Functionalized polyamine synthesis with photoredox catalysis

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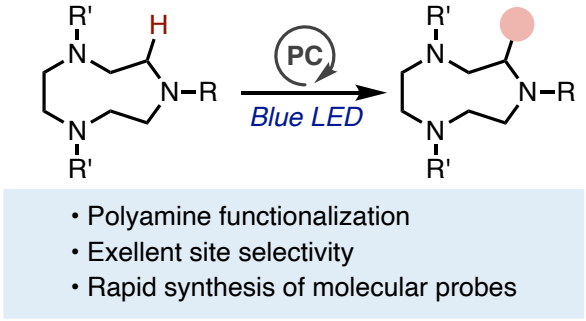
Supporting Information Placeholder



ABSTRACT: Polyamines, such as putrescine and spermidine, are pivotal in various biological processes across living organisms. Despite their significance, structurally modified polyamines offer a less-explored avenue for discovering bioactive compounds. The limitation is attributed to the synthetic difficulty of accessing functionalized polyamines. In this study, we accomplished photoredox-catalyzed functionalization of polyamines to diversify their structure. The rapid functionalization allows attaching fluorophores to the target polyamine, facilitating the development of molecular probes for advancing chemical biology studies.

Polyamines, such as putrescine, spermidine, or cyclen (Figure 1a), are alkylamines having two or more sp^3-nitrogen moieties in their structures. Polyamines are ubiquitously found in almost all living organism such as eukaryotic and prokaryotic cells and are produced during metabolism.[1] They play crucial roles in various biological processes such as cell growth, stabilization of chromatin structure, and differentiation, particularly in mammalian cells. Recent advancements in polyamine-related research in metabolism and molecular functions have garnered attention from a medicinal perspective for developing novel anticancer therapies.[2]

Polyamines are not exclusive to mammalian; they are also present in plant cells, contributing to plant growth and development, and stress tolerance.[3] However, the mechanisms by which polyamines regulate plants remain incompletely elucidated, and the functions of structurally modified polyamines have yet to be thoroughly investigated. To explore novel polyamines as potential bioactive molecules, there is a need for a streamlined synthesis to access functionalized polyamines. From a synthetic perspective, strategies for accessing functionalized polyamines have received limited attention. Polyamine derivatives have predominantly been synthesized using reliable but classical methods, such as the reduction of peptides or substitution reactions.[4,5] For instance, the preparation of benzyl-substituted polyamines requires 6 steps from the starting nitro-phenylalanine (Figure 1b).[5] Synthesizing substituted polyamine derivatives often involves altering starting materials, necessitating additional multi-step syntheses. Consequently, the preparation of polyamine derivatives requires laborious synthetic efforts. In our group, we are exploring molecules that influence plants to impact agrochemical development.[6] Our focus lies in multi-aminated molecules, such as SIM3* or *m*-bisBITC act as efficient stomatal opening inhibitors and stomidazolone as a novel stomatal reducer (Figure 1c). In our quest to discover new bioactive molecules for plants, we are intrigued by the potential of polyamines as a less-explored platform.

To achieve the direct functionalization of polyamines, our attention has turned to the photoredox-catalyzed α-functionalization of alkylamine molecules.[7,8,9] Recent developments in photoredox-catalyzed oxidation of amine moieties allow the formation of α-aminomethyl radical, enabling various transformations. In 2012, Miyake and Nishibayashi reported a pioneering example on photoredox-catalyzed generation of α-aminoalkyl radicals and their addition to electron-deficient alkenes.[9a] Independently, the groups of Reiser[9b], Yoon[9c], and Rueping[9d] reported related transformation for α-functionalization of alkylamines. In 2018, Nicewicz utilized highly reactive acridinium-based photocatalysts to transform carbamate-protected amines.[9e] It should be highlighted that Nicewicz reported C–H alkylation of piperazines, 6-membered dinitrogenated heterocycles, in 2020.[10] In this work, we conducted a study on the photocatalytic transformation of polyamines to investigate its applicability for the preparation of functionalized polyamines (Figure 1d). As the redox potential of an amine moiety can be tuned with substituents, selective functionalization can be achieved with a suitable

photocatalyst. The plausible reaction mechanism is depicted in Figure 1e, where PC^+ is excited by blue light irradiation to give PC^{*+}, which reacts with polyamine to yield amminium radical cation **A**. The resulting radical converts to α-amino radical **B** through spin-center shift. Radical **B** reacts with olefin to form **C**, which then reduced with $PC^{\cdot}$ to provide the product.

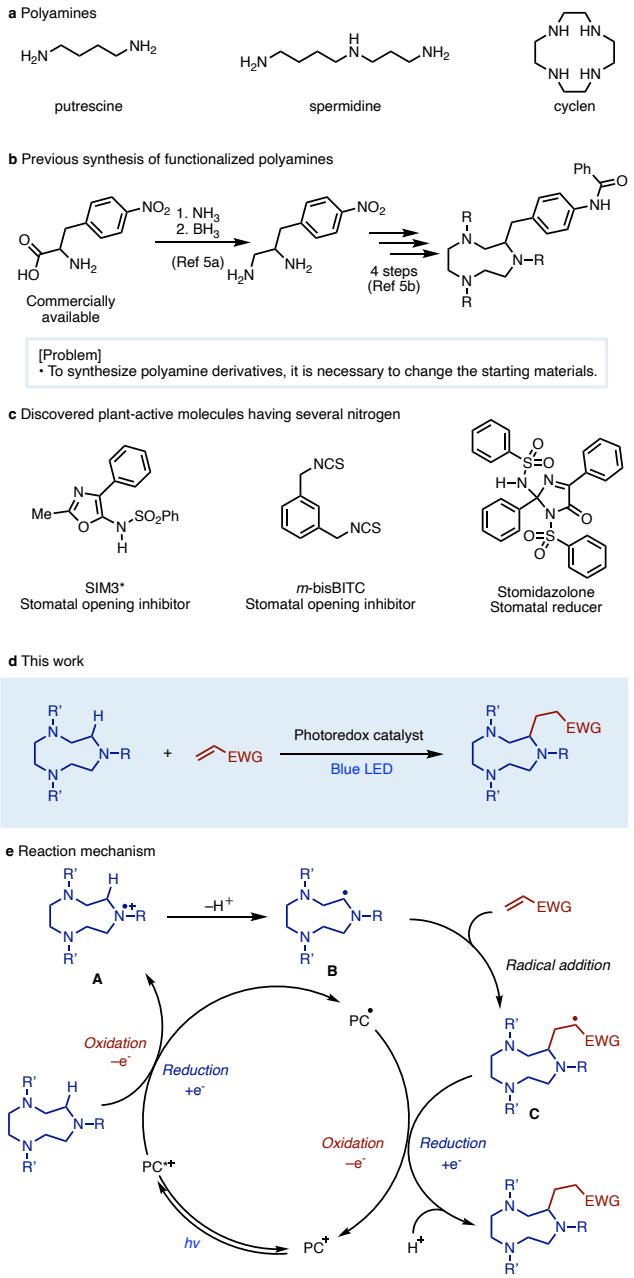


Figure 1. Backgrounds of this research and this work.

Herein we report the photoredox-catalyzed direct functionalization of polyamines. Our investigation began with the reaction of Boc-protected 1,4,7-triazonane **1a** (Figure 2a; Boc = *tert*-butoxycarbonyl). The reaction of 1,4,7-triazonane **1a** with olefin **2a** in the presence of photoredox-catalyst PC1 (E^*_{red} = 2.08 V) in dichloromethane under 456 nm LED light irradiation for **3a** afforded the corresponding product **3a** in 61% isolated yield (HPLC yield 75%). The addition of PC1 or blue light irradiation was crucial for the reaction, as no product was obtained in their absence. Catalyst efficiency was compared in Figure 2b (with 2.0 equiv. of polyamine). The use of acridinium catalysts PC2 (E^*_{red} = 1.88 V) or PC3 (E^*_{red} = 2.17 V) resulted in similar yields (PC1: 63% vs PC2: 61% and PC3: 63%). Other catalysts such as PC4–7 (E^*_{red} = 0.77–1.62 V) were far less effective where almost no products were obtained.

With the optimized reaction in hand, we investigated the scope of olefin and polyamines. A variety of α,β-unsaturated ketones were applicable to the reaction (Figure 2c). The reaction of methyl vinyl ketone afforded **3b** in 58% yield. Aryl vinyl ketones reacted with triazonane to give the products **3c**–**3f** regardless of the electronic effect on the aryl substituents. Other heteroaryl vinyl ketone, such as thienyl vinyl ketone gave **3g** in 33% yield. We then explored the scope of polyamines (Figure 2d). Pivaloyl- or benzoyloxycarbonyl-protected 1,4,7-triazonane reacted nicely to give **4a** and **4b** in 63% and 48% yields, respectively. The pivaloyl-protecting group exhibited higher stability compared to the Boc group, enabling further transformation under the acidic conditions. Benzoyloxycarbonyl deprotection with hydrogen and Pd/C proved orthogonal to the acidic deprotection of the Boc-group. The reaction proceeded smoothly regardless of its ring size; Boc-protected 12-membered tetraazacycle was efficiently converted to **4c** in 83% yield. A much larger 18-membered azacrown ether converted to **4d** in 30% yield, with the reaction selectively occurring adjacent to the nitrogen atom. As functionalized azacrown ethers have been widely employed as functional materials,[11] this transformation can be useful for the syntheses of novel azacrown ether-based materials. Unfortunately, tritosylated 1,4,7-triazonane failed to react. After the reaction, tosylated alkene was observed by LRMS where tosyl radical was generated through detosylation of the starting material.[12]

We then investigated polyamines having different protecting groups (Figure 3). As the detosylation was observed with PC1, we changed the photoredox catalyst to selectively oxidize the most oxidizable aryl-substituted nitrogen, offering site-selective functionalization of polyamines with better yields. After the screening, the employment of PC5, which can oxidize arylamine moiety but not tosylamide or Boc-amide moieties, allowed selective functionalization. Treatment of **1f** with methyl vinyl ketone in the presence of PC5 as a catalyst and CsOAc as a base in dichloromethane for 3 h under 456 nm blue light irradiation selectively proceeded adjacent to the phenylamine moiety, affording **5a** in 54% yield. Other triamines **1g** or **1h** reacted to furnish the corresponding product **5b** or **5c** in 42% or 46% yields, respectively. Cyclic polyamines smoothly converted to **5d** and **5e** in moderate yields. The resulting **5d** could be alkylated under the same conditions to give **5f** in 55% yield. The structure of **5f** was unambiguously confirmed by X-ray crystallographic analysis. When an excess amount of olefin was employed, dialkylation took place to provide **5g** in 22% yield.

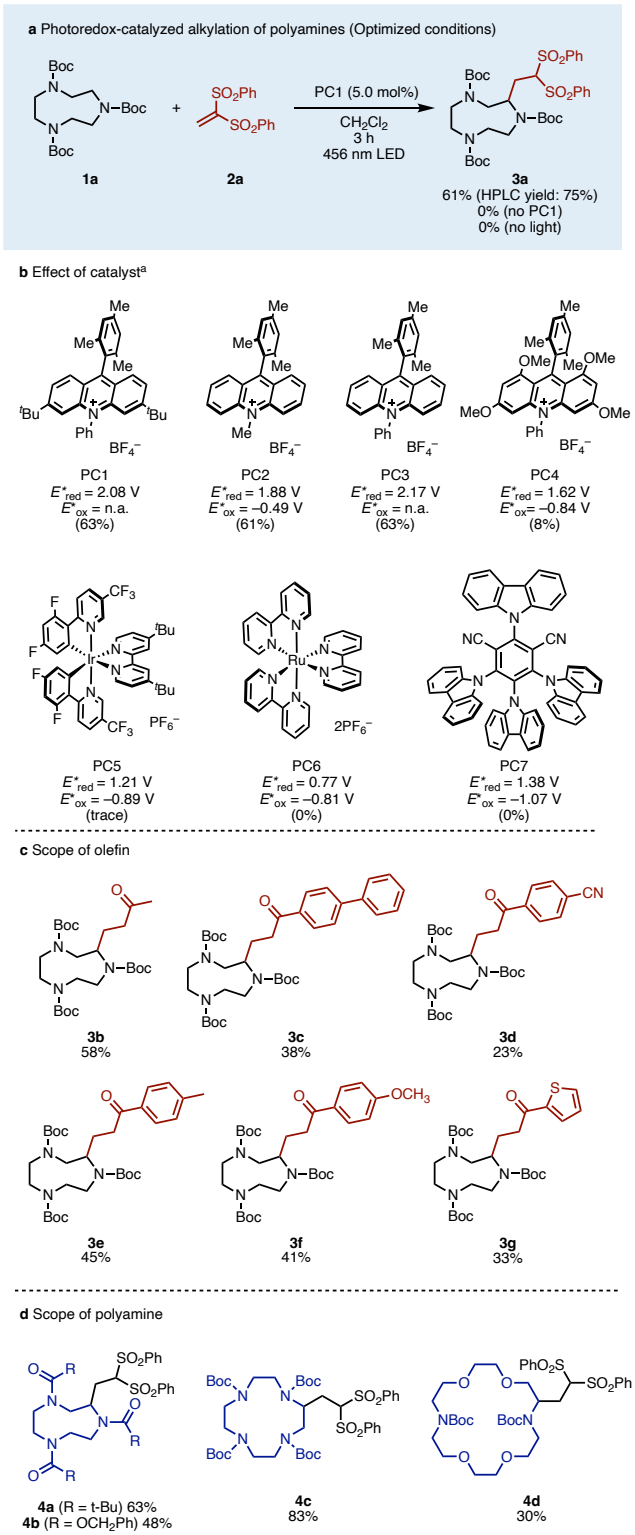


Figure 2. Optimized conditions for photoredox-catalyzed alkylation of polyamines. Reaction conditions: **1** (3.0 equiv.), **2** (0.10 mmol), CH_2Cl_2 (1.0 mL) was used as the solvent. [a]HPLC yields are shown in parentheses. Reaction conditions: **1a** (2.0 equiv.), CH_2Cl_2 (0.50 mL) was used as the solvent.

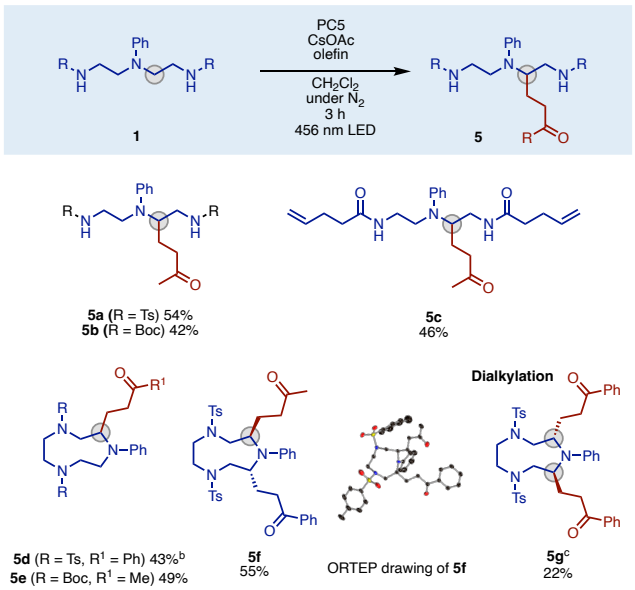


Figure 3. Selective alkylation. [a]Reaction conditions: **1** (3.0 equiv.), methyl vinyl ketone (0.10 mmol), PC5 (5.0 mol%), CsOAc (2.0 equiv.), CH_2Cl_2 (1.0 mL). [b]Reaction conditions: (1.0 mmol scale) Phenyl vinyl ketone (1.0 mmol) was used as the olefin. [c]Reaction conditions: **1** (0.10 mmol), phenyl vinyl ketone (4.0 equiv.), PC5 (5.0 mol%), CsOAc (3.0 equiv.), CH_2Cl_2 (1.0 mL) for 6 h.

Not only alkylation but also arylation and acylation can be conducted (Figure 4a). In the presence of dicyanobenzene, arylation efficiently proceeded to give **6a** in 79% yield.[13] Similarly, **6b** was obtained in 60% yield.[14] Leveraging the rapid direct functionalization of polyamine, we achieved the streamlined synthesis of fluorophore-conjugated polyamines. The reaction of **1a** with alkyne-substituted α,β-unsaturated ketones gave **3h** in 34% yield, with the alkyne moiety remaining intact. Product **3h** was then reacted with azidated fluorophore to give the corresponding products **7a** and **7b** in 88% and 67% yields, respectively. Given the potential bioactivity of polyamines, this methodology can be applied for further chemical biology investigation, such as bioimaging or target identification.[15]

In summary, we have developed a photoredox-catalyzed functionalization of polyamines, enabling the one-step synthesis of polyamine derivatives. This study demonstrates that by adjusting the redox potentials of photoredox catalysts, multiple nitrogen sites in polyamines can be selectively functionalized. In addition to alkylation, arylation and acylation are also viable, enabling the synthesis of a diverse range of functionalized polyamines. The application of this method allows for the rapid synthesis of polyamines with attached fluorophores, suggesting promising prospects for future biological applications.

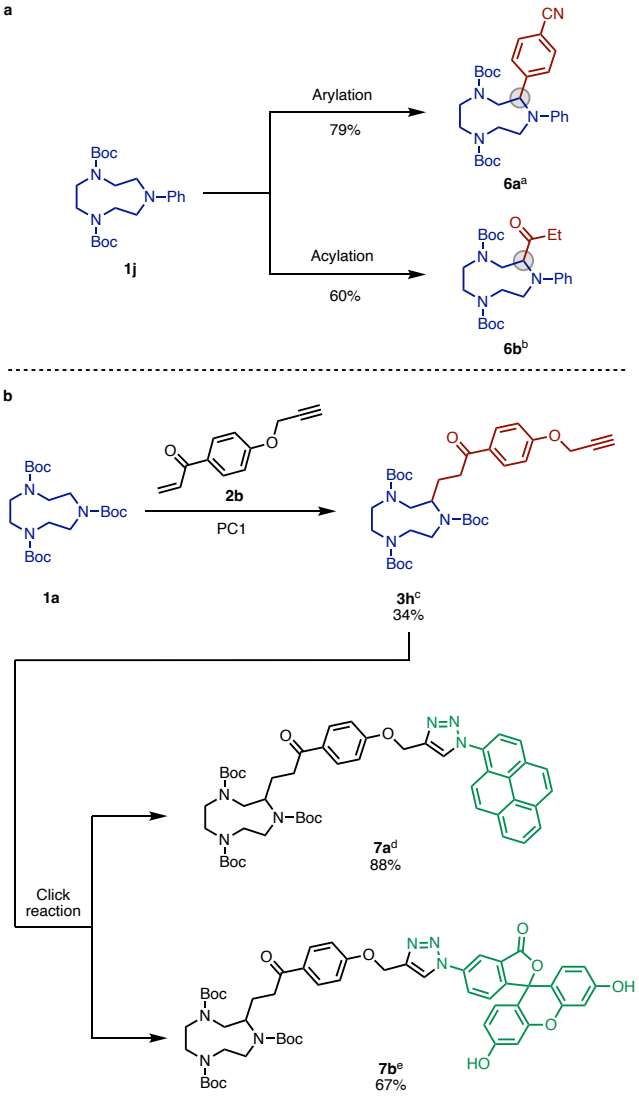


Figure 4. Application of polyamine functionalization. (a) arylation and acylation of polyamines. [a]Reaction conditions: **1j** (3.0 equiv.), 1,4-dicyanobenzene (0.10 mmol), $Ir(ppy)_3$ (1.0 mol%), NaOAc (2.0 equiv.), DMF (0.40 mL) for 12 h. [b]Reaction conditions: **1j** (1.5 equiv.), propionic anhydride (0.10 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (1.0 mol%), $NiCl_2$·glyme (5.0 mol%), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (7.5 mol%), sodium propionate (1.5 equiv.), DMF (2.5 mL) for 16 h. (b) Rapid synthesis of fluorophore-conferring polyamines through a larger scale alkylation. [c]Reaction conditions: **1a** (3.0 equiv.), **2b** (1.0 mmol), PC1 (5.0 mol%), CH_2Cl_2 (1.0 mL) was used as the solvent for 3 h. [d]Reaction conditions: **1a** (0.10 mmol), 5-azidofluorescein (1.1 equiv.), L-ascorbic acid (3.0 equiv.), $CuSO_4$ (2.0 equiv.), DMSO (3.5 mL) was used as the solvent at 60 °C for 24 h. [e]Reaction conditions: **1a** (0.10 mmol), 1-azidopyrene (1.2 equiv.), CuI (50 mol%), THF/H_2O =2:1 (3.0 mL) was used as the solvent at 50 °C for 24 h.

ASSOCIATED CONTENT

Supporting Information

General experimental details, experimental procedure, characterization data, and NMR spectral data (PDF).

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Author Contributions

The manuscript was written through the contributions of all authors. All the authors approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Pegg, A. E.; Casero, R. A. Current Status of the Polyamine Research Field. In Polyamines. Methods in Molecular Biology, vol 720.; Humana Press, 2011; pp 3–35.

(2) Casero, R. A.; Murray Stewart, T.; Pegg, A. E. Polyamine Metabolism and Cancer: Treatments, Challenges and Opportunities. *Nat. Rev. Cancer* **2018**, *18*, 681–695.

(3) Chen, D.; Shao, Q.; Yin, L.; Younis, A.; Zheng, B. Polyamine Function in Plants: Metabolism, Regulation on Development, and Roles in Abiotic Stress Responses. *Front. Plant Sci.* **2019**, *9*, 1945.

(4) (a) Bernecker, A.; Wieneke, R.; Riedel, R.; Seibt, M.; Geyer, A.; Steinem, C. Tailored Synthetic Polyamines for Controlled Biomimetic Silica Formation. *J. Am. Chem. Soc.* **2010**, *132*, 1023–1031. (b) Kim, B. M.; So, S. M.; Choi, H. J. A Concise, Modular Synthesis of Chiral Peraza-Macrocycles Using Chiral Aziridines. *Org. Lett.* **2002**, *4*, 949–952. (c) Pirali, T.; Callipari, G.; Ercolano, E.; Genazzani, A. A.; Giovenzana, G. B.; Tron, G. C. A Concise Entry into Nonsymmetrical Alkyl Polyamines. *Org. Lett.* **2008**, *10*, 4199–4202. (d) Gleede, T.; Yu, F.; Luo, Y.-L.; Yuan, Y.; Wang, J.; Wurm, F. R. Linear Well-Defined Polyamines via Anionic Ring-Opening Polymerization of Activated Aziridines: From Mild Desulfonylation to Cell Transfection. *ACS Macro Lett.* **2020**, *9*, 20–25.

(5) (a) Hayward, M. M.; Adrian, J. C. J.; Schepartz, A. Convenient Syntheses of Bifunctional Metal Chelates. *J. Org. Chem.* **1995**, *60*, 3924–3927. (b) McMurry, T. J.; Brechbiel, M.; Wu, C.; Gansow, O. A. Synthesis of 2-(p-Thiocyanatobenzyl)-1,4,7-Triazacyclononane-1,4,7-Triacetic Acid: Application of the 4-Methoxy-2,3,6-Trimethylbenzenesulfonamide Protecting Group in the Synthesis of Macrocyclic Polyamines. *Bioconjug. Chem.* **1993**, *4*, 236–245.

(6) (a) Toda, Y.; Perry, G. J. P.; Inoue, S.; Ito, E.; Kawakami, T.; Narouz, M. R.; Takahashi, K.; Aihara, Y.; Maeda, B.; Kinoshita, T.; Itami, K.; Murakami, K. Identification of Stomatal-Regulating Molecules from de Novo Arylamine Collection through Aromatic C–H Amination. *Sci. Rep.* **2022**, *12*, 949. (b) Aihara, Y.; Maeda, B.; Goto, K.; Takahashi, K.; Nomoto, M.; Toh, S.; Ye, W.; Toda, Y.; Uchida, M.; Asai, E.; Tada, Y.; Itami, K.; Sato, A.; Murakami, K; Kinoshita, T. Identification and Improvement of Isothiocyanate-Based Inhibitors on Stomatal Opening to Act as Drought Tolerance-Conferring Agrochemicals. *Nat. Commun.* **2023**, *14*, 2665. (c) Kinoshita, T.; Sakakibara, Y.; Hirano, T.; Murakami, K. Switchable quaternary ammonium transformation leading to salinity-tolerance-conferring plant biostimulants. *ChemRxiv* **2023**. DOI: 10.26434/chemrxiv-2023-bwm63. (d) Nakagawa, A.; Sepuru, K. M.; Yip, S. J.; Seo, H.; Coffin, C. M.; Segawa, Y.; Iwasaki, R.; Kato, H.; Kim, S.; Aihara, Y.; Kinoshita,

T.; Itami, K.; Han, S. K.; Murakami, K.; Torii, K. U. Chemical inhibition of stomatal differentiation by perturbation of the master-regulatory bHLH heterodimer via an ACT-Like domain. *bioRxiv* **2023**. DOI: 10.1101/2023.11.02.565226.

(7) (a) Holmberg-Douglas, N.; Nicewicz, D. A. Photoredox-Catalyzed C–H Functionalization Reactions. *Chem. Rev.* **2022**, *122*, 1925–2016. (b) Bortolato, T.; Cuadros, S.; Simionato, G.; Dell'Amico, L. The Advent and Development of Organophotoredox Catalysis. *Chem. Commun.* **2022**, *58*, 1263–1283. (c) Bell, J. D.; Murphy, J. A. Recent Advances in Visible Light-Activated Radical Coupling Reactions Triggered by (i) Ruthenium, (ii) Iridium and (iii) Organic Photoredox Agents. *Chem. Soc. Rev.* **2021**, *50*, 9540–9685. (d) Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A. Photoredox-Mediated Routes to Radicals: The Value of Catalytic Radical Generation in Synthetic Methods Development. *ACS Catal.* **2017**, *7*, 2563–2575. (e) Fukuzumi, S.; Ohkubo, K. Organic Synthetic Transformations Using Organic Dyes as Photoredox Catalysts. *Org. Biomol. Chem.* **2014**, *12*, 6059–6071. (e) Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; et al. Metallaphotoredox: The Merger of Photoredox and Transition Metal Catalysis. *Chem. Rev.* **2022**, *122*, 1485–1542.

(8) (a) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. New Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. *Chem. Rev.* **2020**, *120*, 2613–2692. (b) Chen, W.; Yang, X.; Cao, X. Transition-Metal-Catalyzed Remote C–H Bond Functionalization of Cyclic Amines. *SynOpen* **2022**, *6*, 286–305. (c) Beatty, J. W.; Stephenson, C. R. J. Amine Functionalization via Oxidative Photoredox Catalysis: Methodology Development and Complex Molecule Synthesis. *Acc. Chem. Res.* **2015**, *48*, 1474–1484. (d) Deb, M. L.; Saikia, B. S.; Borpatra, P. J.; Baruah, P. K. Progress of Metal-Free Visible-Light-Driven α-C–H Functionalization of Tertiary Amines: A Decade Journey. *Asian J. Org. Chem.* **2022**, *11*, e202100706. (e) Shi, L.; Xia, W. Photoredox Functionalization of C–H Bonds Adjacent to a Nitrogen Atom. *Chem. Soc. Rev.* **2012**, *41*, 7687–7697.

(9) (a) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. Visible-Light-Mediated Utilization of α-Aminoalkyl Radicals: Addition to Electron-Deficient Alkenes Using Photoredox Catalysts. *J. Am. Chem. Soc.* **2012**, *134*, 3338–3341. (b) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. Visible Light Photoredox Catalysis: Generation and Addition of N-Aryltetrahydroisoquinoline-Derived α-Amino Radicals to Michael Acceptors. *Org. Lett.* **2012**, *14*, 672–675. (c) Espelt, L. R.; Wiensch, E. M.; Yoon, T. P. Brønsted Acid Cocatalysts in Photocatalytic Radical Addition of α-Amino C–H Bonds across Michael Acceptors. *J. Org. Chem.* **2013**, *78*, 4107–4114. (d) Zhu, S.; Das, A.; Bui, L.; Zhou, H.; Curran, D. P.; Rueping, M. Oxygen Switch in Visible-Light Photoredox Catalysis: Radical Additions and Cyclizations and Unexpected C–C-Bond Cleavage Reactions. *J. Am. Chem. Soc.* **2013**, *135*, 1823–1829. (e) McManus, J. B.; Onuska, N. P. R.; Nicewicz, D. A. Generation and Alkylation of α-Carbamyl Radicals via Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 9056–9060.

(10) McManus, J. B.; Onuska, N. P. R.; Jeffreys, M. S.; Goodwin, N. C.; Nicewicz, D. A. Site-Selective C–H Alkylation of Piperazine Substrates via Organic Photoredox Catalysis. *Org. Lett.* **2020**, *22*, 679–683.

(11) (a) Onitsuka, H.; Fujigaya, T.; Nakashima, N.; Shiraki, T. Control of the Near Infrared Photoluminescence of Locally Functionalized Single-Walled Carbon Nanotubes via Doping by Azacrown-Ether Modification. *Chem. Eur. J.* **2018**, *24*, 9393–9398. (b) Späth, A.; Koch, C.; König, B. Luminescent Hybrids Combining a Metal Complex and a Crown Ether – Receptors for Peptidic Ammonium Phosphates. *Eur. J. Inorg. Chem.* **2010**, 2926–2935. (c) Zheng, Z.; Zhang, Q.; Yu, Z.; Yang, M.; Zhou, H.; Wu, J.; Tian, Y. Four new two-photon absorbing imidazo[4,5-f]1,10-phenanthroline dye derivatives with different dipole moment orientation based on different groups: synthesis, optical characterization and bioimaging. *J. Mater. Chem. C*, **2013**, 1, 822–830.

(12) Xuan, J.; Li, B.-J.; Feng, Z.-J.; Sun, G.-D.; Ma, H.-H.; Yuan, Z.-W.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. Desulfonylation of Tosyl Amides through Catalytic Photoredox Cleavage of N–S Bond Under Visible-Light Irradiation. *Chem. Asian J.* **2013**, *8*, 1090–1094.

(13) McNally, A.; Prier, C. K.; MacMillan, D. W. C. Discovery of an α-Amino C–H Arylation Reaction Using the Strategy of Accelerated Serendipity. *Science* **2011**, *334*, 1114–1117.

(14) Joe, C. L.; Doyle, A. G. Direct Acylation of C(sp^3)–H Bonds Enabled by Nickel and Photoredox Catalysis. *Angew. Chem. Int. Ed.* **2016**, *55*, 4040–4043.

(15) (a) Qian, X.; Xu, Z. Fluorescence Imaging of Metal Ions Implicated in Diseases. *Chem. Soc. Rev.* **2015**, *44*, 4487–4493. (b) Sun, X.; Liu, T.; Sun, J.; Wang, X. Synthesis and Application of Coumarin Fluorescence Probes. *RSC Adv.* **2020**, *10*, 10826–10847.