

Article

Visible Light Promotes Cascade Trifluoromethylation/Cyclization, Leading to Trifluoromethylated Polycyclic Quinazolinones, Benzimidazoles and Indoles

Ransong Ma ¹, Yuanyuan Ren ¹, Zhoubin Deng ¹, Ke-Hu Wang ¹, Junjiao Wang ¹, Danfeng Huang ¹, Yulai Hu ^{1,2,*}  and Xiaobo Lv ³

¹ College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, China

² State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

³ Shanghai Sinofluoro Chemicals Co., Ltd., Shanghai 201321, China

* Correspondence: huyl@nwnu.edu.cn

Abstract: Efficient visible-light-induced radical cascade trifluoromethylation/cyclization of inactivated alkenes with CF₃Br, which is a nonhygroscopic, noncorrosive, cheap and industrially abundant chemical, was developed in this work, producing trifluoromethyl polycyclic quinazolinones, benzimidazoles and indoles under mild reaction conditions. The method features wide functional group compatibility and a broad substrate scope, offering a facile strategy to pharmaceutically produce valuable CF₃-containing polycyclic *aza*-heterocycles.

Keywords: bromotrifluoromethane; visible-light induction; trifluoromethylation; cyclization; polycyclic quinazolinone; polycyclic benzimidazole; polycyclic indole



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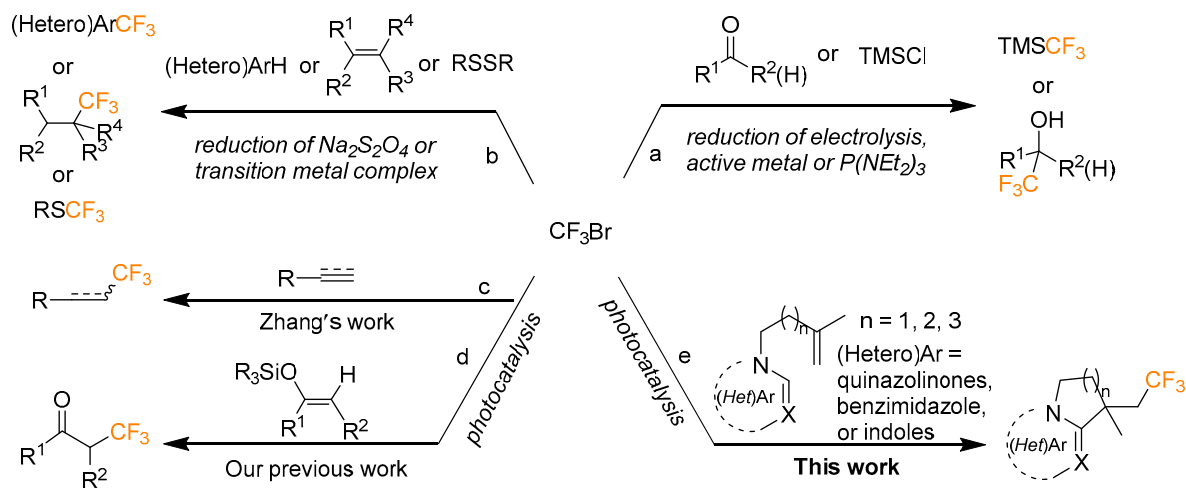
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1. Introduction

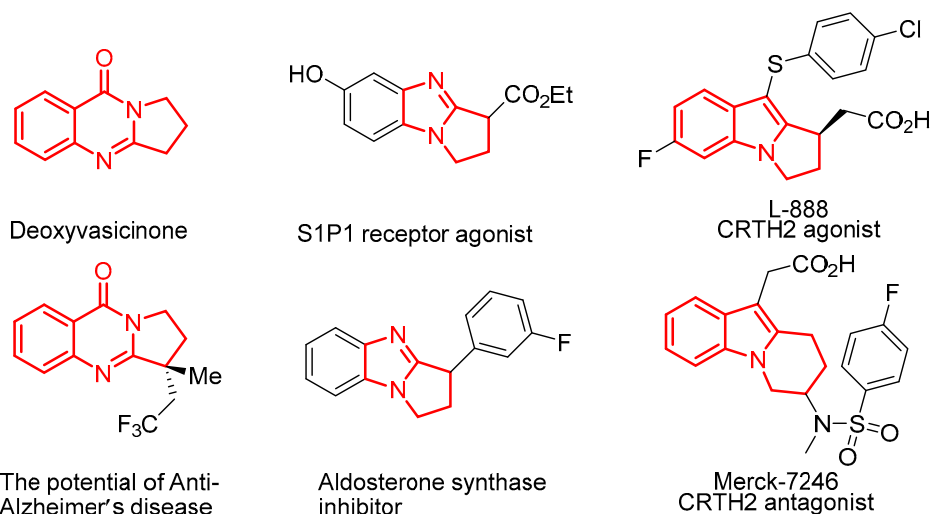
Organofluorides are ubiquitous in pharmaceuticals, agrochemicals and functional materials owing to their high lipophilicity, improved metabolic stability and enhanced bioactivity compared with their parent molecules [1–6]. Until now, more than 340 fluorinated pharmaceuticals and 420 fluorinated agrochemicals have been registered and used commercially, which account for 20% of clinical drugs and 35% of commercial agrochemicals, respectively [7,8]. Thus, organofluorides have become increasingly important in developing new pharmaceuticals and agrochemicals. Among the various organofluorides, trifluoromethyl compounds are of great importance due to their frequent appearance in drug and pesticide molecules. This fact has stimulated intensive investigations of trifluoromethylation in organic compounds, and various trifluoromethylation methodologies have been developed. In particular, the appearance of versatile trifluoromethylation reagents such as the Togni [9–11], Umemoto [12], Ruppert–Prakash [13,14] and Langlois [15] reagents [16,17] have greatly pushed forward the development of trifluoromethylation methodologies through electrophilic, nucleophilic and radical processes. However, all of these reagents are expensive, and none of them are commercially available in bulk quantities for the time-being. Hence, the exploration of new cost-effective and atom-economic trifluoromethylation methods using easily available trifluoromethylation reagents in bulk quantities in industry is of great value. To address this question, cost-effective and readily available trifluoroacetic acid (TFA), trifluoroacetic anhydride (TFAA) and triflic anhydride (Tf₂O) have recently been investigated as trifluoromethylation reagents under diverse catalysis by Zhang, Stephenson, Qing and Ritter, etc. [18–29].

As an extinguishant and refrigerant (R-13B1), CF₃Br is available in large quantities at a low price (21 USD/kg) in industry. Although CF₃Br has been tested as a trifluoromethylation reagent before, it has not been fully investigated in the trifluoromethylation process compared to other trifluoromethylation reagents. Screening of the literature shows that

CF_3Br can be reduced to a trifluoromethyl anion via electrochemical reduction [30,31], active metal reduction [32,33], or by $\text{P}(\text{NEt}_2)_3$ [34] to react with aldehydes or ketones to give alcohols, or to react with TMSCl to give TMSCF_3 (Scheme 1a). Secondly, CF_3Br can be reduced to a trifluoromethyl radical by $\text{Na}_2\text{S}_2\text{O}_4$ [35] or the transition metal complex [36–39] to couple with aromatic rings or alkenes to give trifluoromethyl compounds (Scheme 1b). In 2018, Zhang's group reported that CF_3Br could be activated by visible-light catalysis to produce a trifluoromethyl radical and induce a radical addition reaction with alkenes and alkynes (Scheme 1c) [40]. This process features an environmentally friendly and sustainable strategy to activate CF_3Br . In our previous work, the visible-light-induced trifluoromethylation of *O*-silyl enol ether was initially tested using CF_3Br as trifluoromethyl reagent under visible-light catalysis (Scheme 1d) [41]. As our research on CF_3Br is on-going, we herein report a visible-light-induced radical cascade trifluoromethylation/cyclization reaction, which provides a series of trifluoromethylated polycyclic quinazolinones, benzimidazoles and indoles, using CF_3Br as a trifluoromethyl source (Scheme 1e). This transformation provides a facile way to construct polycyclic *aza*-heterocycles, which are usually found in various pharmaceutical compounds (Scheme 2). Moreover, this approach features a low-cost trifluoromethyl source and wide substrate tolerance compared with other methods [42–48].



Scheme 1. Trifluoromethylation with CF_3Br as the trifluoromethylation source.

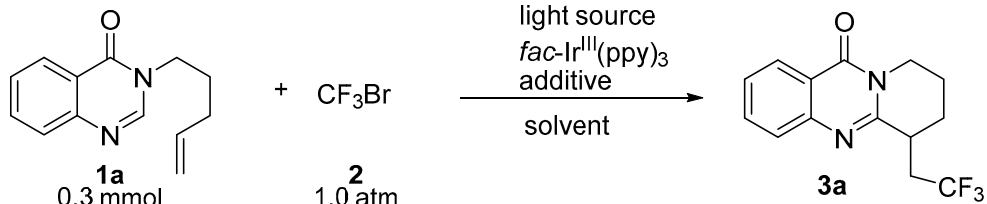


Scheme 2. Representative biologically active *aza*-heterocycles.

2. Results and Discussion

The initial investigation commenced with the reaction of 3-(pent-4-en-1-yl)quinazoline-4(3H)-one (**1a**) and CF₃Br (**2**) in the presence of tris(2-phenylpyridine)iridium (*fac*-Ir^{III}(ppy)₃) in acetonitrile (CH₃CN) under the irradiation of a 5 W blue LED (460–465 nm). The anticipated product **3a** was obtained with only a 5% yield (Table 1, entry 1). In view of the great influence of solvent effects on the reaction, various commonly used solvents including dichloromethane (DCM), toluene (Tol), tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), *N,N*-dimethylformamide (DMF) and *N*-methyl pyrrolidone (NMP) were tested; NMP proved to be the most suitable solvent, in which the product **3a** was obtained in a 30% yield (Table 1, entries 2–7). Subsequently, the screening of different light sources and their strength showed that the 5 W blue LED was optimal for the reaction (Table 1, entries 8–10). To further improve the product yield, several Lewis acids were examined. Notably, the addition of LiCl (1.0 equiv.) as an additive significantly accelerated the reaction rate, and the desired product **3a** was obtained in an 83% yield (Table 1, entries 11–15). Afterwards, the screening of the loading of the photocatalyst (PC) indicated that 1 mol % of *fac*-Ir^{III}(ppy)₃ was still the most suitable amount (Table 1, entries 14, 16 and 17). Finally, control experiments showed that a photocatalyst or light source is necessary for this transformation because there was no product formed in the absence of the photocatalyst or blue LED light (Table 1, entries 18 and 19). Thus, the optimal reaction conditions were to perform the reaction with 1 equiv. of 3-(pent-4-en-1-yl)quinazoline-4(3H)-one, under 1 atm CF₃Br, in the presence of *fac*-Ir^{III}(ppy)₃ in NMP, under the irradiation of a 5 W blue LED, with 1 equiv. of LiCl as the additive.

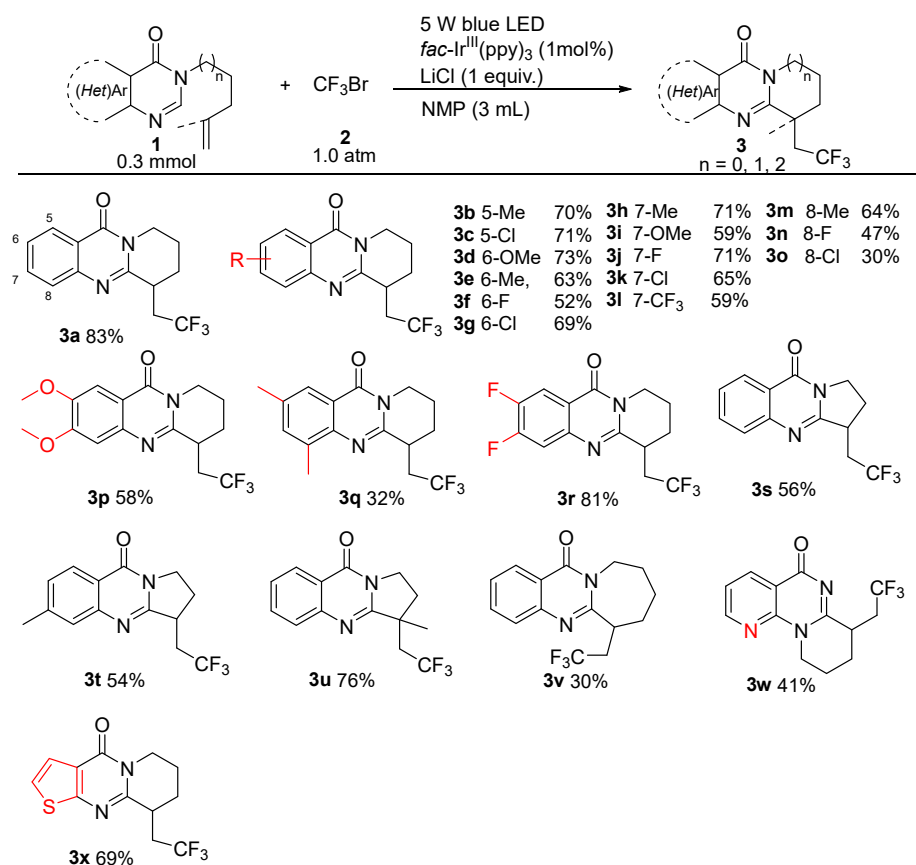
Table 1. Optimization of Reaction Conditions ^a.

|  <p>Reaction scheme: 1a (0.3 mmol) + 2 (1.0 atm) $\xrightarrow[\text{solvent}]{\text{light source, } fac\text{-Ir}^{\text{III}}(\text{ppy})_3, \text{additive}}$ 3a</p> | | | | | |
|---|-------------|---------------|---------------------------|--------------------|------------------------|
| Entry | PC (x mol%) | Light Source | Additive | Solvent | Yield ^b (%) |
| 1 | 1.0 mol% | 5 W blue LED | - | CH ₃ CN | 5% |
| 2 | 1.0 mol% | 5 W blue LED | - | DCM | 15% |
| 3 | 1.0 mol% | 5 W blue LED | - | Toluene | 3% |
| 4 | 1.0 mol% | 5 W blue LED | - | THF | 3% |
| 5 | 1.0 mol% | 5 W blue LED | - | DMSO | trace |
| 6 | 1.0 mol% | 5 W blue LED | - | DMF | 24% |
| 7 | 1.0 mol% | 5 W blue LED | - | NMP | 30% |
| 8 | 1.0 mol% | 10 W blue LED | - | NMP | 30% |
| 9 | 1.0 mol% | 15 W blue LED | - | NMP | 30% |
| 10 | 1.0 mol% | 5 W white LED | - | NMP | 21% |
| 11 | 1.0 mol% | 5 W blue LED | 20% Sc (OTf) ₃ | NMP | 45% |
| 12 | 1.0 mol% | 5 W blue LED | 20% In (OTf) ₃ | NMP | 38% |
| 13 | 1.0 mol% | 5 W blue LED | 100% LiF | NMP | 35% |
| 14 | 1.0 mol% | 5 W blue LED | 100% LiCl | NMP | 83% |
| 15 | 1.0 mol% | 5 W blue LED | 100% LiBr | NMP | 38% |
| 16 | 0.5 mol% | 5 W blue LED | 100% LiCl | NMP | 78% |
| 17 | 0.25 mol% | 5 W blue LED | 100% LiCl | NMP | 72% |
| 18 | - | 5 W blue LED | 100% LiCl | NMP | 0% |
| 19 | 1.0 mol% | - | 100% LiCl | NMP | 0% |

^a Reaction conditions: **1a** (0.3 mmol, 1 equiv.), PC = *fac*-Ir^{III}(ppy)₃; additive, solvent (3 mL) and CF₃Br (1.0 atm) in a 50 mL Schlenk flask; room temperature, 5 W blue LED light irradiation; time = 16 h. ^b Isolated yield.

With the optimal reaction conditions in hand, the substrate scopes were investigated. First, various *N*-alkenyl quinazolinones **1** were examined (Scheme 3). The results indicated

that substrates containing both electron-donating (methyl and methoxy) and electron-withdrawing groups (fluoro-, chloro- and trifluoromethyl) at the 5-, 6-, 7- or 8-position of the quinazolinone ring were well tolerated and provided the corresponding ring-fused quinazolinones in 30% to 73% yields (Scheme 3, **3b–3o**). *N*-alkenyl quinazolinones possessing disubstituted benzene rings reacted well to generate the desired products **3p–3r** in 32–81% yields (Scheme 3, **3p–3r**). In addition, five- and seven-membered cyclized products **3s–3v** were acquired in 30–76% yields (Scheme 3, **3s–3v**). Finally, when the benzene ring of the quinazolinone was replaced by a pyridine or thiophene moiety, the corresponding products **3w** and **3x** were isolated in 41% and 69% yields (Scheme 3, **3w** and **3x**).

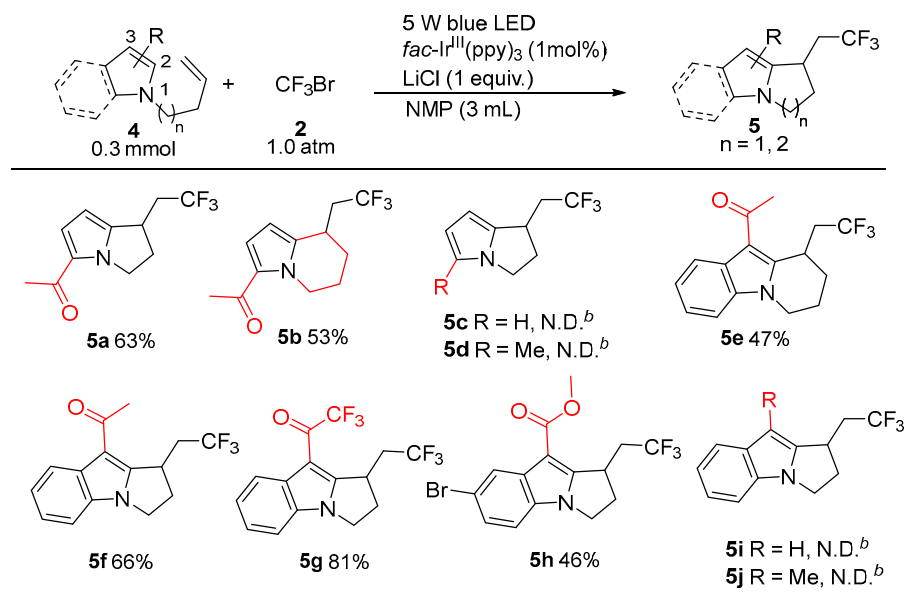


Scheme 3. Scope of quinazolinone-derived substrates ^a. ^a Reaction conditions: **1a** (0.3 mmol, 1 equiv.), PC = *fac*-Ir^(III)(ppy)₃ (0.003 mmol, 1 mol %); LiCl (0.3 mmol), NMP (3 mL) and CF₃Br (1.0 atm) in a 50 mL Schlenk flask; room temperature, 5 W blue LED light irradiation; time = 16 h. Isolated yield.

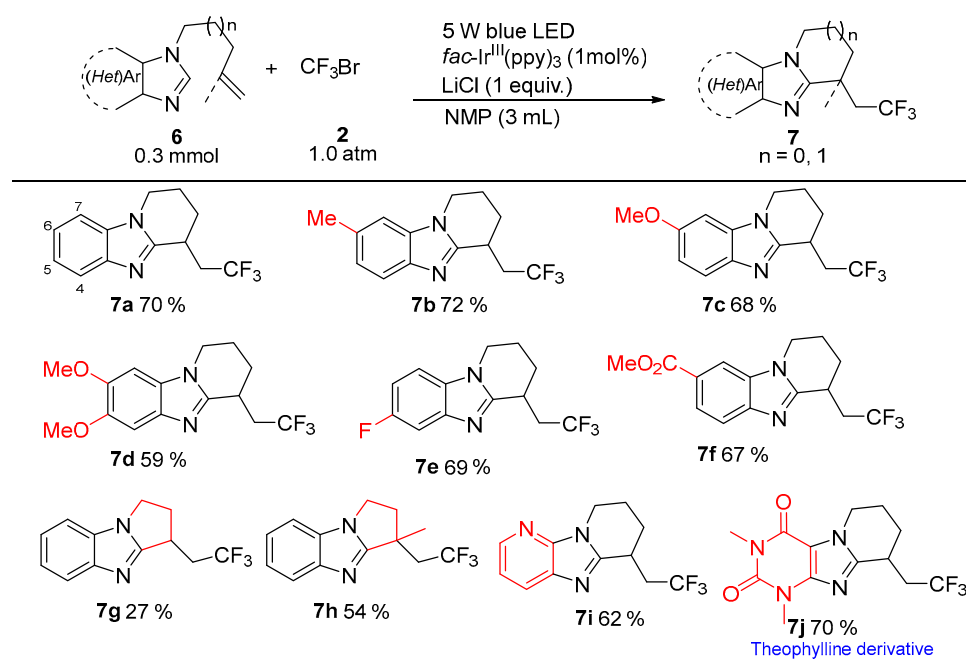
Next, various *N*-alkenyl pyrroles and *N*-alkenyl indoles **4** were applied in the standard conditions. As illustrated in Scheme 4, *N*-alkenyl pyrroles with acetyl groups at the 2-position gave five- and six-membered cyclization products (Scheme 4, **5a** and **5b**). However, pyrroles with methyl at the 2-position and without substituents failed to produce the desired product (Scheme 4, **5c** and **5d**). These results indicated that electron-withdrawing substitution on the pyrrole was favorable to the reaction. Afterwards, *N*-alkenyl indoles containing different substituents were also examined in this transformation. Similarly, indoles with electron-withdrawing substituents (e.g., Ac, CF₃CO and CO₂Me) at the 3-position produced the desired products (Scheme 4, **5e–5h**), while no desired product was detected when the R group at the 3-position was H or methyl (Scheme 4, **5i** and **5j**).

In order to further investigate the substrate generalities, various *N*-alkenyl benzimidazoles **6** were applied to the reaction (Scheme 5). When 1-(pent-4-en-1-yl)-1H-benzimidazole reacted with CF₃Br under the standard reaction conditions, the six-membered cyclic product **7a** was produced in a 70% yield. The other derivatives of 1-(pent-4-en-1-yl)-1H-benzimidazole with both electron-donating and electron-withdrawing groups on their

phenyl rings also produced the corresponding products in good yields (Scheme 5, **7b–7f**). Subsequently, the reaction was extended to linear and branched *N*-butenyl benzimidazole, and the corresponding five-membered cyclization products **7g** and **7h** were also generated smoothly, albeit with decreased yields (Scheme 5, **7g** and **7h**). Moreover, 7-azobenzimidazole and theophylline were successfully used in this reaction to give the products **7i** and **7j** with good yields of 62% and 70% (Scheme 5, **7i** and **7j**).



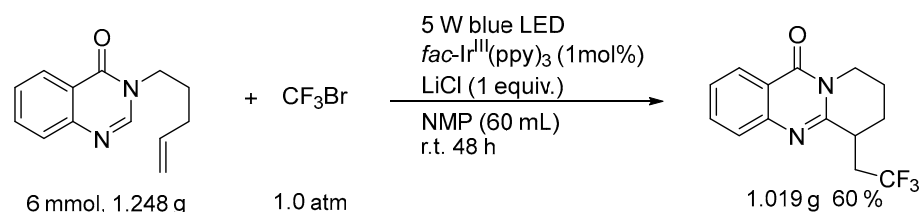
Scheme 4. Scope of pyrrole- and indole-derived substrates ^a. ^a Reaction conditions: **1a** (0.3 mmol, 1 equiv.), PC = $\text{fac-Ir}^{\text{III}}(\text{ppy})_3$ (0.003 mmol, 1 mol %); LiCl (0.3 mmol), NMP (3 mL) and CF_3Br (1.0 atm) in a 50 mL Schlenk flask; room temperature, 5 W blue LED light irradiation; time = 16 h. Isolated yield. ^b N.D.: not detected.



Scheme 5. Scope of benzimidazole-derived substrates ^a. ^a Reaction conditions: **1a** (0.3 mmol, 1 equiv.), PC = $\text{fac-Ir}^{\text{III}}(\text{ppy})_3$ (0.003 mmol, 1 mol %); LiCl (0.3 mmol), NMP (3 mL) and CF_3Br (1.0 atm) in a 50 mL Schlenk flask; room temperature, 5 W blue LED light irradiation; time = 16 h. Isolated yield.

3. Gram-Scale Synthesis

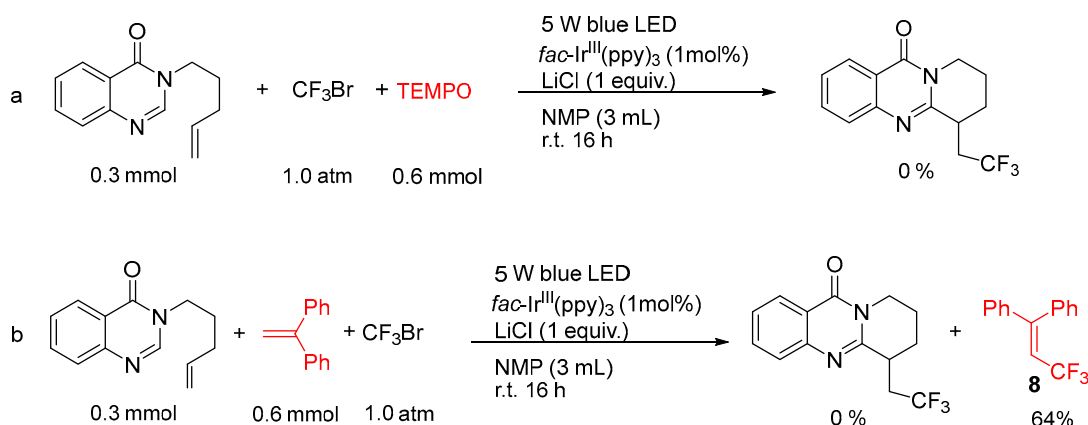
To probe the practical utility of this trifluoromethylation process, a gram-scale reaction of 3-(pent-4-en-1-yl) quinazolin-4(3H)-one was performed with 1 mol % catalyst loading, which proceeded smoothly to produce the desired product **3a** in a 60% yield (Scheme 6). Experimental details and characterization data for products are in Supplementary Materials.



Scheme 6. Gram-scale synthesis.

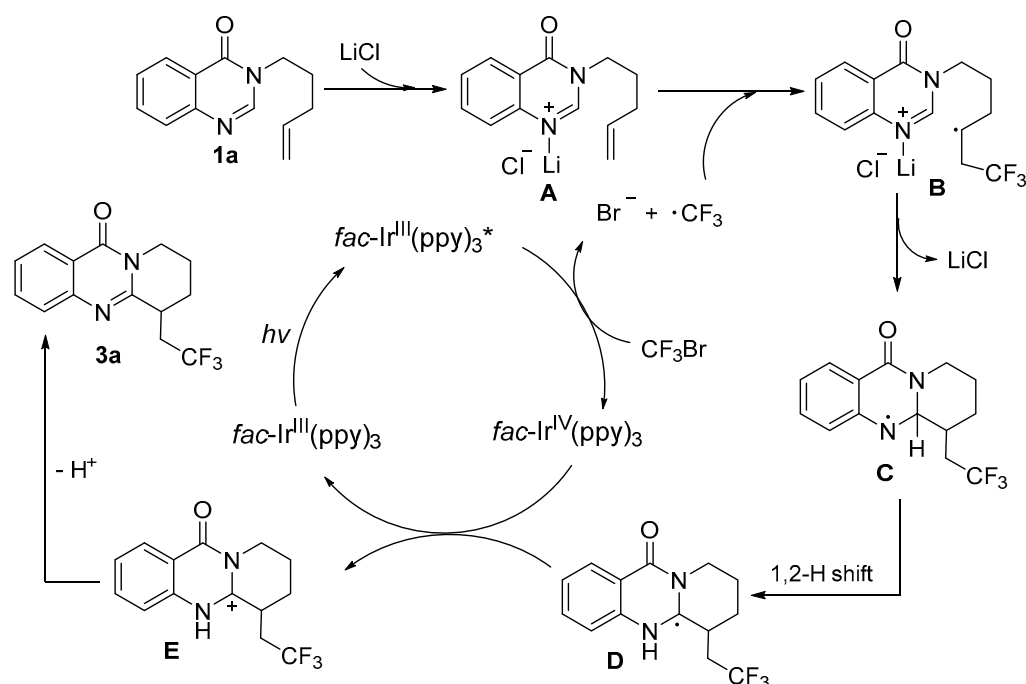
4. Proposed Mechanism

To probe the reaction mechanism, the radical scavenger 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO, 2.0 equiv.) was added in the reaction of **1a** with CF_3Br under the standard reaction conditions. The formation of the product **3a** was completely inhibited (Scheme 7, a). When radical scavenger 1,1-diphenylethylene (2.0 equiv.) was added to the reaction, product **3a** was not formed; only the trifluoromethyl radical trapping compound (3,3,3-trifluoroprop-1-ene-1,1-diyl)dibenzene **8** as produced in a yield of 64% (Scheme 7, b). These results imply that the trifluoromethyl radical was involved as the reactive species in the reaction.



Scheme 7. Mechanistic experiments.

In light of our experimental results and the literature descriptions [47,48], a reaction mechanism is tentatively proposed in Scheme 8. Under the activation of LiCl, *N*-alkenyl quinazolinones **1a** convert to more electrophilic lithium-activated *N*-alkenyl quinazolinones **A**. Meanwhile, the visible light induced the transformation of the photocatalyst $\text{fac-Ir}(\text{ppy})_3$ to the excited-state $\text{fac-Ir}(\text{ppy})_3^*$, which reduced CF_3Br to generate a trifluoromethyl radical along with the generation of the $\text{fac-Ir}(\text{ppy})_3$ complex via a single-electron transfer (SET). Then, the addition of the trifluoromethyl radical onto the C = C bond of lithium-activated *N*-alkenyl quinazolinones **A** gave radical intermediate **B**, which underwent intramolecular radical cyclization to offer the intermediate **C**, followed by a further 1,2-hydrogen shift process to yield the intermediate **D**. The intermediate **D** was then oxidized by $\text{fac-Ir}(\text{ppy})_3$ to form the cation **E**. Finally, product **3a** was obtained with the loss of a proton.



Scheme 8. Proposed reaction mechanism.

5. Conclusions

In conclusion, we have developed efficient visible-light-induced radical trifluoromethylation/cyclization for the synthesis of potential bioactive trifluoromethylated polycyclic quinazolinones, benzimidazoles and indoles. This system has the advantages of high step-economy and low-cost, which renders this protocol highly attractive for the synthesis of CF₃-containing polycyclic *aza*-heterocycles.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules27238389/s1>, Experimental details and characterization data for products **3a–3x**, **5a**, **5b**, **5e–5h** and **7a–7j** [42,46,47,49–51].

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Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are available from the authors.

References

1. Purser, S.; Moore, P.R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320–330. [\[CrossRef\]](#)
2. Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Aceña, J.L.; Soloshonok, V.A.; Izawa, K.; Liu, H. Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II–III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem. Rev.* **2016**, *116*, 422–518. [\[CrossRef\]](#)
3. Meanwell, N.A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822–5880. [\[CrossRef\]](#)
4. Zafrani, Y.; Parvari, G.; Amir, D.; Ghindes-Azaria, L.; Elias, S.; Pevzner, A.; Fridkin, G.; Berliner, A.; Gershonov, E.; Eichen, Y.; et al. Modulation of the H-Bond Basicity of Functional Groups by α -Fluorine-Containing Functions and its Implications for Lipophilicity and Bioisosterism. *J. Med. Chem.* **2021**, *64*, 4516–4531. [\[CrossRef\]](#)
5. Tiz, D.B.; Bagnoli, L.; Rosati, O.; Marini, F.; Sancineto, L.; Santi, C. New Halogen-Containing Drugs Approved by FDA in 2021: An Overview on Their Syntheses and Pharmaceutical Use. *Molecules* **2022**, *27*, 1643. [\[CrossRef\]](#)
6. Zhang, C.; Yan, K.; Fu, C.; Peng, H.; Hawker, C.J.; Whittaker, A.K. Biological Utility of Fluorinated Compounds: From Materials Design to Molecular Imaging, Therapeutics and Environmental Remediation. *Chem. Rev.* **2022**, *122*, 167–208. [\[CrossRef\]](#)
7. Inoue, M.; Sumii, Y.; Shibata, N. Contribution of Organofluorine Compounds to Pharmaceuticals. *ACS Omega* **2020**, *5*, 10633–10640. [\[CrossRef\]](#)
8. Ogawa, Y.; Tokunaga, E.; Kobayashi, O.; Hirai, K.; Shibata, N. Current Contributions of Organofluorine Compounds to the Agrochemical Industry. *iScience* **2020**, *23*, 101467. [\[CrossRef\]](#)
9. Charpentier, J.; Früh, N.; Togni, A. Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents. *Chem. Rev.* **2015**, *115*, 650–682. [\[CrossRef\]](#)
10. Wang, X.; Studer, A. Iodine(III) Reagents in Radical Chemistry. *Acc. Chem. Res.* **2017**, *50*, 1712–1724. [\[CrossRef\]](#)
11. Zeng, H.; Luo, Z.; Han, X.; Li, C.-J. Metal-Free Construction of the C(sp³)–CF₃ Bond: Trifluoromethylation of Hydrazones with Togni's Reagent under Mild Conditions. *Org. Lett.* **2019**, *21*, 5948–5951. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Umemoto, T. Electrophilic Perfluoroalkylating Agents. *Chem. Rev.* **1996**, *96*, 1757–1778. [\[CrossRef\]](#)
13. Prakash, G.K.S.; Yudin, A.K. Perfluoroalkylation with Organosilicon Reagents. *Chem. Rev.* **1997**, *97*, 757–786. [\[CrossRef\]](#)
14. Liu, X.; Xu, C.; Wang, M.; Liu, Q. Trifluoromethyltrimethylsilane: Nucleophilic Trifluoromethylation and Beyond. *Chem. Rev.* **2015**, *115*, 683–730. [\[CrossRef\]](#)
15. Shen, J.; Xu, J.; He, L.; Liang, C.; Li, W. Application of Langlois' reagent (NaSO₂CF₃) in C–H functionalisation. *Chin. Chem. Lett.* **2022**, *33*, 1227–1235. [\[CrossRef\]](#)
16. Zanardi, A.; Novikov, M.A.; Martin, E.; Benet-Buchholz, J.; Grushin, V.V. Direct Cupration of Fluoroform. *J. Am. Chem. Soc.* **2011**, *133*, 20901–20913. [\[CrossRef\]](#)
17. Barthelemy, A.-L.; Anselmi, E.; Le, T.-N.; Vo-Thanh, G.; Guillot, R.; Miqueu, K.; Magnier, E. Divergent Synthesis of 1,2-Benzothiazine and Benzo[d]thiazole Analogues Containing a S-Trifluoromethyl Sulfoximine Group: Preparation and New Properties of the Adachi Reagent. *J. Org. Chem.* **2019**, *84*, 4086–4094. [\[CrossRef\]](#)
18. Shi, G.; Shao, C.; Pan, S.; Yu, J.; Zhang, Y. Silver-Catalyzed C–H Trifluoromethylation of Arenes Using Trifluoroacetic Acid as the Trifluoromethylating Reagent. *Org. Lett.* **2015**, *17*, 38–41. [\[CrossRef\]](#)
19. Lin, J.; Li, Z.; Kan, J.; Huang, S.; Su, W.; Li, Y. Photo-driven redox-neutral decarboxylative carbon-hydrogen trifluoromethylation of (hetero)arenes with trifluoroacetic acid. *Nat. Commun.* **2017**, *8*, 14353. [\[CrossRef\]](#)
20. Yang, B.; Yu, D.; Xu, X.-H.; Qing, F.-L. Visible-Light Photoredox Decarboxylation of Perfluoroarene Iodine(III) Trifluoroacetates for C–H Trifluoromethylation of (Hetero)arenes. *ACS Catal.* **2018**, *8*, 2839–2843. [\[CrossRef\]](#)
21. Beatty, J.W.; Douglas, J.J.; Cole, K.P.; Stephenson, C.R.J. A scalable and operationally simple radical trifluoromethylation. *Nat. Commun.* **2015**, *6*, 7919. [\[CrossRef\]](#)
22. Zhang, M.; Chen, J.; Huang, S.; Xu, B.; Lin, J.; Su, W. Photocatalytic fluoroalkylations of (hetero)arenes enabled by the acid-triggered reactivity umpolung of acetoxime esters. *Chem. Catal.* **2022**, *2*, 1793–1806. [\[CrossRef\]](#)
23. Ouyang, Y.; Xu, X.-H.; Qing, F.-L. Trifluoromethanesulfonic Anhydride as a Low-Cost and Versatile Trifluoromethylation Reagent. *Angew. Chem. Int. Ed.* **2018**, *57*, 6926–6929. [\[CrossRef\]](#)
24. Lee, K.; Lee, S.; Kim, N.; Kim, S.; Hong, S. Visible-Light-Enabled Trifluoromethylative Pyridylation of Alkenes from Pyridines and Triflic Anhydride. *Angew. Chem. Int. Ed.* **2020**, *59*, 13379–13384. [\[CrossRef\]](#)
25. Zhang, M.; Lin, J.-H.; Xiao, J.-C. A Readily Available Trifluoromethylation Reagent and Its Difunctionalization of Alkenes. *Org. Lett.* **2021**, *23*, 6079–6083. [\[CrossRef\]](#)
26. Yang, Y.-F.; Lin, J.-H.; Xiao, J.-C. Starting from Styrene: A Unified Protocol for Hydrotrifluoromethylation of Diversified Alkenes. *Org. Lett.* **2021**, *23*, 9277–9282. [\[CrossRef\]](#) [\[PubMed\]](#)
27. Jia, H.; Häring, A.P.; Berger, F.; Zhang, L.; Ritter, T. Trifluoromethyl Thianthrenium Triflate: A Readily Available Trifluoromethylating Reagent with Formal CF³⁺, CF₃•, and CF₃[−] Reactivity. *J. Am. Chem. Soc.* **2021**, *143*, 7623–7628. [\[CrossRef\]](#)
28. Jia, H.; Ritter, T. α -Thianthrenium Carbonyl Species: The Equivalent of an α -Carbonyl Carbocation. *Angew. Chem. Int. Ed.* **2022**, *61*, e202208978. [\[CrossRef\]](#)
29. Li, Y.; Liang, X.; Niu, K.; Gu, J.; Liu, F.; Xia, Q.; Wang, Q.; Zhang, W. Visible-Light-Induced Photocatalyst-Free Radical Trifluoromethylation. *Org. Lett.* **2022**, *24*, 5918–5923. [\[CrossRef\]](#)

30. Sibille, S.; d'Incan, E.; Leport, L.; Perichon, J. Electrosynthesis of alcohols from organic halides and ketones or aldehydes. *Tetrahedron Lett.* **1986**, *27*, 3129–3132. [[CrossRef](#)]
31. Surya Prakash, G.K.; Deffieux, D.; Yudin, A.K.; Olah, G.A. Convenient and Safe Electrochemical Synthesis of (Trifluoromethyl)trimethylsilane1a. *Synlett* **1994**, *1994*, 1057–1058. [[CrossRef](#)]
32. Francèse, C.; Tordeux, M.; Wakselman, C. Synthesis of trifluoromethyl-substituted methanols: A Barbier procedure under pressure. *J. Chem. Soc. Chem. Commun.* **1987**, *9*, 642–643. [[CrossRef](#)]
33. Grobe, J.; Hegge, J. Facile Aluminum Induced Synthesis of (Trifluoromethyl)trimethylsilane. *Synlett* **1995**, *1995*, 641–642. [[CrossRef](#)]
34. Bürger, H.; Dittmar, T.; Pawelke, G. A simple one-pot synthesis of α -trifluoromethyl-substituted enamines by C-trifluoromethylation of dialkylamides with $P(NEt_2)_3CF_3Br$. *J. Fluorine Chem.* **1995**, *70*, 89–93. [[CrossRef](#)]
35. Qi, Q.; Shen, Q.; Lu, L. Polyfluoroalkylation of 2-aminothiazoles. *J. Fluor. Chem.* **2012**, *133*, 115–119. [[CrossRef](#)]
36. Natte, K.; Jagadeesh, R.V.; He, L.; Rabeah, J.; Chen, J.; Taeschler, C.; Ellinger, S.; Zaragoza, F.; Neumann, H.; Brückner, A.; et al. Palladium-Catalyzed Trifluoromethylation of (Hetero)Arenes with CF_3Br . *Angew. Chem. Int. Ed.* **2016**, *55*, 2782–2786. [[CrossRef](#)]
37. Zhang, K.-F.; Bian, K.-J.; Li, C.; Sheng, J.; Li, Y.; Wang, X.-S. Nickel-Catalyzed Carbofluoroalkylation of 1,3-Enynes to Access Structurally Diverse Fluoroalkylated Allenes. *Angew. Chem. Int. Ed.* **2019**, *58*, 5069–5074. [[CrossRef](#)]
38. Li, Q.; Fan, W.; Peng, D.; Meng, B.; Wang, S.; Huang, R.; Liu, S.; Li, S. Cobalt-Tertiary-Amine-Mediated Hydroxytrifluoromethylation of Alkenes with CF_3Br and Atmospheric Oxygen. *ACS Catal.* **2020**, *10*, 4012–4018. [[CrossRef](#)]
39. Peng, D.; Fan, W.; Zhao, X.; Chen, W.; Wen, Y.; Zhang, L.; Li, S. Zinc-Brønsted acid mediated practical hydrotrifluoromethylation of alkenes with CF_3Br . *Org. Chem. Front.* **2021**, *8*, 6356–6363. [[CrossRef](#)]
40. Ren, Y.-Y.; Zheng, X.; Zhang, X. Bromotrifluoromethane: A Useful Reagent for Hydrotrifluoromethylation of Alkenes and Alkynes. *Synlett* **2018**, *29*, 1028–1032.
41. Ma, R.; Deng, Z.; Wang, K.-H.; Wang, J.; Huang, D.; Su, Y.; Hu, Y.; Lv, X. Photoinduced Trifluoromethylation with CF_3Br as a Trifluoromethyl Source: Synthesis of α - CF_3 -Substituted Ketones. *ACS Omega* **2022**, *7*, 14357–14362. [[CrossRef](#)]
42. Zheng, J.; Deng, Z.; Zhang, Y.; Cui, S. Copper-Catalyzed Divergent Trifluoromethylation/Cyclization of Unactivated Alkenes. *Adv. Synth. Catal.* **2016**, *358*, 746–751. [[CrossRef](#)]
43. Hu, Q.; Yu, W.-L.; Luo, Y.-C.; Hu, X.-Q.; Xu, P.-F. A Photosensitizer-Free Radical Cascade for Synthesizing CF_3 -Containing Polycyclic Quinazolinones with Visible Light. *J. Org. Chem.* **2022**, *87*, 1493–1501. [[CrossRef](#)]
44. Zhu, H.; Liu, H.; Feng, X.; Guo, R.; Chen, X.; Pan, Z.; Zhang, L. Copper(I)-promoted trifluoromethylation of indole derivatives with concomitant C–C bond formation to access fused tricyclic indoles. *Tetrahedron Lett.* **2015**, *56*, 1703–1705. [[CrossRef](#)]
45. Li, S.; Wang, Y.; Wu, Z.; Shi, W.; Lei, Y.; Davies, P.W.; Shu, W. A Radical-Initiated Fragmentary Rearrangement Cascade of Ene-Ynamides to [1,2]-Annulated Indoles via Site-Selective Cyclization. *Org. Lett.* **2021**, *23*, 7209–7214. [[CrossRef](#)] [[PubMed](#)]
46. Lin, S.; Cui, J.; Chen, Y.; Li, Y. Copper-Catalyzed Direct Cycloaddition of Imidazoles and Alkenes to Trifluoromethylated Tricyclic Imidazoles. *J. Org. Chem.* **2021**, *86*, 15768–15776. [[CrossRef](#)]
47. Sun, B.; Huang, P.; Yan, Z.; Shi, X.; Tang, X.; Yang, J.; Jin, C. Self-Catalyzed Phototandem Perfluoroalkylation/Cyclization of Unactivated Alkenes: Synthesis of Perfluoroalkyl-Substituted Quinazolinones. *Org. Lett.* **2021**, *23*, 1026–1031. [[CrossRef](#)]
48. Liu, L.; Zhang, W.; Xu, C.; He, J.; Xu, Z.; Yang, Z.; Ling, F.; Zhong, W. Electrosynthesis of CF_3 -Substituted Polycyclic Quinazolinones via Cascade Trifluoromethylation/Cyclization of Unactivated Alkene. *Adv. Synth. Catal.* **2022**, *364*, 1319–1325. [[CrossRef](#)]
49. Yang, J.; Sun, B.; Ding, H.; Huang, P.-Y.; Tang, X.-L.; Shi, R.-C.; Yan, Z.-Y.; Yu, C.-M.; Jin, C. Photo-triggered self-catalyzed fluoroalkylation/cyclization of unactivated alkenes: Synthesis of quinazolinones containing the CF_2R group. *Green Chem.* **2021**, *23*, 575–581. [[CrossRef](#)]
50. Yang, R.; Yi, D.; Shen, K.; Fu, Q.; Wei, J.; Lu, J.; Yang, L.; Wang, L.; Wei, S.; Zhang, Z. Indole and Pyrrole Derivatives as Pre-photocatalysts and Substrates in the Sulfonyl Radical-Triggered Relay Cyclization Leading to Sulfonylated Heterocycles. *Org. Lett.* **2022**, *24*, 2014–2019. [[CrossRef](#)]
51. Wang, Y.-X.; Qi, S.-L.; Luan, Y.-X.; Han, X.-W.; Wang, S.; Chen, H.; Ye, M. Enantioselective Ni–Al Bimetallic Catalyzed exo-Selective C–H Cyclization of Imidazoles with Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 5360–5364. [[CrossRef](#)] [[PubMed](#)]