct atom economic strategy for azetidines. However, this transformation development has faced challenges associated with the activation of the two C-H bonds. Photoredox catalysis has emerged as an important and popular research area, and its notable features include the ability to form reactive radical species under mild reaction conditions to elucidate useful transformations, including radical-involved C-H functionalization[23–29] and versatile cycloadditions.[30–35] Numerous carbon-carbon single-bond formations at the α-C of aliphatic amines have been achieved through the intermediates of imino cations[36,37] or α-aminoalkyl radicals[38–44] via oxidation to the radical cation with subsequent proton loss. We envisioned that the radical addition of α-aminoalkyl radicals to alkynes to form vinyl radicals could initiate the 1,5-hydrogen atom transfer (HAT)/intramolecular cyclization process,[45–49] while few studies have reported on 5-*endo*-trig cyclization leading to five-membered rings,[45] 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.[50–56] 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 alkynes (Figure 1C),[57] and heteroleptic Cu (I)(Xantphos)(2,9-diisopropyl-1,10-phenanthroline)PF_4 was used as the photosensitizer. The mechanism study showed that the intermediate of the α-aminoalkyl radical[58] was added to the alkyne, 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 alkynes and linear alkyl amines with an unproductive loss of more valuable amine functionality. We hypothesized that the cleavage of the C1-N3 bond could 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.[45] 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,[59,60] 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 alkynes, which were involved in the functionalization of both C(sp^3)-H bonds at the α-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-economical 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.[61,62] 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 sp^3 C-H activation.[63–66]

RESULTS

Investigations of the reaction conditions were carried out using 4-ethynyl-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).

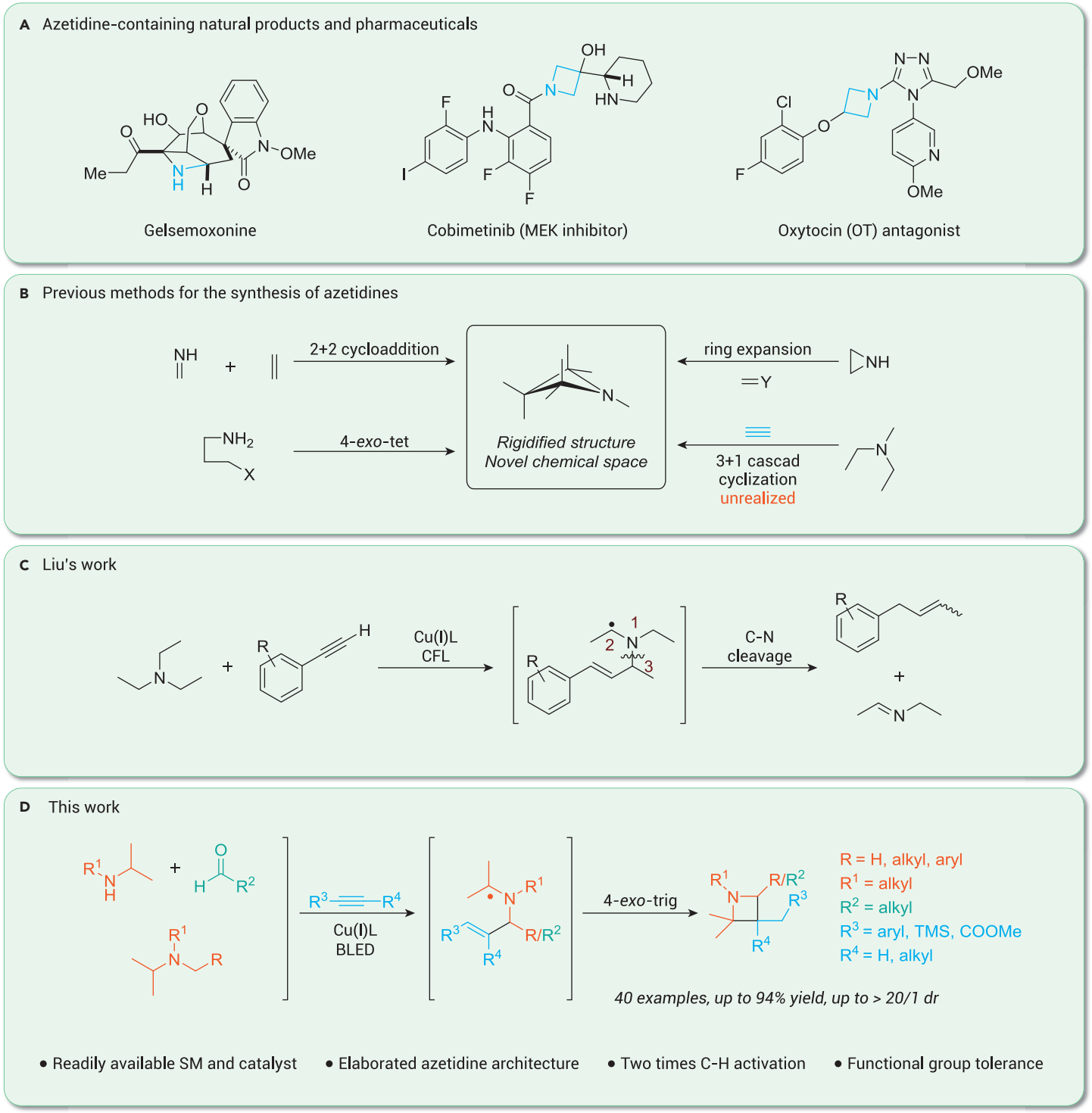
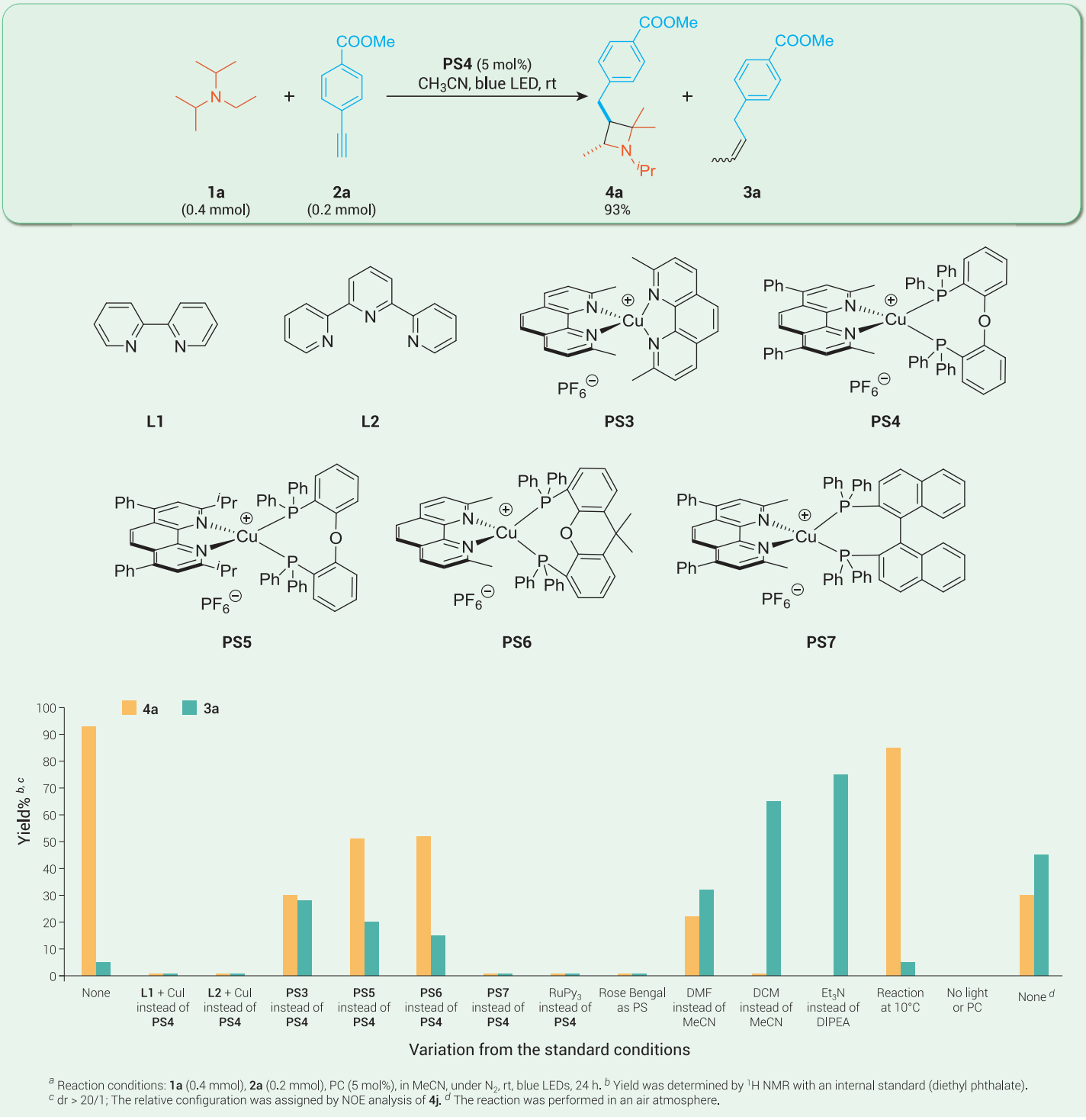


Figure 1. Previous research and work from this study

Notably, the most effective Cu (I) photosensitizer was [(DPEphos)(bcp)Cu]PF_6, **PS4**.[55,59] The product yields of the reactions by other Cu-based photosensitizers, such as dipyridine **L1**+**CuI**, tripyridine **L2**+**CuI**, homoleptic N/N Cu (I) **PS3**,[48,67] and heteroleptic P/N Cu (I) photosensitizers (**PS5**, **PS6**, and **PS7**)[51,68] were generally lower than **PS4** (entries 2–7, Figure 2). In addition, the steric hindrance derived from isopropyl substitution on **PS5** 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*-trig cyclization rather than C-N bond cleavage. Common photocatalysts, such as Ru $(bpy)_3Cl_2 \cdot 6H_2O$ (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_3N (2 equiv) was used as the reducing and reacting agent, we obtained allylbenzene **3a** as the major product (75%) (entry 12, Figure 2).[57,56] 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)[69,70] Various arylalkynes could react under the



[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), PC (5 mol%), in MeCN, under N_2, rt, blue LEDs, 24 h. [b] Yield was determined by ^{1}H NMR with an internal standard (diethyl phthalate). [c] dr > 20/1; The relative configuration was assigned by NOE analysis of **4j**. [d] The reaction was performed in an air atmosphere.

Figure 2. Evaluation of the photocatalysts and other reaction parameters[a]

optimal conditions, giving fully substituted azetidines with good to excellent yields (**4b**–**4n**), depending on whether they were electron deficient, with substitutions such as CF_3, 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

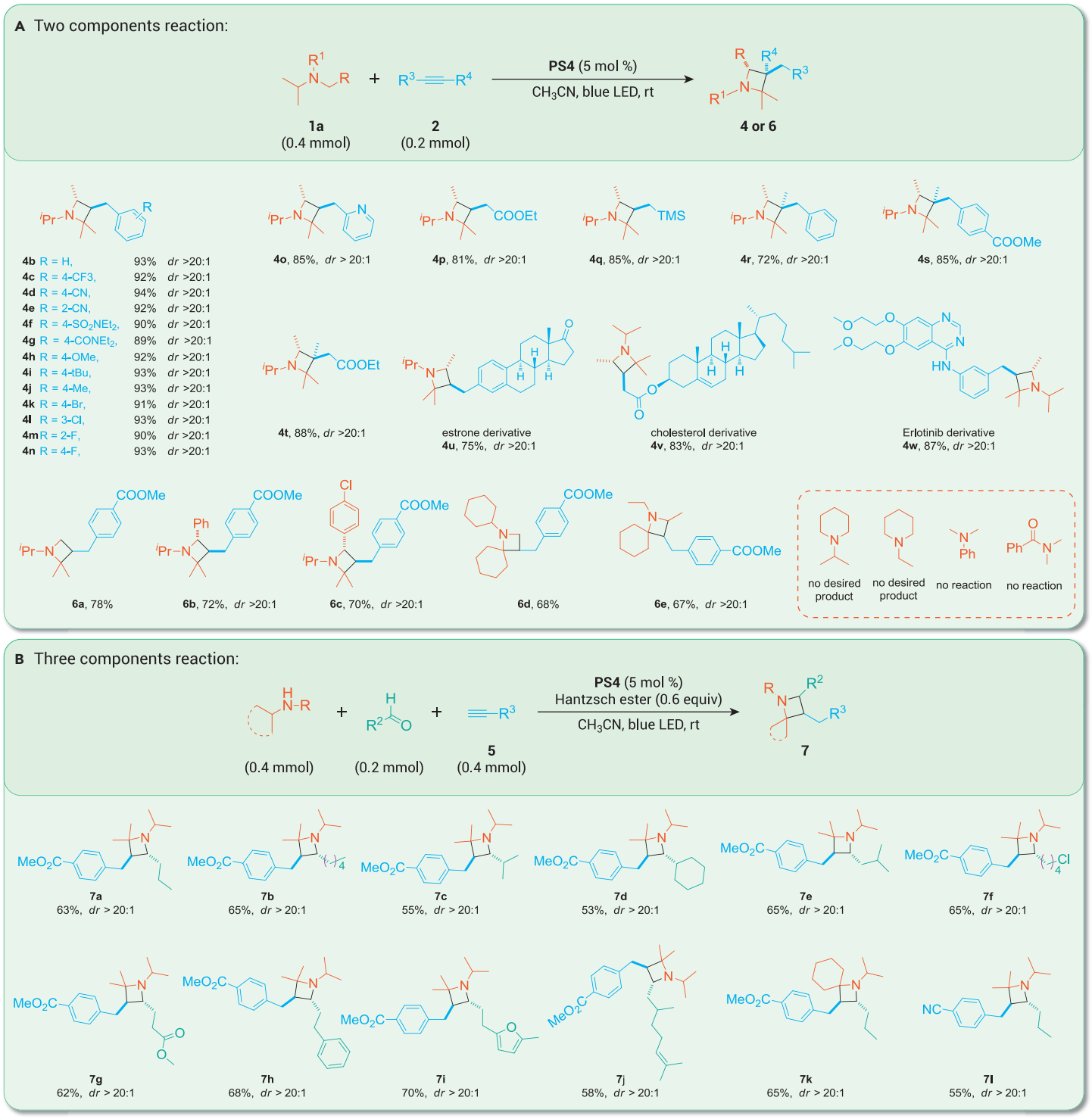


Figure 3. Substrate scope study

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**).

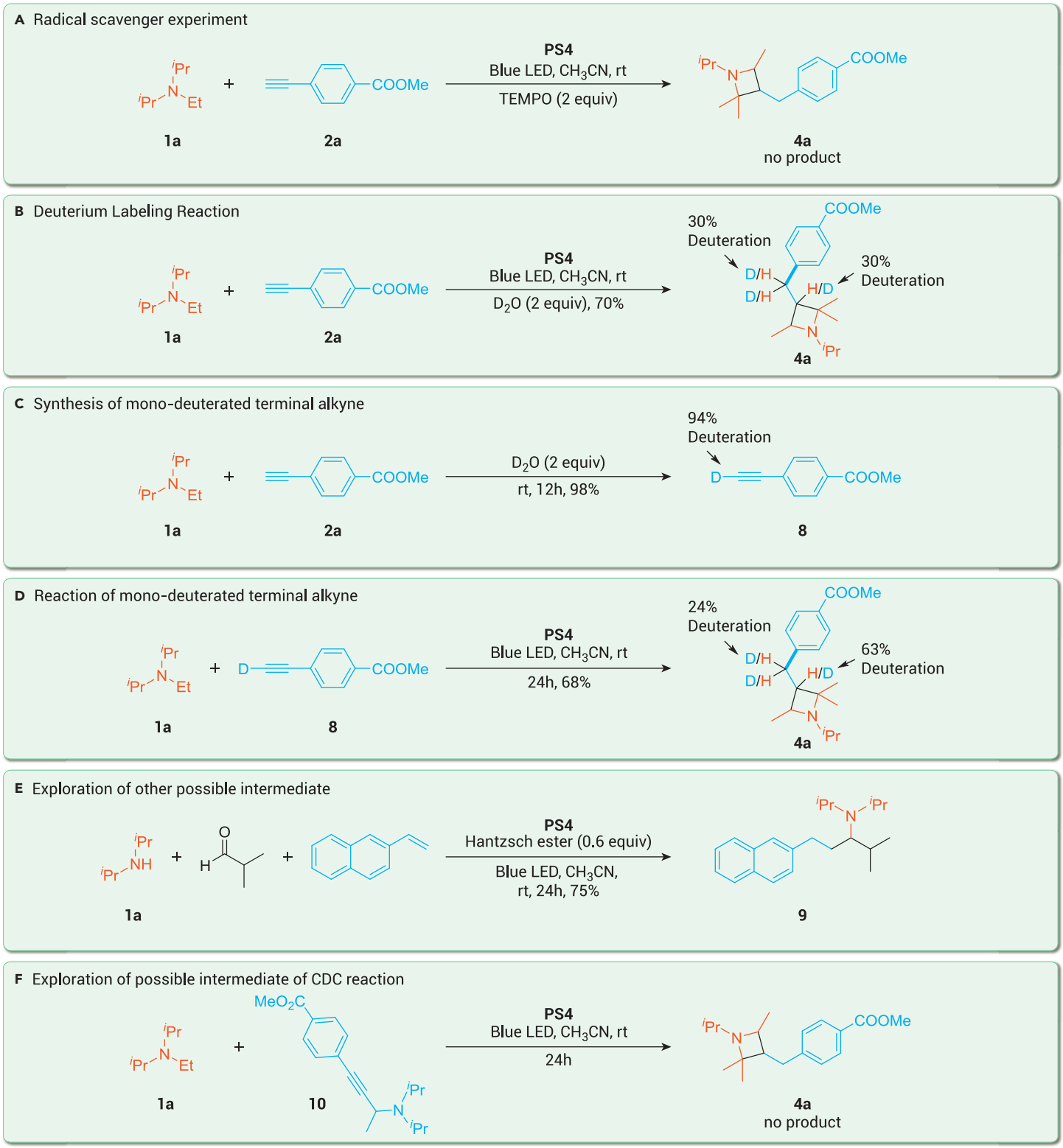


Figure 4. Deuterium labeling experiments and radical probe

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 D_2O, 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 D_2O, 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 ***d*-8**, 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 ***d*-8** (Figure 4D). Accordingly,

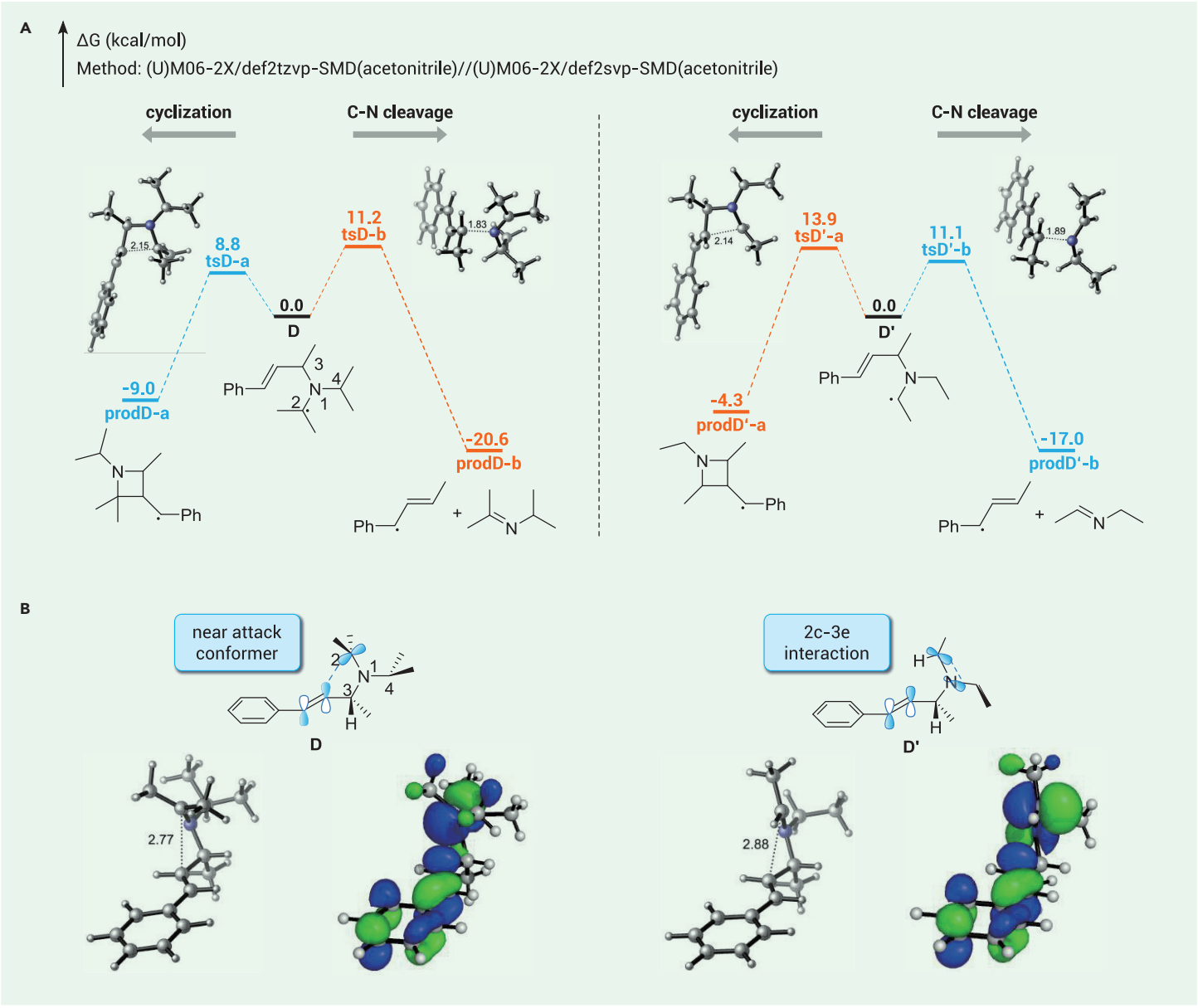


Figure 5. DFT calculation studies (A) Computed free energy surfaces of the cyclization and C-N bond cleavage pathways for the tertiary D radical and secondary D′ radical, and (B) optimized geometries and orbitals of the singly occupied molecular and π antibonding orbitals.

using alkene as the substrate instead of alkyne in the three-component reaction, the formation of tertiary amine **9** supported the generation of the α-amino radical, from the secondary amine and aldehyde (Figure 4E). With propargyl amine **10**, 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 π 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 π orbital. Consequently, the tertiary radical was already in the near-attack conformation for cyclization. In sharp contrast, the SOMO pointed away from the olefin π orbital in the secondary radical D′, and the secondary radical was in the plane of N1C2C3C4; thus, favorable 2c-3e interactions developed between the radical and adjacent nitrogen lone pair, 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)* [$E_{1/2}(Cu^{I}*/Cu^{0})$ = +0.63 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 α-aminoalkyl radical **B** was generated through deprotonation. The addition of α-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,

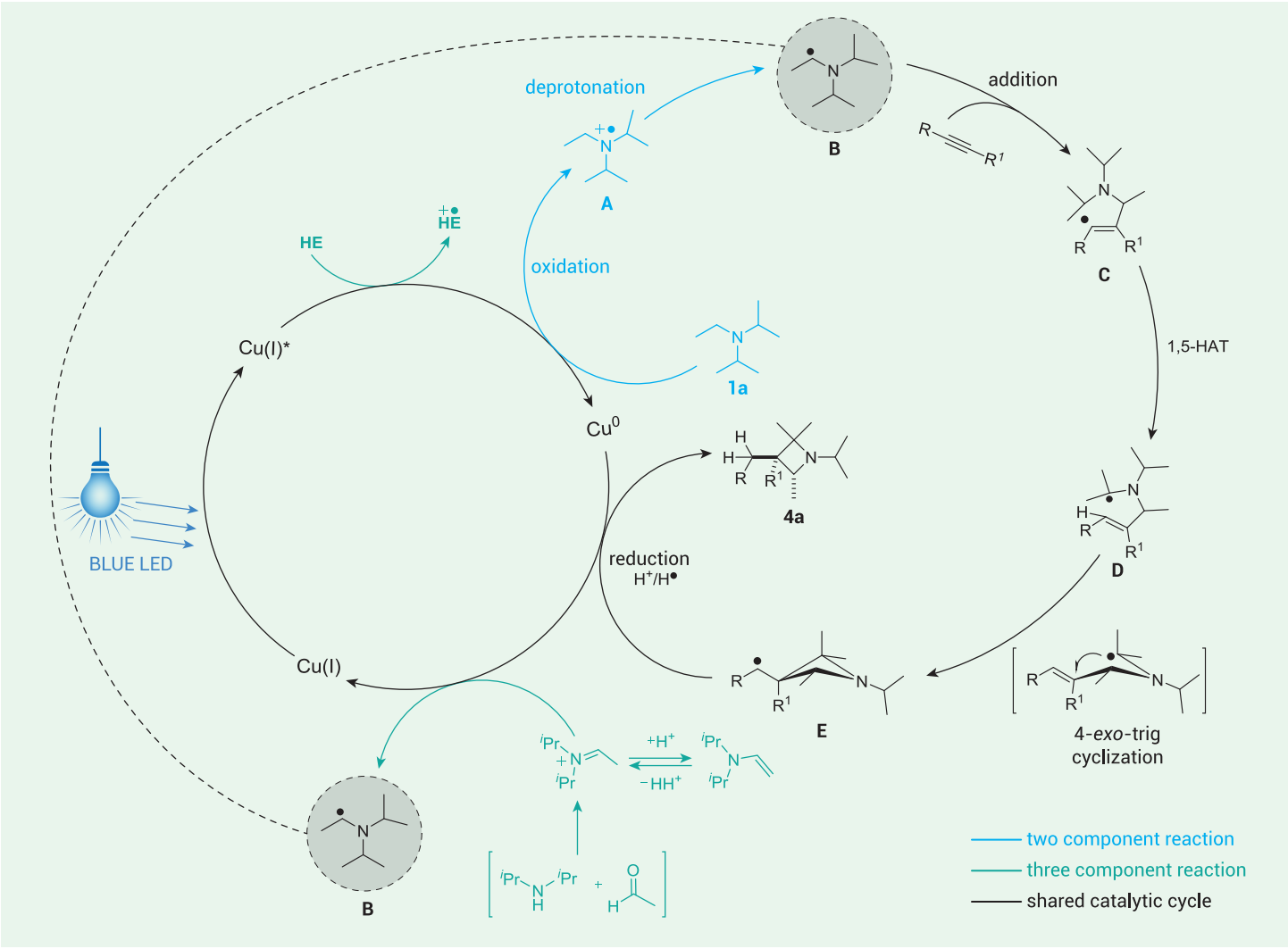


Figure 6. Proposed reaction mechanism

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 ($E_{1/2}(Cu^I/Cu^0)$ = −1.63 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 α-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 α-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.

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)Cu]PF_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_3CN (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.

REFERENCES

1. Carreira, E.M., and Fessard, T.C. (2014). Four-membered ring-containing spirocycles: synthetic strategies and opportunities. Chem. Rev. ***114***, 8257–8322. https://doi.org/10.1021/cr500127b.
2. Han, M., Song, C., Jeong, N., and Hahn, H.-G. (2014). Exploration of 3-Aminoazetidines as triple reuptake inhibitors by bioisosteric modification of 3-α-Oxyazetidine. ACS Med. Chem. Lett. ***5***, 999–1004. https://doi.org/10.1021/ml500187a.
3. Han, Y., Han, M., Shin, D., Song, C., and Hahn, H.G. (2012). Exploration of novel 3-substituted azetidine derivatives as triple reuptake inhibitors. J. Med. Chem. ***55***, 8188–8192. https://doi.org/10.1021/jm3008294.
4. Marson, C.M. (2011). New and unusual scaffolds in medicinal chemistry. Chem. Soc. Rev. ***40***, 5514–5533. https://doi.org/10.1039/c1cs15119c.
5. Brown, A., Brown, T.B., Calabrese, A., Ellis, D., Puhalo, N., Ralph, M., and Watson, L. (2010). Triazole oxytocin antagonists: identification of an aryloxyazetidine replacement for a biaryl substituent. Bioorg. Med. Chem. Lett. ***20***, 516–520. https://doi.org/10.1016/j.bmcl.2009.11.097.

6. Kitajima, M., Kogure, N., Yamaguchi, K., Takayama, H., and Aimi, N. (2003). Structure reinvestigation of gelsemoxonine, a constituent of gelsemium elegans, reveals a novel, azetidine-containing indole alkaloid. Org. Lett. **5**, 2075–2078. https://doi.org/10.1021/ol0344725.
7. Antermite, D., Degennaro, L., and Luisi, R. (2017). Recent advances in the chemistry of metallated azetidines. Org. Biomol. Chem. **15**, 34–50. https://doi.org/10.1039/c6ob01665k.
8. Couty, F., and Evano, G. (2009). Azetidines: new tools for the synthesis of nitrogen heterocycles. Synlett **2009**, 3053–3064.
9. Bott, T.M., and West, F.G. (2012). Preparation and synthetic applications of azetidines. Heterocycles **84**, 223–264. https://doi.org/10.3987/rev-11-sr(p)9.
10. Brandi, A., Cicchi, S., and Cordero, F.M. (2008). Novel syntheses of azetidines and azetidinones. Chem. Rev. **108**, 3988–4035. https://doi.org/10.1021/cr800325e.
11. Jensen, K.L., Nielsen, D.U., and Jamison, T.F. (2015). A general strategy for the synthesis of enantiomerically pure azetidines and aziridines through nickel-catalyzed cross-coupling. Chem. Eur. J. **21**, 7379–7383. https://doi.org/10.1002/chem.201500886.
12. Kenis, S., D'hooghe, M., Verniest, G., Reybroeck, M., Dang Thi, T.A., Pham The, C., Thi Pham, T., Tornroos, K.W., Van Tuyen, N., and De Kimpe, N. (2013). Nucleophile-directed selective transformation of cis-1-Tosyl-2-tosyloxymethyl-3-(trifluoromethyl) aziridine into aziridines, azetidines, and benzo-fused dithianes, oxathianes, dioxanes, and (thio)morpholines. Chem. Eur. J. **19**, 5966–5971. https://doi.org/10.1002/chem.201204485.
13. Becker, M.R., Wearing, E.R., and Schindler, C.S. (2020). Synthesis of azetidines via visiblelight-mediated intermolecular [2+2] photocycloadditions. Nat. Chem. **12**, 898–905. https://doi.org/10.1038/s41557-020-0541-1.
14. Sakamoto, R., Inada, T., Sakurai, S., and Maruoka, K. (2016). [2 + 2] Photocycloadditions between the carbon–nitrogen double bonds of imines and carbon–carbon double bonds. Org. Lett. **18**, 6252–6255. https://doi.org/10.1021/acs.orglett.6b03003.
15. Kumarasamy, E., Kandappa, S.K., Raghunathan, R., Jockusch, S., and Sivaguru, J. (2017). Realizing an aza paternò–büchi reaction. Angew. Chem. Int. Ed. **56**, 7056–7061. https://doi.org/10.1002/anie.201702273.
16. Marichev, K.O., Wang, K., Dong, K., Greco, N., Massey, L.A., Deng, Y., Arman, H., and Doyle, M.P. (2019). Synthesis of chiral tetrasubstituted azetidines from donor–acceptor azetines via asymmetric copper(I)-catalyzed imido-ylide [3+1]-cycloaddition with metalloenolcarbenes. Angew. Chem. Int. Ed. **58**, 16188–16192. https://doi.org/10.1002/anie.201909929.
17. Schmid, S.C., Guzei, I.A., and Schomaker, J.M. (2017). A stereoselective [3+1] ring expansion for the synthesis of highly substituted methylene azetidines. Angew. Chem. Int. Ed. **56**, 12229–12233. https://doi.org/10.1002/anie.201705202.
18. Han, J.-Q., Zhang, H.-H., Xu, P.-F., and Luo, Y.-C. (2016). Lewis acid and (Hypo)iodite relay catalysis allows a strategy for the synthesis of polysubstituted azetidines and tetrahydroquinolines. Org. Lett. **18**, 5212–5215. https://doi.org/10.1021/acs.orglett.6b02430.
19. Zhang, H.-H., Luo, Y.-C., Wang, H.-P., Chen, W., and Xu, P.F. (2014). $TiCl_4$ promoted formal [3 + 3] cycloaddition of cyclopropane 1,1-diesters with azides: synthesis of highly functionalized triazinines and azetidines. Org. Lett. **16**, 4896–4899. https://doi.org/10.1021/ol5024079.
20. Malik, S., and Nadir, U.K. (2008). A facile synthesis of 1-arenesulfonylazetidines through reaction of 1-arenesulfonylaziridines with dimethylsulfoxonium methylide generated under microwave irradiation. Synlett **2008**, 108–110. https://doi.org/10.1055/s-2007-1000838.
21. Garima Srivastava, V.P., and Yadav, L.D.S. (2010). The first example of ring expansion of N-tosylaziridines to 2-aroyl-N-tosylazetidines with nitrogen ylides in an aqueous medium. Green. Chem. **12**, 1460–1465. https://doi.org/10.1039/c004736h.
22. Ghosh, A., Mandal, S., Chattaraj, P.K., and Banerjee, P. (2016). Ring Expansion of Donor–Acceptor Cyclopropane via Substituent Controlled Selective N-Transfer of Oxaziridine: Synthetic and Mechanistic Insights. Org. Lett. **18**, 4940–4943. https://doi.org/10.1021/acs.orglett.6b02417.
23. Yu, X.-Y., Chen, J.-R., and Xiao, W.-J. (2021). Visible light-driven radical-mediated C–C bond cleavage/functionalization in organic synthesis. Chem. Rev. **121**, 506–561. https://doi.org/10.1021/acs.chemrev.0c00030.
24. Chen, Y., Lu, L.-Q., Yu, D.-G., Zhu, C.J., and Xiao, W.J. (2019). Visible light-driven organic photochemical synthesis in China. Sci. China **62**, 24–57. https://doi.org/10.1007/s11426-018-9399-2.
25. An, X.-D., and Yu, S. (2018). Photoredox-catalyzed $C(sp^2)$–N coupling reactions. Tetrahedron Lett. **59**, 1605–1613. https://doi.org/10.1016/j.tetlet.2018.03.050.
26. Zhu, J., Yang, W.-C., Wang, X.-d., and Wu, L. (2018). Photoredox catalysis in C–S bond construction: recent progress in Photo-catalyzed formation of sulfones and sulfoxides. Adv. Synth. Catal. **360**, 386–400. https://doi.org/10.1002/adsc.201701194.
27. Ravelli, D., Protti, S., and Fagnoni, M. (2016). Carbon–carbon bond forming reactions via photogenerated intermediates. Chem. Rev. **116**, 9850–9913. https://doi.org/10.1021/acs.chemrev.5b00662.
28. Chen, J.-R., Hu, X.-Q., Lu, L.-Q., and Xiao, W.-J. (2016). Visible light photoredox-controlled reactions of N-radicals and radical ions. Chem. Soc. Rev. **45**, 2044–2056. https://doi.org/10.1039/c5cs00655d.
29. Schwinger, D.P., and Bach, T. (2020). Chiral 1,3,2-Oxazaborolidine catalysts for enantioselective photochemical reactions. Acc. Chem. Res. **53**, 1933–1943. https://doi.org/10.1021/acs.accounts.0c00379.
30. Brimioulle, R., and Bach, T. (2013). Enantioselective lewis acid catalysis of intramolecular enone [2+2] photocycloaddition reactions. Science **342**, 840–843. https://doi.org/10.1126/science.1244809.
31. Lu, Z., and Yoon, T.P. (2012). Visible light photocatalysis of [2+2] styrene cycloadditions by energy transfer. Angew. Chem. Int. Ed. **51**, 10329–10332. https://doi.org/10.1002/anie.201204835.
32. Müller, C., Bauer, A., Maturi, M.M., Cuquerella, M.C., Miranda, M.A., and Bach, T. (2011). Enantioselective intramolecular [2 + 2]-photocycloaddition reactions of 4-substituted quinolones catalyzed by a chiral sensitizer with a hydrogen-bonding Motif. J. Am. Chem. Soc. **133**, 16689–16697. https://doi.org/10.1021/ja207480q.
33. Coote, S.C., and Bach, T. (2013). Enantioselective intermolecular [2+2] photocycloadditions of isoquinolone mediated by a chiral hydrogen-bonding template. J. Am. Chem. Soc. **135**, 14948–14951. https://doi.org/10.1021/ja408167r.
34. Zou, Y.-Q., Duan, S.-W., Meng, X.-G., Hu, X.Q., Gao, S., Chen, J.R., and Xiao, W.J. (2012). Visible light induced intermolecular [2+2]-cycloaddition reactions of 3-ylideneoxindoles through energy transfer pathway. Tetrahedron **68**, 6914–6919. https://doi.org/10.1016/j.tet.2012.06.011.
35. Condie, A.G., González-Gómez, J.C., and Stephenson, C.R.J. (2010). Visible-light photoredox catalysis: aza-Henry reactions via C–H functionalization. J. Am. Chem. Soc. **132**, 1464–1465. https://doi.org/10.1021/ja909145y.
36. Lin, W., Cao, T., Fan, W., Han, Y., Kuang, J., and Luo, H. (2014). Enantioselective Double Manipulation of Tetrahydroisoquinolines with Terminal Alkynes and Aldehydes under Copper(I) Catalysis. Angew. Chem. Int. Ed **53**, 277–281. https://doi.org/10.1002/anie.201308699.
37. Zhao, H., and Leonori, D. (2021). Minimization of back-electron transfer enables the elusive sp3 C–H functionalization of secondary anilines. Angew. Chem. Int. Ed. **60**, 7669–7674. https://doi.org/10.1002/anie.202100051.
38. Call, A., Casadevall, C., Acuña-Parés, F., Casitas, A., and Lloret-Fillol, J. (2017). Dual cobalt–copper light-driven catalytic reduction of aldehydes and aromatic ketones in aqueous media. Chem. Sci. **8**, 4739–4749. https://doi.org/10.1039/c7sc01276d.
39. Constantin, T., Zanini, M., Regni, A., Sheikh, N.S., Julia, F., and Leonori, D. (2020). Aminoalkyl radicals as halogen-atom transfer agents for activation of alkyl and aryl halides. Science **367**, 1021–1026. https://doi.org/10.1126/science.aba2419.
40. Nakajima, K., Miyake, Y., and Nishibayashi, Y. (2016). Synthetic utilization of α-aminoalkyl radicals and related species in visible light photoredox catalysis. Acc. Chem. Res. **49**, 1946–1956. https://doi.org/10.1021/acs.accounts.6b00251.
41. Trowbridge, A., Reich, D., and Gaunt, M.J. (2018). Multicomponent synthesis of tertiary alkylamines by photocatalytic olefin-hydroaminoalkylation. Nature **561**, 522–527. https://doi.org/10.1038/s41586-018-0537-9.
42. Thullen, S.M., and Rovis, T. (2017). A Mild hydroaminoalkylation of conjugated dienes using a unified cobalt and photoredox catalytic system. J. Am. Chem. Soc. **139**, 15504–15508. https://doi.org/10.1021/jacs.7b09252.
43. Zhong, L.-J., Li, Y., An, D.-L., and Li, J.-H. (2021). Heteroannulation of N-Fluoro-N-alkylsulfonamides with terminal alkynes via remote C(sp3)–H functionalization. ACS Catal. **11**, 383–389. https://doi.org/10.1021/acscatal.0c03853.
44. Wu, X., and Zhu, C. (2020). Radical functionalization of remote C(sp3)–H bonds mediated by unprotected alcohols and amides. CCS Chem. **2**, 813–828. https://doi.org/10.31635/ccschem.020.202000234.
45. Sarkar, S., Cheung, K.P.S., and Gevorgyan, V. (2020). C–H functionalization reactions enabled by hydrogen atom transfer to carbon-centered radicals. Chem. Sci. **11**, 12974–12993. https://doi.org/10.1039/d0sc04881j.
46. Chu, J.C.K., and Rovis, T. (2018). Complementary strategies for directed $C(sp^3)$–H functionalization: a comparison of transition-metal-catalyzed activation, hydrogen atom transfer, and carbene/nitrene transfer. Angew. Chem. Int. Ed. **57**, 62–101. https://doi.org/10.1002/anie.201703743.
47. Stateman, L.M., Nakafuku, K.M., and Nagib, D.A. (2018). Remote C–H functionalization via selective hydrogen atom transfer. Synthesis **50**, 1569–1586. https://doi.org/10.1055/s-0036-1591930.
48. Curran, D.P., Kim, D., Liu, H.T., and Shen, W. (1988). Translocation of radical sites by intramolecular 1,5-hydrogen atom transfer. J. Am. Chem. Soc. **110**, 5900–5902. https://doi.org/10.1021/ja00225a052.
49. Heiba, E.-A.I., and Dessau, R.M. (1967). Free-radical isomerization. I. novel rearrangement of vinyl radicals. J. Am. Chem. Soc. **89**, 3772–3777. https://doi.org/10.1021/ja00991a017.
50. Hossain, A., Bhattacharyya, A., and Reiser, O. (2019). Copper's rapid ascent in visible-light photoredox catalysis. Science **364**, eaav9713. https://doi.org/10.1126/science.aav9713.
51. Minozzi, C., Caron, A., Grenier-Petel, J.-C., Santandrea, J., and Collins, S.K. (2018). Heteroleptic copper(I)-based complexes for photocatalysis: combinatorial assembly, discovery, and optimization. Angew. Chem. Int. Ed. **57**, 5477–5481. https://doi.org/10.1002/anie.201800144.
52. Deldaele, C., Michelet, B., Baguia, H., Kajouj, S., Romero, E., Moucheron, C., and Evano, G. (2018). A general copper-based photoredox catalyst for organic synthesis: scope, application in natural product synthesis and mechanistic insights. Chimia **72**, 621–629. https://doi.org/10.2533/chimia.2018.621.
53. Hernandez-Perez, A.C., and Collins, S.K. (2016). Heteroleptic Cu-based sensitizers in photoredox catalysis. Acc. Chem. Res. **49**, 1557–1565. https://doi.org/10.1021/acs.accounts.6b00250.
54. Reiser, O. (2016). Shining light on copper: unique opportunities for visible-light-catalyzed atom transfer radical addition reactions and related processes. Acc. Chem. Res. **49**, 1990–1996. https://doi.org/10.1021/acs.accounts.6b00296.
55. Jacob, C., Baguia, H., Dubart, A., Oger, S., and Thilmany, P. (2022). A general synthesis of azetidines by copper-catalysed photoinduced anti-Baldwin radical cyclization of ynamides. Nat. Commun. **13**, 560–568. https://doi.org/10.1038/s41467-022-28098-x.

56. Bao, H., Zhou, B., Luo, S.-P., Xu, Z., Jin, H., and Liu, Y. (2020). P/N heteroleptic Cu(I)-photosensitizer-catalyzed deoxygenative radical alkylation of aromatic alkynes with alkyl aldehydes using dipropylamine as a traceless linker agent. ACS Catal. ***10***, 7563–7572. https://doi.org/10.1021/acscatal.0c02454.
57. Zheng, L., Jiang, Q., Bao, H., Zhou, B., Luo, S.P., Jin, H., Wu, H., and Liu, Y. (2020). Tertiary amines acting as alkyl radical equivalents enabled by a P/N heteroleptic Cu(I) photosensitizer. Org. Lett. ***22***, 8888–8893. https://doi.org/10.1021/acs.orglett.0c03236.
58. Andrieux, C.P., and Savéant, J.M. (1970). Electrodimerization. J. Electroanal. Chem. ***26***, 223–235. https://doi.org/10.1016/s0022-0728(70)80307-2.
59. Cao, Z., Li, J., Zhang, G., et al. (2021). Photo-induced copper-catalyzed sequential 1,n-HAT enabling the formation of cyclobutanols. Nat. Commun. ***12***, 6404–6412. https://doi.org/10.1038/s41467-021-26670-5.
60. Luo, S.-P., Mejía, E., Friedrich, A., Pazidis, A., Junge, H., Surkus, A.E., Jackstell, R., Denurra, S., Gladiali, S., Lochbrunner, S., and Beller, M. (2013). Photocatalytic water reduction with copper-based photosensitizers: a noble-metal-free system. Angew. Chem. Int. Ed. ***52***, 419–423. https://doi.org/10.1002/anie.201205915.
61. Brown, A., Ellis, D., Wallace, O., and Ralph, M. (2010). Identification of a urea bioisostere of a triazole oxytocin antagonist. Bioorg. Med. Chem. Lett. ***20***, 1851–1853. https://doi.org/10.1016/j.bmcl.2010.01.143.
62. Maetani, M., Zoller, J., Melillo, B., Verho, O., Kato, N., and Pu, J. (2017). Synthesis of a Bicyclic Azetidine with In Vivo Antimalarial Activity Enabled by Stereospecific, Directed C(sp3)–H Arylation. J. Am. Chem. Soc. ***139***, 11300–11306. https://doi.org/10.1021/jacs.7b06994.
63. Xu, G.-Q., Xu, J.-T., Feng, Z.-T., Liang, H., Wang, Z.Y., Qin, Y., and Xu, P.F. (2018). Dual C(sp^3)–H bond functionalization of N-heterocycles through sequential visible-light photocatalyzed dehydrogenation/[2+2] cycloaddition reactions. Angew. Chem. Int. Ed. ***57***, 5110–5114. https://doi.org/10.1002/anie.201710523.
64. Mori, K., Kurihara, K., Yabe, S., Yamanaka, M., and Akiyama, T. (2014). Double C(sp^3)–H bond functionalization mediated by sequential hydride shift/cyclization process: diastereoselective construction of polyheterocycles. J. Am. Chem. Soc. ***136***, 3744–3747. https://doi.org/10.1021/ja412706d.
65. Mori, K., Isogai, R., Kamei, Y., Yamanaka, M., and Akiyama, T. (2018). Chiral magnesium bisphosphate-catalyzed asymmetric double C(sp^3)–H bond functionalization based on sequential hydride shift/cyclization process. J. Am. Chem. Soc. ***140***, 6203–6207. https://doi.org/10.1021/jacs.8b02761.
66. Zhuang, Z., Herron, A.N., Liu, S., and Yu, J.-Q. (2021). Rapid construction of tetralin, chromane, and indane motifs via cyclative C–H/C–H coupling: four-step total synthesis of (±)-russujaponol F. J. Am. Chem. Soc. ***143***, 687–692. https://doi.org/10.1021/jacs.0c12484.
67. Hernandez-Perez, A.C., Vlassova, A., and Collins, S.K. (2012). Toward a visible light mediated photocyclization: Cu-based sensitizers for the synthesis of [5] helicene. Org. Lett. ***14***, 2988–2991. https://doi.org/10.1021/ol300983b.
68. Cuttell, D.G., Kuang, S.-M., Fanwick, P.E., McMillin, D.R., and Walton, R.A. (2002). Simple Cu(I) complexes with unprecedented excited-state lifetimes. J. Am. Chem. Soc. ***124***, 6–7. https://doi.org/10.1021/ja012247h.
69. Li, H., Guo, L., Feng, X., Huo, L., Zhu, S., and Chu, L. (2020). Sequential C–O decarboxylative vinylation/C–H arylation of cyclic oxalates via a nickel-catalyzed multicomponent radical cascade. Chem. Sci. ***11***, 4904–4910. https://doi.org/10.1039/d0sc01471k.
70. Brunckova, J., Crich, D., and Yao, Q. (1994). Intramolecular hydrogen atom abstraction in carbohydrates and nucleosides: inversion of an α- to β-mannopyranoside and genera-tion of thymidine C-4′ radicals. Tetrahedron Lett. ***35***, 6619–6622. https://doi.org/10.1016/s0040-4039(00)73450-2.
71. Li, C.-J. (2009). Cross-Dehydrogenative Coupling (CDC): exploring C–C bond formations beyond functional group transformations. Acc. Chem. Res. ***42***, 335–344. https://doi.org/10.1021/ar800164n.
72. Li, Z., and Li, C.-J. (2004). CuBr-catalyzed efficient alkynylation of sp3 C–H bonds adjacent to a nitrogen atom. J. Am. Chem. Soc. ***126***, 11810–11811. https://doi.org/10.1021/ja0460763.
73. Wei, C., and Li, C.-J. (2002). Enantioselective direct-addition of terminal alkynes to imines catalyzed by copper(I)pybox complex in water and in toluene. J. Am. Chem. Soc. ***124***, 5638–5639. https://doi.org/10.1021/ja026007t.
74. Huang, L., Ye, L., Li, X.-H., Li, Z.L., Lin, J.S., and Liu, X.Y. (2016). Stereoselective radical cyclization cascades triggered by addition of diverse radicals to alkynes to construct 6(5)–6–5 fused rings. Org. Lett. ***18***, 5284–5287. https://doi.org/10.1021/acs.orglett.6b02599.

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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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