

1,2-Aminosulfonylation of Alkenes via a Photoexcited Cu(I)-Substrate Complex: A Three-Component Coupling Approach

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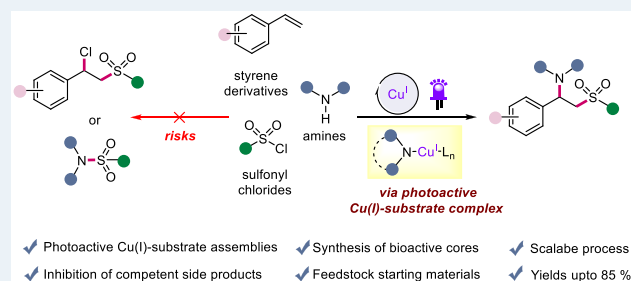
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Supporting Information

ABSTRACT: We report a Cu(I)-photocatalyzed three-component coupling process to achieve regioselective, vicinal 1,2-amino-sulfonylations of alkenes. The critical aspect of this methodology is found in the utilization of in situ generated photoactive Cu(I)-amine substrate complexes, which facilitate the formal oxidation of Cu(I) to Cu(III) in a stepwise manner. In this way, the conceivable two-component chlorosulfonylation of alkenes is effectively suppressed, allowing the combination of styrene derivatives, sulfonyl chlorides, and amines. Furthermore, this protocol can be used to facilitate late-stage functionalization, thereby enabling the diversification of biomolecules.

KEYWORDS: copper, photocatalysis, three-component couplings, ATRA reaction, substrate complex



INTRODUCTION

Atom transfer radical addition (ATRA) reaction, first developed by Kharasch^{1–3} in the mid-1900s, is a key method for alkene difunctionalization, extensively employed in synthesizing pharmaceuticals, agrochemicals, and advanced materials.^{4–6} Conventional ATRA reactions often require strong oxidizing agents or toxic organometallic compounds, limiting their compatibility with functional groups.^{7–13} However, the recent resurgence of photoredox catalysis, especially using Ru(II)- and Ir(III)-polypyridyl complexes, has transformed radical chemistry, enabling mild, energy-efficient carbon–carbon and carbon–heteroatom bond formation.^{14–19} Barton²⁰ and Stephenson's²¹ seminal works provide examples of ATRAs using these metal complexes. Despite these advances, the high costs and environmental impact of these catalysts have driven interest in Cu(I)-photoredox catalysis, which offers not only economic benefits and sustainable alternatives but also advantages for this process through inner-sphere mechanisms.^{22–29}

Cu(I)-based photocatalysts enable two- and three-component ATRA reactions due to their ability to achieve multiple oxidation states and accommodate flexible ligand architectures, thereby enhancing strategies for the 1,2-difunctionalization of alkenes (Scheme 1A).^{6,30} Several light-mediated Cu(I)-photocatalyzed two-component ATRA transformations were reported by us^{31–35} in the recent past, and with relevance to this study, the chlorosulfonylation of the alkenes³⁶ (Scheme 1B(a)).

Multicomponent reactions (MCRs) have further expanded radical chemistry, enabling complex molecular assemblies in a single step.^{4,6,30} In this context, reports from the groups of

Akita³⁷ (Scheme 1B(b)), Masson,^{4,38–41} Greaney⁴² (Scheme 1B(c)), and Dilman⁴³ demonstrate innovative three-component transformations utilizing radical precursors with non-nucleophilic counterparts, contrasting a report from our group⁴⁴ with a radical precursor having a nucleophilic counterion that was nevertheless outcompeted by an external nucleophile (Scheme 1B(b)). A noteworthy contribution in this regard is the divergent Ritter-type aminosulfonylation by the Xu group (Scheme 1B(d)), which provides valuable insight into MCRs involving sulfonyl chlorides as a radical precursor in the presence of a nucleophilic counterpart.⁴⁵ Furthermore, the pioneering studies by Fu and Peters on the utilization of in situ-produced photoactive Cu(I)–heteronucleophile complexes that initiate single-electron transfer (SET) to form C–C or C–heteroatom bonds have unveiled new possibilities in photocatalysis (Scheme 1B(e)).^{46–50} Several MCRs were reported from the Zhang group employing photoactive Cu(I)-substrate assemblies, specifically Cu(I)–carbazolid⁵¹ (Scheme 1B(e)) and Cu(I)–acetylide⁵² complexes to promote the carbofunctionalization of olefins.

Building on the findings of these studies, we envisioned the development of a light-induced Cu(I)-catalyzed coupling of sulfonyl chlorides, alkenes, and amines (Scheme 1C). This

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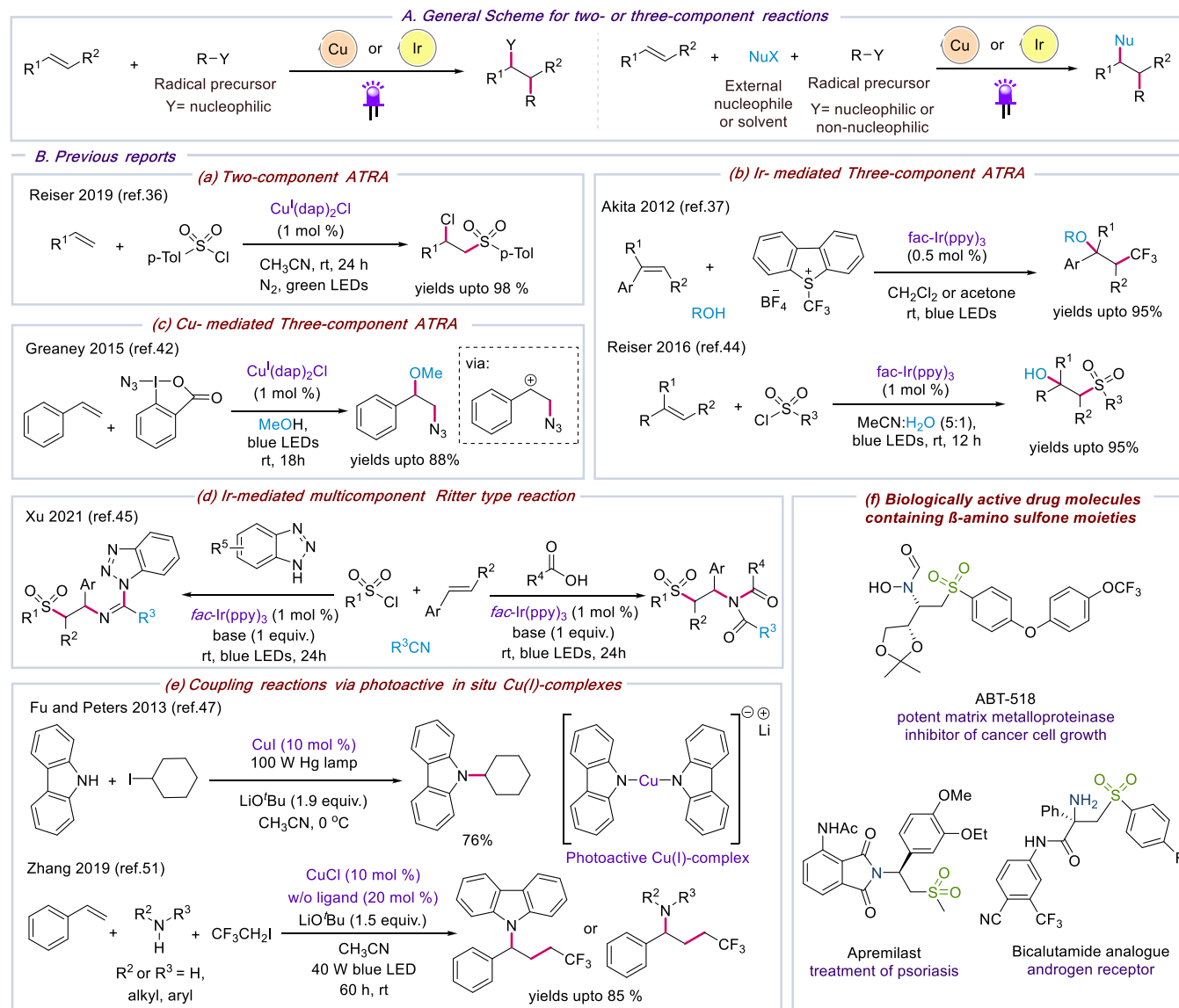
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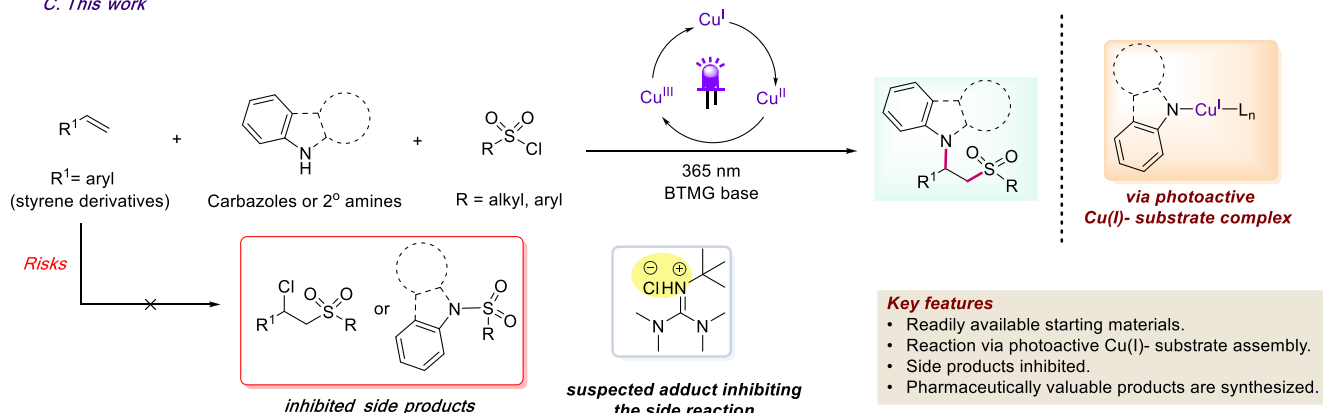
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Scheme 1. (A) General Scheme for Two- or Three-Component Reactions, (B) State-of-the-Art for the Cu(I)-Photocatalyzed Reaction and β -Amino Sulfone Derivatives with a Biological Value, and (C) Schematic Representation of the 1,2-Aminosulfonylation of Alkenes via Photoexcited Cu(I)-Substrate Complexes



C. This work



approach poses significant challenges due to possible two-component couplings, resulting in the chlorosulfonation of alkenes³⁶ or the formation of sulfonamides rather than yielding the desired three-component product. Nevertheless, such a

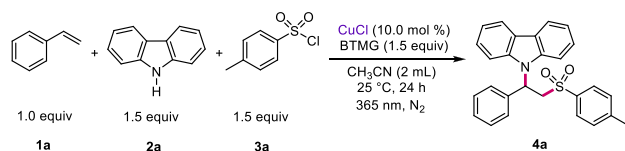
vicinal aminosulfonylation of alkenes would represent a valuable addition to the ATRA toolbox, particularly due to the significance of drug molecules like Apremilast,⁵³ ABT-518,⁵⁴ and Bicalutamide⁵⁵ analogues, which incorporate this functional

group pattern (Scheme 1B(f)). It needs to be pointed out that a seemingly obvious alternative, i.e., carrying out the 2-component chlorosulfonylation followed by a substitution with an amine nucleophile, is not possible due to the rapid elimination of HCl giving rise to vinyl sulfones (see Supporting Information for details).

RESULTS AND DISCUSSION

As a model reaction, we chose styrene (**1a**), 9H-carbazole (**2a**) as the nucleophile, and *p*-toluenesulfonyl chloride (**3a**) as the radical precursor. After thorough screening of the reaction conditions (see Supporting Information for details), we found that irradiating the chosen coupling partners in acetonitrile as solvent at 365 nm (1 W) in the presence of CuCl (10 mol %) and 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (BTMG) (1.5 equiv) for 24 h at room temperature gave the desired product **4a** in 88% yield (Table 1, entry 1). Changing the oxidation state of the

Table 1. Reaction Optimization^a



entry	deviations	% yield ^b
1	none	88
2	CuCl ₂ instead of CuCl	traces
3	[Cu(dap) ₂]Cl (1 mol %) 365 nm	70
4	[Cu(dap) ₂]Cl (1 mol %) 530 nm	n.d.
5	LiO ^t Bu instead of BTMG	32
6	TMG instead of BTMG	traces
7	400 nm	55
8	385 nm	60
9	without irradiation	n.d.
10	without CuCl	traces
11	without base	n.d.
12	in air	n.d.

^aConditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), **3a** (0.3 mmol, 1.5 equiv), CuCl (10 mol %), BTMG (1.5 equiv), CH₃CN (2.0 mL), 365 nm, 25 °C, N₂, 24 h. ^bDetermined by NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. n.d. = not detected.

copper source using CuCl₂ (Table 1, entry 2) yielded only traces of the desired product. This was unforeseen, considering that Cu(II)–phenanthroline complexes can be a convenient precursor for the catalytically active Cu(I) species.³⁶ Unexpectedly, using [Cu(dap)₂]Cl (dap = 2,9-bis(*para*-anisyl)-1,10-phenanthroline) as a photocatalyst resulted in a comparatively diminished yield of the desired product; nonetheless, the reaction was effective solely at 365 nm (Table 1, entries 3 and 4), contrasting with previously reported processes that operated under 455 or 530 nm irradiation.³⁶ We reason that the highly basic reaction conditions result in the substitution of the neutral dap ligands with deprotonated and thus more nucleophilic carbazoles. Although a reduced catalyst loading is possible for [Cu(dap)₂]Cl, we selected CuCl as the most economically viable copper source. BTMG as a base proved to be crucial for the process, and examining organic bases similar to BTMG, such as tetramethylguanidine (Table 1, entry 6), was unsuccessful. Employing inorganic bases such as LiO^tBu (Table 1, entry 5), LiOH, or KO^tBu (see Supporting Information) gave

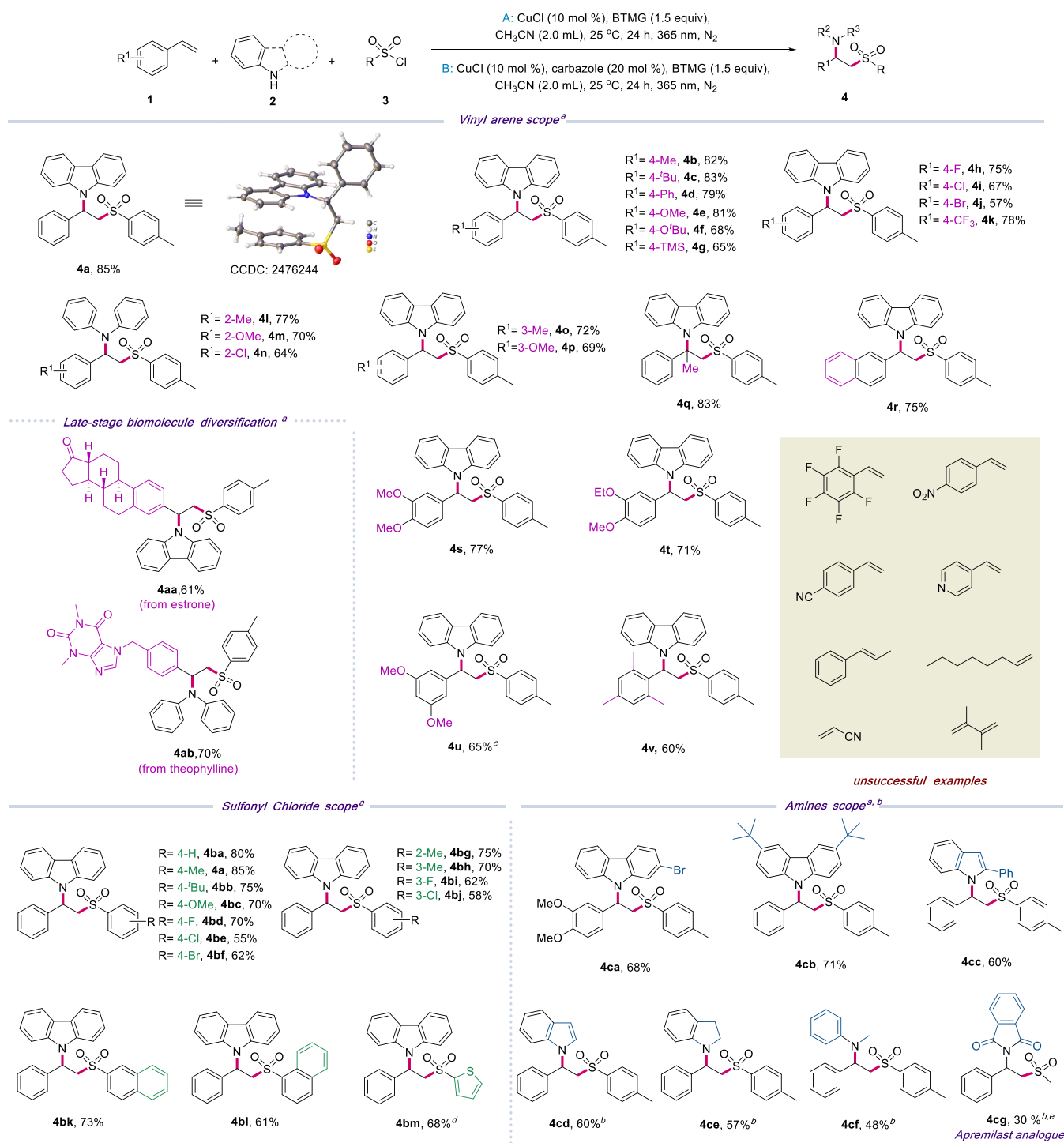
4a in a low yield of 32% at best, but in parallel the undesired 2-component chlorosulfonylation product (cf. Scheme 1B(a)) was also formed. Consistent with the results from Fu and co-workers,⁴⁷ our protocol selectively utilizes BTMG with high basicity (pK_a = 24.3 in acetonitrile), enabling the efficient deprotonation of carbazole and formation of the photoactive Cu(I)–carbazole complex. Additionally, the conjugate acid of BTMG, [C₉H₂₁N₃H]⁺, exhibits significant stability, as evidenced by its elevated pK_a value, which may effectively trap the Cl[−] counteranion (Scheme 1C) from *p*-toluenesulfonyl chloride and consequently suppress the two-component process.⁵⁶ Control experiments indicate the necessity of light, copper, a base, and inert gas conditions (Table 1, entries 9–12).

After establishing the optimized conditions, we explored the scope of the aminosulfonylation of the alkenes (Scheme 2). A wide variety of vinyl arenes were tolerated in this methodology, giving 1,2-aminosulfonylated adducts **4** with isolated yields of up to 85%. The structure of product **4a** was unambiguously confirmed by single-crystal X-ray diffraction. Both electron-donating and -accepting substituents on the aromatic moiety of styrene were well tolerated. Additionally, base-sensitive groups (**4g**, TMS) and steric hindrance from ortho–ortho-disubstitution (**4v**) did not significantly impact the reaction. Moreover, the mono- and disubstituted alkoxy styrene derivatives **4e**, **4p**, and **4s–u** were efficient coupling partners despite having previously failed to undergo the 2-component chlorosulfonylation of the olefins.³⁶ Limitations were observed with *p*-cyano-, perfluoro-, and *p*-nitro-substituted derivatives of styrene as well as alkynes, giving neither the desired products **4** nor the undesired two-component ATRA chlorosulfonylated products.³⁶ This again was unexpected in light of the fact that especially the latter two proved to be suitable substrates for the chlorosulfonylation. α -Methylstyrene was an amenable coupling partner giving **4q**, whereas *trans*- β -substituted styrene moieties did not give the desired product. Unactivated alkenes like 1-octene failed to give the desired product, but using [Cu(dap)₂]Cl instead of CuCl under the standard reaction conditions gave the two-component chlorosulfonylation³⁶ product (see Supporting Information for details). Not surprisingly, a pyridyl moiety is not tolerated, showing cross-reactivity with sulfonyl chloride. Two examples of late-stage functionalization (**4aa**, **4ab**) demonstrate the title reaction in more complex settings.

Variation of the sulfonyl chloride was broadly possible, tolerating various electron-withdrawing and -donating substituents in aryl-substituted ones, but also heteroaryl or substituted derivatives can be coupled (**4ba–4bm**).

Turning to the amine component, substituted 9H-carbazoles were briefly explored, giving rise to **4ca** and **4cb**. Also, 2-phenyl-substituted indole gave desired product **4cc** in decent yield.

However, less extended π -systems such as indoles or anilines were problematic under the conditions employed so far, possibly due to the hypsochromic shift of the absorption maximum of the in situ-formed Cu–N complexes, which can no longer carry out the initial photoinduced SET (see Supporting Information for UV–vis experiments). To overcome this problem, we adopted the strategy by Fu and co-workers, who demonstrated the use of additional ligands in combination with Cu-salts as photocatalysts to perform coupling reactions of amines with alkyl halides.^{48,57} Screening several conditions (see Supporting Information for details), we found that 9H-carbazole as the additive (20 mol %) increased the yield of **4cd** from 20% to 60%. Applying these modified conditions, we could also achieve

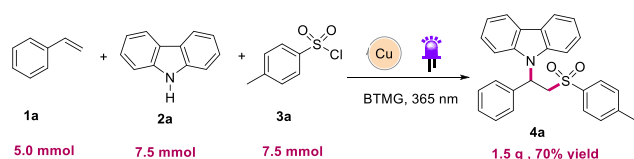
Scheme 2. Substrate Scope for Aminosulfonylation of the Alkenes^a

^aReaction conditions: Condition A^a: 1 (alkene) (0.2 mmol, 1.0 equiv), 2 (carbazole or indole derivatives) (0.3 mmol, 1.5 equiv), 3 (sulfonyl chlorides) (0.3 mmol, 1.5 equiv), CuCl (10 mol %), BTMG (1.5 equiv), CH₃CN (2 mL), 365 nm (1 W), 25 °C, N₂, 24 h; Condition B^b: 1 (alkene) (0.2 mmol, 1.0 equiv), 2 (amines with a less extended π -system) (0.3 mmol, 1.5 equiv), 3 (sulfonyl chlorides) (0.3 mmol, 1.5 equiv), CuCl (10 mol %), carbazole (20 mol %), BTMG (1.5 equiv), CH₃CN (2 mL), 365 nm (1 W), 25 °C, N₂, 24 h; Isolated yields of the products are given; ^{c,d}Obtained as an inseparable mixture with the chlorosulfonylated side product (¹H NMR yields are determined using 1,1,2,2-tetrachloroethane as an internal standard); ^e365 nm (2 W) was used for irradiation.

moderate yields for other amines (4cd–4cf) with small amounts (<15%) of the competing carbazole product 4a. To extend the applicability of our protocol, we successfully prepared an apremilast^{58,59} analogue 4cg in moderate yield.

A 25-fold scale-up in a conventional batch setup was achieved by extending the reaction time to 48 h (Scheme 3), producing 4a in gram quantities with a slightly reduced yield of 70% (5 mmol scale) compared to 85% (0.2 mmol scale).

Scheme 3. Scale-Up Experiment of the Aminosulfonylation Reaction^a



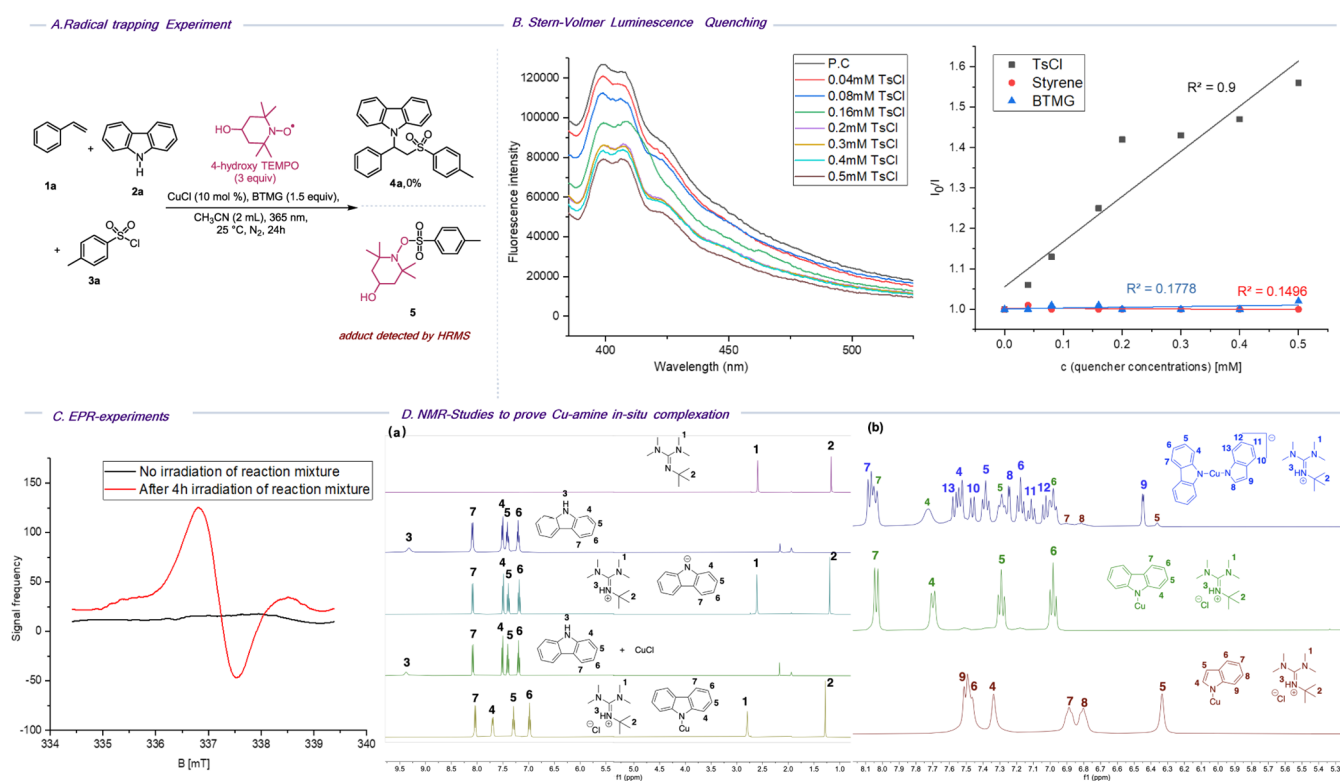
^aReaction conditions: **1a** (5.0 mmol, 1.0 equiv), **2a** (7.5 mmol, 1.5 equiv), **3a** (7.5 mmol, 1.5 equiv), CuCl (10 mol %), BTMG (1.5 equiv), CH₃CN (50 mL), 365 nm, 25 °C, N₂, 48 h.

Probing the radical pathway, upon the addition of 4-hydroxy TEMPO, a complete shutdown of the title reaction is observed (Scheme 4A). Additionally, in the presence of compound **3a**, the fluorescence emission intensity of the Cu(I)–carbazolide substrate complex **8** was significantly reduced (Scheme 4B).

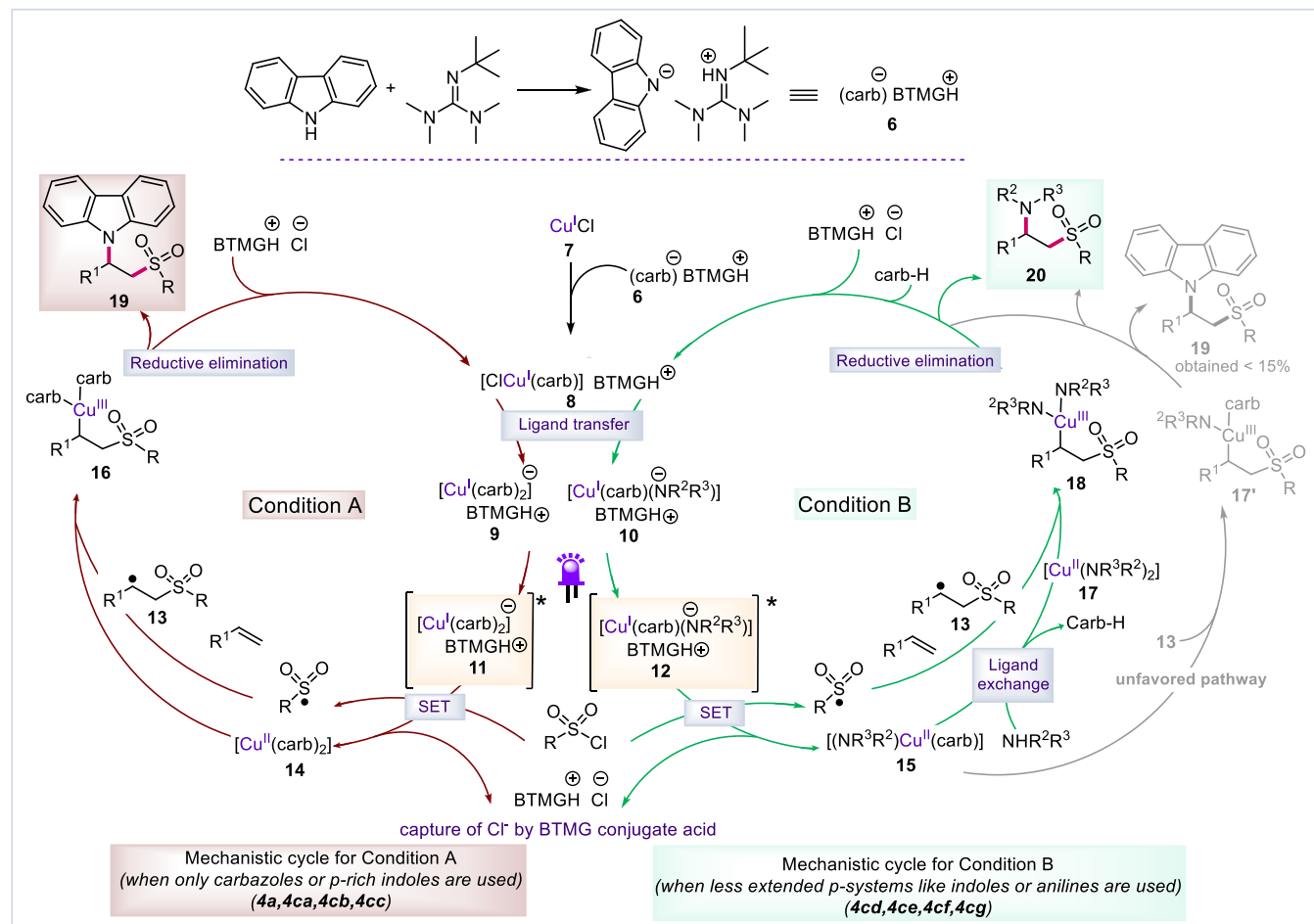
Furthermore, ¹H NMR studies confirmed the in situ formation of the Cu(I)–amine complex. The observed chemical shift displacements clearly indicate coordination of the anionic carbazole to the metal center, leading to the formation of the [Cu–carbazole] complex (Scheme 4D(a)). This species shows distinct resonances compared to the free anionic carbazole. Upon the addition of indole (Scheme 4D(b)), new spectral features appeared, attributable to the formation of two additional species: a minor component assigned to [Cu–indolide] and a major species corresponding to the heteroleptic [indolide–Cu–carbazole][−] complex. Moreover, the initial [Cu–carbazole] complex remains present in a proportion comparable to that of the heteroleptic species. The relative NMR integral ratios of the three species were determined as 1.30:1.15:0.21.

Based on our experimental data, DFT calculations (see Supporting Information for details) and literature precedent,^{48,57,60} a plausible mechanistic pathway is depicted in Scheme 5. The Cu-salt **7** combines with the carbazole–BTMG adduct **6** to generate the substrate complex **8**. Consistent with the methodology previously reported by Fu and co-workers,⁴⁶ we propose that a ligand transfer may occur to generate a Cu(I)-complex **9** having coordinated two carbazoles or a heteroleptic Cu complex **10** having coordinated to a carbazole and another amine. The excitation of intermediates **9** and **10** triggers single-electron transfer (SET) that reduces sulfonyl chlorides, producing sulfonyl radicals, which subsequently yield oxidized Cu(II) intermediates **14** and **15**, as demonstrated by the EPR experiment (Scheme 4C). We reason that the counteranion chloride is bound by the conjugate acid of the BTMG⁵⁶ base, which inhibits the formation of the undesired chlorosulfonylated, i.e., 2-component ATRA product. In the mechanistic cycle for condition B, we propose the presence of the bis-amide Cu(II)-complex **17** due to the higher concentration of the amine nucleophile, being supported by DFT calculations (taken indole as model) that suggest that ligand exchange of different Cu(II)–carbazolide/indolide species is facile (see Supporting Information for details). The sulfonyl radical is captured by the alkene, resulting in the formation of the radical addition intermediate **13**, which is further coordinated to yield the Cu(III) intermediates **16** or **18**. Reductive elimination yields products **19** and **20**, accompanied by the regeneration of Cu(I) intermediate **8**. To better understand the selectivity of product formation, we evaluated the reductive elimination energy barriers for different Cu(III) intermediates. The findings indicate that the barrier for the reductive elimination of Cu(III)-bis-indolide intermediate **18** to give **20** is lower than

Scheme 4. Mechanistic Investigations: (A) Radical Trapping Experiments, (B) Stern–Volmer Quenching, (C) EPR Experiments, and (D) NMR Studies on Cu–Amine In Situ Complexation



Scheme 5. Plausible Reaction Mechanism



the reductive elimination of either N-ligand in the heteroleptic indole–carbazole Cu(III) intermediate **17'**. This suggests that product **20** is preferentially formed from intermediate **18** rather than from **17'** (see [Supporting Information](#) for details).

METHODS

General Procedure A. An oven-dried glass vial (5 mL size) equipped with a stirring bar was charged with CuCl (2 mg, 0.02 mmol, 10 mol %), amine **2** (0.3 mmol, 1.5 equiv), and sulfonyl chloride **3** (0.3 mmol, 1.5 equiv) followed by the addition of dry CH₃CN (2 mL). The reaction vial was sealed with a rubber septum, and the mixture was degassed by sparging nitrogen gas for 10 min. 2-*tert*-Butyl-1,1,3,3-tetramethylguanidine (BTMG) (64 μ L, 0.3 mmol, 1.5 equiv) and alkene **1** (0.2 mmol, 1.0 equiv) were added sequentially under nitrogen flow. The reaction mixture was irradiated at 365 nm for 24 h at 25 °C. The reaction mixture was transferred to a round-bottomed flask and concentrated in vacuo. The crude mixture was purified on silica using hexanes and ethyl acetate as an eluent to afford product **4**.

General Procedure B. An oven-dried glass vial (5 mL size) equipped with a stirring bar was charged with CuCl (2 mg, 0.02 mmol, 10 mol %), carbazole* (7 mg, 0.04 mmol, 20 mol %), amine **2** (0.3 mmol, 1.5 equiv), and sulfonyl chloride **3** (0.3 mmol, 1.5 equiv) followed by the addition of dry CH₃CN (2 mL). The reaction vial was sealed with a rubber septum, and the mixture was degassed by sparging nitrogen gas for 10 min. 2-*tert*-Butyl-1,1,3,3-tetramethylguanidine (BTMG) (64 μ L, 0.3 mmol, 1.5 equiv) and alkene **1** (0.2 mmol, 1.0 equiv) were added

sequentially under nitrogen flow. The reaction mixture was irradiated at 365 nm for 24 h at 25 °C. The reaction mixture was transferred to a round-bottom flask and concentrated in vacuo. The crude mixture was purified on silica using hexanes and ethyl acetate as the eluents to afford product **4**.

*In the case of less extended π -systems like indoles or anilines (particularly for products **4cd**, **4ce**, and **4cf**), carbazole is used as a ligand.

CONCLUSIONS

We have developed a Cu(I)-photocatalyzed three-component coupling strategy for the efficient 1,2-aminosulfonylation of alkenes using amines and sulfonyl chloride derivatives. This method effectively addresses key challenges, such as undesired two-component side reactions, with the BTMG base playing a crucial role in minimizing byproduct formation. Beyond achieving high selectivity, this approach offers significant potential for late-stage functionalization and the synthesis of bioactive molecules, making it a valuable tool for organic synthesis and pharmaceutical development.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.5c05213>. The primary research data of this study are openly available in Radar4Chem at DOI: 10.22000/b3kn8ap2p6chy9be.

Experimental procedures, mechanistic studies, X-ray crystal data, analytical data, DFT calculations, and ^1H and ^{13}C spectra of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Kharasch, M. S.; Urry, W. H.; Jensen, E. V. ADDITION OF DERIVATIVES OF CHLORINATED ACETIC ACIDS TO OLEFINS. *J. Am. Chem. Soc.* **1945**, *67*, 1626.
- (2) Kharasch, M. S.; Jensen, E. V.; Urry, W. H. Addition of Carbon Tetrachloride and Chloroform to Olefins. *Science* **1945**, *102*, 128.
- (3) Kharasch, M. S.; Skell, P. S.; Fisher, P. Reactions of Atoms and Free Radicals in Solution. XII. The Addition of Bromo Esters to Olefins. *J. Am. Chem. Soc.* **1948**, *70*, 1055–1059.
- (4) Courant, T.; Masson, G. Recent Progress in Visible-Light Photoredox-Catalyzed Intermolecular 1,2-Difunctionalization of Double Bonds via an ATRA-Type Mechanism. *J. Org. Chem.* **2016**, *81*, 6945–6952.
- (5) Cheung, K. P. S.; Sarkar, S.; Gevorgyan, V. Visible Light-Induced Transition Metal Catalysis. *Chem. Rev.* **2022**, *122*, 1543–1625.
- (6) Engl, S.; Reiser, O. Copper-Photocatalyzed ATRA Reactions: Concepts, Applications, and Opportunities. *Chem. Soc. Rev.* **2022**, *51*, 5287–5299.
- (7) Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. Rate Constants for Halogen Atom Transfer from Representative α -Halo Carbonyl Compounds to Primary Alkyl Radicals. *J. Org. Chem.* **1989**, *54*, 1826–1831.
- (8) Baciocchi, E.; Muraglia, E. Synthesis of γ -Haloesters and γ -Ketoesters by Homolytic Addition of Carbon Radicals Generated by α -Haloesters and Triethylborane to Alkenes and Silyl Enol Ethers. *Tetrahedron Lett.* **1994**, *35*, 2763–2766.
- (9) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. Powerful Solvent Effect of Water in Radical Reaction: Triethylborane-Induced Atom-Transfer Radical Cyclization in Water. *J. Am. Chem. Soc.* **2000**, *122*, 11041–11047.
- (10) Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. Triethylborane-Induced Bromine Atom-Transfer Radical Addition in Aqueous Media: Study of the Solvent Effect on Radical Addition Reactions. *J. Org. Chem.* **2001**, *66*, 7776–7785.
- (11) Matyjaszewski, K. From Atom Transfer Radical Addition to Atom Transfer Radical Polymerization. *Curr. Org. Chem.* **2002**, *6*, 67–82.
- (12) Pintauer, T.; Matyjaszewski, K. Atom Transfer Radical Polymerization (ATRP) and Addition (ATRA) and Applications. *Encyclopedia of Radicals in Chemistry, Biology and Materials*; John Wiley & Sons, Ltd, 2012.
- (13) Williams, T. M.; Stephenson, C. R. J. Atom Transfer Radical Addition Using Photoredox Catalysis. *Visible Light Photocatalysis in Organic Chemistry*; John Wiley & Sons, Ltd, 2018; pp 73–92.
- (14) Narayanam, J. M. R.; Stephenson, C. R. J. Visible Light Photoredox Catalysis: Applications in Organic Synthesis. *Chem. Soc. Rev.* **2011**, *40*, 102–113.
- (15) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322–5363.
- (16) Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis. *Chem. Rev.* **2016**, *116*, 10035–10074.
- (17) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81* (16), 6898–6926.
- (18) Ravelli, D.; Protti, S.; Fagnoni, M. Carbon–Carbon Bond Forming Reactions via Photogenerated Intermediates. *Chem. Rev.* **2016**, *116*, 9850–9913.
- (19) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. Visible-Light Photocatalysis: Does It Make a Difference in Organic Synthesis? *Angew. Chem., Int. Ed.* **2018**, *57*, 10034–10072.
- (20) Barton, D. H. R.; Csiba, M. A.; Jaszberenyi, J. C. $\text{Ru}(\text{bpy})_3^{2+}$ -Mediated Addition of Se-Phenyl p-tolueneselenosulfonate to Electron Rich Olefins. *Tetrahedron Lett.* **1994**, *35*, 2869–2872.
- (21) Wallentin, C.-J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. Visible Light-Mediated Atom Transfer Radical Addition via Oxidative and Reductive Quenching of Photocatalysts. *J. Am. Chem. Soc.* **2012**, *134*, 8875–8884.
- (22) Pirtsch, M.; Paria, S.; Matsuno, T.; Isobe, H.; Reiser, O. $[\text{Cu}(\text{dap})_2\text{Cl}]$ As an Efficient Visible-Light-Driven Photoredox Catalyst in Carbon–Carbon Bond-Forming Reactions. *Chem.—Eur. J.* **2012**, *18*, 7336–7340.
- (23) Paria, S.; Reiser, O. Copper in Photocatalysis. *ChemCatChem* **2014**, *6*, 2477–2483.
- (24) Reiser, O. Shining Light on Copper: Unique Opportunities for Visible-Light-Catalyzed Atom Transfer Radical Addition Reactions and Related Processes. *Acc. Chem. Res.* **2016**, *49*, 1990–1996.
- (25) Wang, F.; Chen, P.; Liu, G. Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* **2018**, *51*, 2036–2046.

- (26) Nicholls, T. P.; Bissember, A. C. Developments in Visible-Light-Mediated Copper Photocatalysis. *Tetrahedron Lett.* **2019**, *60*, 150883.
- (27) Hossain, A.; Bhattacharyya, A.; Reiser, O. Copper's Rapid Ascent in Visible-Light Photoredox Catalysis. *Science* **2019**, *364*, No. eaav9713.
- (28) Zhong, M.; Pannecoucke, X.; Jubault, P.; Poisson, T. Recent Advances in Photocatalyzed Reactions Using Well-Defined Copper(I) Complexes. *Beilstein J. Org. Chem.* **2020**, *16*, 451–481.
- (29) Beaudelot, J.; Oger, S.; Peruško, S.; Phan, T.-A.; Teunens, T.; Moucheron, C.; Evano, G. Photoactive Copper Complexes: Properties and Applications. *Chem. Rev.* **2022**, *122*, 16365–16609.
- (30) Song, L.; Cai, L.; Van der Eycken, E. V.; Gong, L. Recent Advances in Copper-Catalyzed Multicomponent Reactions with Photoinduction. *Coord. Chem. Rev.* **2025**, *528*, 216428.
- (31) Rawner, T.; Knorn, M.; Lutsker, E.; Hossain, A.; Reiser, O. Synthesis of Trifluoromethylated Sulfones from Alkenols Using a Copper Photoredox Catalyst. *J. Org. Chem.* **2016**, *81*, 7139–7147.
- (32) Rawner, T.; Lutsker, E.; Kaiser, C. A.; Reiser, O. The Different Faces of Photoredox Catalysts: Visible-Light-Mediated Atom Transfer Radical Addition (ATRA) Reactions of Perfluoroalkyl Iodides with Styrenes and Phenylacetylenes. *ACS Catal.* **2018**, *8*, 3950–3956.
- (33) Engl, S.; Reiser, O. Copper Makes the Difference: Visible Light-Mediated Atom Transfer Radical Addition Reactions of Iodoform with Olefins. *ACS Catal.* **2020**, *10*, 9899–9906.
- (34) Reichle, A.; Koch, M.; Sterzel, H.; Großkopf, L.; Floss, J.; Rehbein, J.; Reiser, O. Copper(I) Photocatalyzed Bromonitroalkylation of Olefins: Evidence for Highly Efficient Inner-Sphere Pathways. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202219086.
- (35) Abderrazak, Y.; Reiser, O. Copper Photocatalyzed Divergent Access to Organic Thio- and Isothiocyanates. *ACS Catal.* **2024**, *14*, 4847–4855.
- (36) Hossain, A.; Engl, S.; Lutsker, E.; Reiser, O. Visible-Light-Mediated Regioselective Chlorosulfonylation of Alkenes and Alkynes: Introducing the Cu(II) Complex [Cu(dap)Cl₂] to Photochemical ATRA Reactions. *ACS Catal.* **2019**, *9*, 1103–1109.
- (37) Yasu, Y.; Koike, T.; Akita, M. Three-Component Oxytrifluoromethylation of Alkenes: Highly Efficient and Regioselective Difunctionalization of C-C Bonds Mediated by Photoredox Catalysts. *Angew. Chem., Int. Ed.* **2012**, *51*, 9567–9571.
- (38) Courant, T.; Masson, G. Photoredox-Initiated α -Alkylation of Imines through a Three-Component Radical/Cationic Reaction. *Chem.—Eur. J.* **2012**, *18*, 423–427.
- (39) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. One Pot and Selective Intermolecular Aryl- and Heteroaryl-Trifluoromethylation of Alkenes by Photoredox Catalysis. *Chem. Commun.* **2014**, *50*, 14197–14200.
- (40) Dagousset, G.; Carboni, A.; Magnier, E.; Masson, G. Photoredox-Induced Three-Component Azido- and Aminotrifluoromethylation of Alkenes. *Org. Lett.* **2014**, *16*, 4340–4343.
- (41) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. Three-Component Photoredox-Mediated Chloro-, Bromo-, or Iodotrifluoromethylation of Alkenes. *Synthesis* **2015**, *47*, 2439–2445.
- (42) Fumagalli, G.; Rabet, P. T. G.; Boyd, S.; Greaney, M. F. Three-Component Azidation of Styrene-Type Double Bonds: Light-Switchable Behavior of a Copper Photoredox Catalyst. *Angew. Chem., Int. Ed.* **2015**, *54*, 11481–11484.
- (43) Smirnov, V. O.; Maslov, A. S.; Kokorekin, V. A.; Korlyukov, A. A.; Dilman, A. D. Photoredox Generation of the Trifluoromethyl Radical from Borate Complexes via Single Electron Reduction. *Chem. Commun.* **2018**, *54*, 2236–2239.
- (44) Pagire, S. K.; Paria, S.; Reiser, O. Synthesis of β -Hydroxysulfones from Sulfonyl Chlorides and Alkenes Utilizing Visible Light Photocatalytic Sequences. *Org. Lett.* **2016**, *18*, 2106–2109.
- (45) Guo, S.-Q.; Yang, H.-Q.; Wang, A.-L.; Jiang, Y.-Z.; Xu, G.-Q.; Luo, Y.-C.; Chen, Z.-X.; Xu, P.-F. Divergent Ritter-Type Amination via Photoredox Catalytic Four-Component Radical-Polar Crossover Reactions. *Green Chem.* **2021**, *23*, 9571–9576.
- (46) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. Photoinduced Ullmann C–N Coupling: Demonstrating the Viability of a Radical Pathway. *Science* **2012**, *338*, 647–651.
- (47) Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. Transition-Metal-Catalyzed Alkylations of Amines with Alkyl Halides: Photoinduced, Copper-Catalyzed Couplings of Carbazoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 5129–5133.
- (48) Matier, C. D.; Schwaben, J.; Peters, J. C.; Fu, G. C. Copper-Catalyzed Alkylation of Aliphatic Amines Induced by Visible Light. *J. Am. Chem. Soc.* **2017**, *139*, 17707–17710.
- (49) Ahn, J. M.; Peters, J. C.; Fu, G. C. Design of a Photoredox Catalyst That Enables the Direct Synthesis of Carbamate-Protected Primary Amines via Photoinduced, Copper-Catalyzed N-Alkylation Reactions of Unactivated Secondary Halides. *J. Am. Chem. Soc.* **2017**, *139*, 18101–18106.
- (50) Lee, H.; Ahn, J. M.; Oyala, P. H.; Citek, C.; Yin, H.; Fu, G. C.; Peters, J. C. Investigation of the C–N Bond-Forming Step in a Photoinduced, Copper-Catalyzed Enantioconvergent N–Alkylation: Characterization and Application of a Stabilized Organic Radical as a Mechanistic Probe. *J. Am. Chem. Soc.* **2022**, *144*, 4114–4123.
- (51) Xiong, Y.; Ma, X.; Zhang, G. Copper-Catalyzed Intermolecular Carboamination of Alkenes Induced by Visible Light. *Org. Lett.* **2019**, *21*, 1699–1703.
- (52) Zhang, Y.; Sun, Y.; Chen, B.; Xu, M.; Li, C.; Zhang, D.; Zhang, G. Copper-Catalyzed Photoinduced Enantioselective Dual Carbofunctionalization of Alkenes. *Org. Lett.* **2020**, *22*, 1490–1494.
- (53) Man, H.-W.; Schafer, P.; Wong, L. M.; Patterson, R. T.; Corral, L. G.; Raymon, H.; Blease, K.; Leisten, J.; Shirley, M. A.; Tang, Y.; Babusis, D. M.; Chen, R.; Stirling, D.; Muller, G. W. Discovery of (S)-N-[2-[(1-(3-Ethoxy-4-Methoxyphenyl)-2-Methanesulfonyl)ethyl]-1,3-Dioxo-2,3-Dihydro-1H-Isoindol-4-yl]acetamide (Apremilast), a Potent and Orally Active Phosphodiesterase 4 and Tumor Necrosis Factor- α Inhibitor. *J. Med. Chem.* **2009**, *52*, 1522–1524.
- (54) Stokvis, E.; Rosing, H.; Crul, M.; Rieser, M. J.; Heck, A. J. R.; Schellens, J. H. M.; Beijnen, J. H. Quantitative Analysis of the Novel Anticancer Drug ABT-518, a Matrix Metalloproteinase Inhibitor, plus the Screening of Six Metabolites in Human Plasma Using High-Performance Liquid Chromatography Coupled with Electrospray Tandem Mass Spectrometry. *J. Mass Spectrom.* **2004**, *39*, 277–288.
- (55) Tesei, A.; Leonetti, C.; Di Donato, M.; Gabucci, E.; Porru, M.; Varchi, G.; Guerrini, A.; Amadori, D.; Arienti, C.; Pignatta, S.; Paganelli, G.; Caraglia, M.; Castoria, G.; Zoli, W. Effect of Small Molecules Modulating Androgen Receptor (SARMs) in Human Prostate Cancer Models. *PLoS One* **2013**, *8*, No. e62657.
- (56) Samanta, A.; Pramanik, S.; Mondal, S.; Maity, S. Zinc Acetate-Promoted Blocking of the ATRA Process with Alkyl Halides Enabling Photochemical Alkylamination of Olefins. *Chem. Commun.* **2022**, *58*, 8400–8403.
- (57) He, J.; Chen, C.; Fu, G. C.; Peters, J. C. Visible-Light-Induced, Copper-Catalyzed Three-Component Coupling of Alkyl Halides, Olefins, and Trifluoromethylthiolate to Generate Trifluoromethyl Thioethers. *ACS Catal.* **2018**, *8*, 11741–11748.
- (58) Syu, J.-F.; Gopula, B.; Jian, J.-H.; Li, W.-S.; Kuo, T.-S.; Wu, P.-Y.; Henschke, J. P.; Hsieh, M.-C.; Tsai, M.-K.; Wu, H.-L. Asymmetric Synthesis of β -Aryl β -Imido Sulfones Using Rhodium Catalysts with Chiral Diene Ligands: Synthesis of Apremilast. *Org. Lett.* **2019**, *21*, 4614–4618.
- (59) Narode, H.; Gayke, M.; Eppa, G.; Yadav, J. S. A Review on Synthetic Advances toward the Synthesis of Apremilast, an Anti-Inflammatory Drug. *Org. Process Res. Dev.* **2021**, *25*, 1512–1523.
- (60) Bartoszewicz, A.; Matier, C. D.; Fu, G. C. Enantioconvergent Alkylations of Amines by Alkyl Electrophiles: Copper-Catalyzed Nucleophilic Substitutions of Racemic α -Halolactams by Indoles. *J. Am. Chem. Soc.* **2019**, *141*, 14864–14869.

NOTE ADDED AFTER ASAP PUBLICATION

The abstract graphic was missing the phenyl ring in the version of this paper that was published ASAP October 13, 2025. The corrected version was posted October 13, 2025.