Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

Published on 05 August 2026
Licence and permissions

Cite this: DOI: 10.1039/d6ob01060a

Received 10th July 2026,
Accepted 4th August 2026

DOI: 10.1039/d6ob01060a

rsc.li/obc

Photoinduced radical Truce–Smiles rearrangement driven by halogen bond interactions

Vivek Kumar,[a] Ananthakrishna Panuganti,[a] Fathima Beevi V,[a] Rositha Kuniyil *[b] and Veera Reddy Yatham *[a]

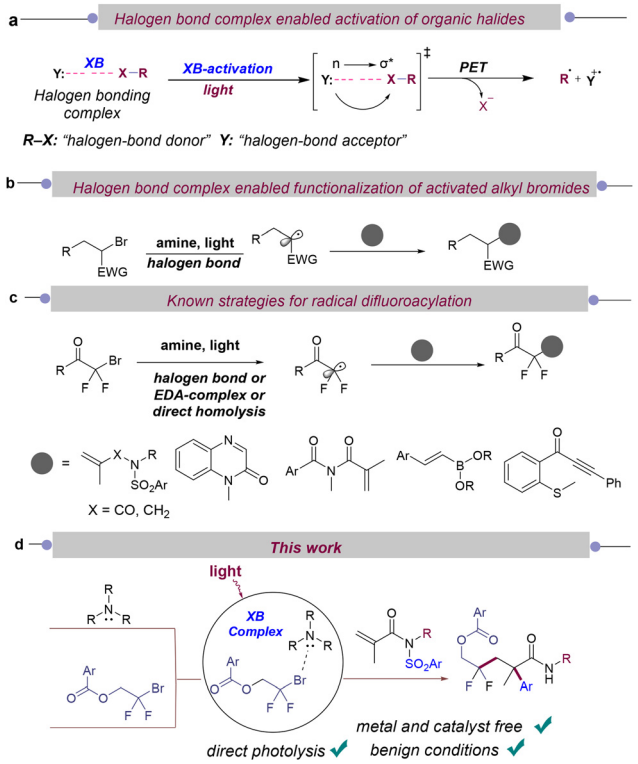
Herein, we report a halogen-bond-assisted catalyst-free protocol for the difluoroalkylation of alkenes *via* a radical Truce–Smiles rearrangement. It was found that the amine plays a dual role as a halogen-bond donor as well as a precursor of α-amino alkyl radicals, which act as reductants. Key advantages of this protocol include mild reaction conditions, broad substrate compatibility, and the potential for further applications in the synthesis of pharmaceutically relevant molecules.

C–X bond activation remains a fundamental challenge in synthetic organic chemistry, because the high strength of the C–X bond and the narrow range of reduction potentials[1a] (−1.5 V to −2.5 V) render the generalization of a C–X activation protocol very difficult. The problem is even more acute in the case of alkyl halides, which lack a structural or electronic bias in favour of C–X cleavage. Thus, while there have been significant efforts towards the development of robust and general C–X activation protocols, a mild, broad, and synthetically undemanding methodology for the C–X bond activation of challenging alkyl halides remains to be developed. Of late, halogen bonding has emerged as an attractive mediator for efficient radical generation *via* C–X bond lysis. Halogen bonding (XB) is a noncovalent interaction in which a halogen atom (X) in one molecule interacts with an electron-rich site, such as the lone pair of a Lewis base (Y).[1b–k] It is to be noted that C–Br bonds, despite being more accessible, form weaker halogen bonds and thus are less commonly activated.[1,2] Difluorinated organic molecules hold significant value in pharmaceuticals, agrochemicals and materials science owing to their distinctive properties, including high hydrophobicity, enhanced metabolic stability and altered biological activity.[3] Given these advantages, scientists have developed numerous (catalytic) strategies for synthesizing difluoroalkylated organic compounds.[4]

Among these strategies, radical-mediated intermolecular carbodifluoroalkylation of alkenes has emerged as a particularly versatile and widely explored tool, allowing the rapid introduction of a difluoroalkyl group along with a second functional group into alkenes *via* the formation of two new C–C bonds.[5,6] The incorporation of the second functional group, in particular, significantly increases the synthetic utility of the products.

With advances in visible-light photocatalysis,[7] a range of difluoroalkylating reagents have been employed to generate difluoroalkyl radicals for alkene difunctionalization in the presence of photocatalysts.[4a,b] Recently, a few research groups have developed catalyst-free, photoinduced methods for generating difluoroacyl radicals from activated brominated compounds. These precursors possess relatively low reduction potentials, making the formation of difluoroacyl radicals facile under mild photochemical conditions[8] (Scheme 1). In 2022, Martin and co-workers developed a photocatalytic halogen atom transfer (XAT) strategy to generate difluoroalkyl radicals from difluoroalkyl bromides ($E_r^{\circ} = -1.74$ V, see the SI) for the hydrodifluoroalkylation of alkenes. Although effective, the protocol requires both a photocatalyst and a thiol, increasing reagent consumption and reducing the overall sustainability of the process. Moreover, when the reaction was performed without the photocatalyst, only a 12% yield was achieved, demonstrating the limited efficiency of direct radical generation under catalyst-free conditions.[9] However, to date, no catalyst-free, photoinduced difunctionalization of alkenes using unactivated difluoroalkyl bromides has been reported. Our group has recently started exploring photoinduced catalyst-free organic transformations,[10] and in this direction, we sought to develop a halogen-bond-assisted strategy for the carbodifluoroalkylation of alkenes *via* a radical Truce–Smiles rearrangement (Scheme 1d). In particular, we have previously found that α-aminoalkyl radicals, obtained after reductant upconversion,[11] are potent reductants that can drive product formation after SET processes.[10d] We make use of a similar strategy herein.

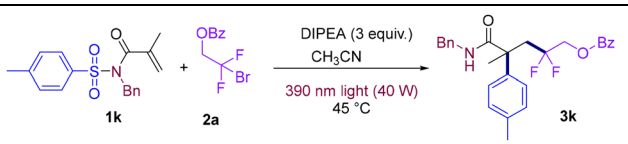
[a]*School of Chemistry, Indian Institute of Science Education and Research, Thiruvananthapuram 695551, India. E-mail: reddy@iisertvm.ac.in*
[b]*Department of Chemistry, Indian Institute of Technology, Palakkad 678557, India. E-mail: rosithak@iitpkd.ac.in*



Scheme 1 Known reports.

In order to optimize the carbodifluoroalkylation of alkenes *via* a radical Truce–Smiles rearrangement, several parameters were tested (see the SI). We found that when the reaction mixture, consisting of **1k** (1 equiv.), **2a** (1 equiv.), DIPEA (3 equiv.) and CH_3CN as the solvent, was irradiated at 45 °C for 24 hours, product **3k** was formed in 60% yield (Table 1, entry 1). Testing alternative amines ($^nBu_3N$ and Et_3N) and different solvents did not result in improved yields (Table 1, entries 2 and 3; for further optimization details, see the SI). Interestingly, adding water (20 μL) to the reaction mixture significantly enhanced the yield to 72% (Table 1, entry 4). Control experiments revealed that no product formation occurred in the absence of either light or DIPEA (Table 1, entries 5 and 6).

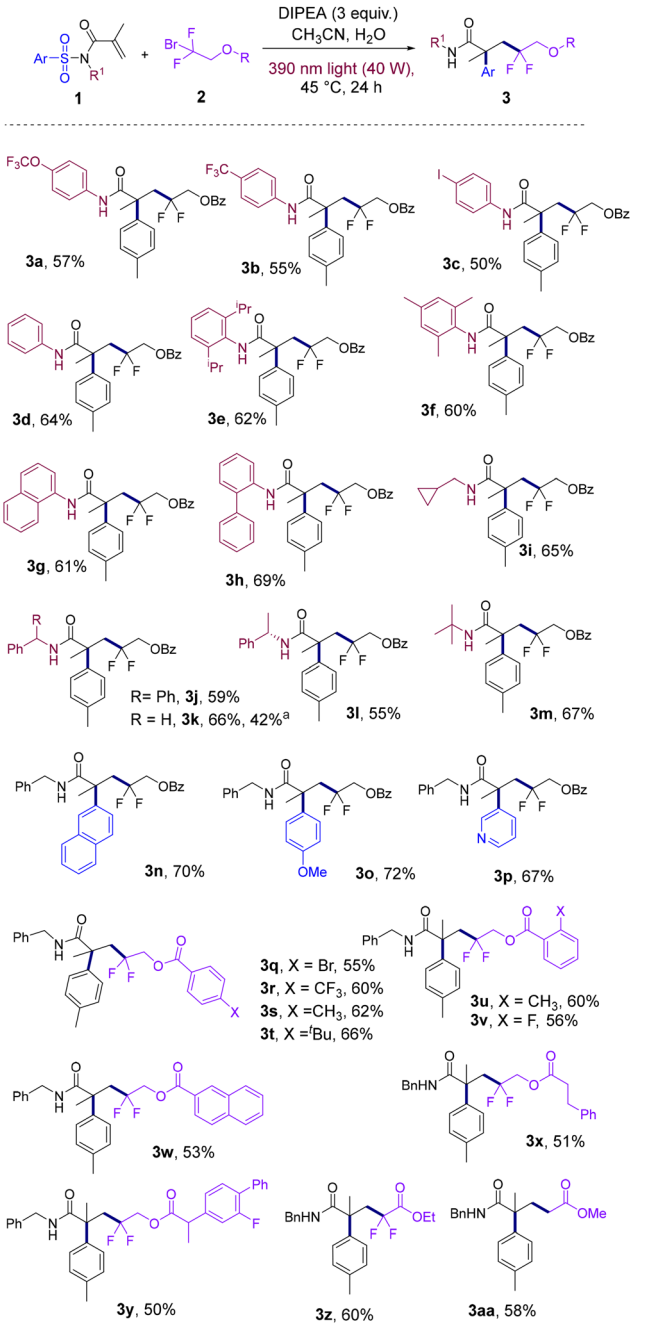
Table 1 Optimization of reaction conditions[a]



Entry	Reaction condition variation	**3k**[b] (%)
1	Using DIPEA	60
2	Using $^nBu_3N$ instead of DIPEA	56
3	Using DMF instead of CH_3CN	55
4	Using DIPEA + 20 μL water	72
5	Without DIPEA	0
6	Without light	0

[a] Reaction conditions: **1k** (0.1 mmol), **2a** (0.2 mmol), amine (0.3 mmol), solvent (1 mL) at 45 °C for 24 h. Light source placed 3 cm away from the reaction vial. [b] NMR yields using 1,3,5 trimethoxybenzene as an internal standard.

With the optimal reaction conditions in hand, we next explored the substrate scope of acrylamides by varying the substituents on *N*-aryl and *N*-aryl sulfonyl groups and 2,2-difluoroethyl arylcarboxylates (Scheme 2).



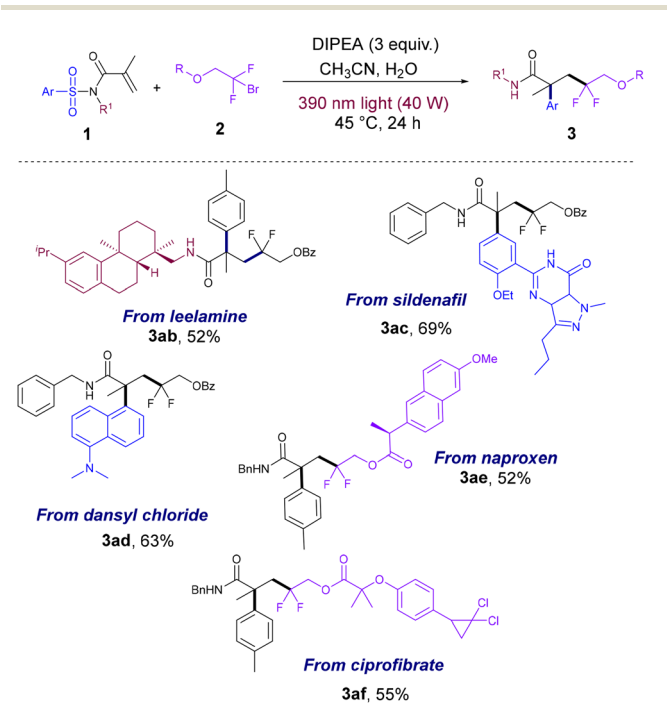
Scheme 2 Substrate scope of acrylamides. **1** (0.1 mmol), **2** (0.2 mmol), DIPEA (0.3 mmol), CH_3CN (2 mL) and H_2O (40 μL) at 45 °C for 24 h. Light source placed 3 cm away from the reaction vial. Isolated yields, average of at least two independent runs. [a] Using **1k** (1 mmol), **2a** (2 mmol), DIPEA (3 mmol), CH_3CN (10 mL) at 45 °C for 48 h.

Initially, variations in the *N*-aryl/alkyl groups were investigated. A variety of *para*-substituted (–OCF_3, –CF_3, –I) *N*-aryl groups were tolerated under our reaction conditions and afforded the products (**3a–3c**) in moderate yields (50–57%). Sterically different substituted *N*-aryl groups smoothly converted to the corresponding products (**3d–3h**) in good yields (60–69%). A diverse range of alkyl- and benzyl-substituted *N*-aryl groups afforded good yields of the products (**3i–3m**, 55–67%). Next, we employed different substituted *N*-aryl sulfonyl groups. 2-Naphthyl-, 4-methoxyphenyl- and 3-pyridyl-substituted sulfonyl groups afforded good yields of the products (**3n–3p**, 67–72%). Finally, we tested different substituted 2,2-difluoroethyl aryl/alkylcarboxylates. Electron-withdrawing and electron-donating groups (–Br, –CF_3, –F, –CH_3, –^{t}Bu) were well tolerated (**3q–3w**, 53–66% yield), indicating that the electronic properties of the substituents have only a slight impact on reaction efficiency. Furthermore, a variety of 2,2-difluoroethyl alkylcarboxylates were subjected to the standard reaction conditions, affording the corresponding products (**3x–3aa**) in moderate to good yields (50–60%).

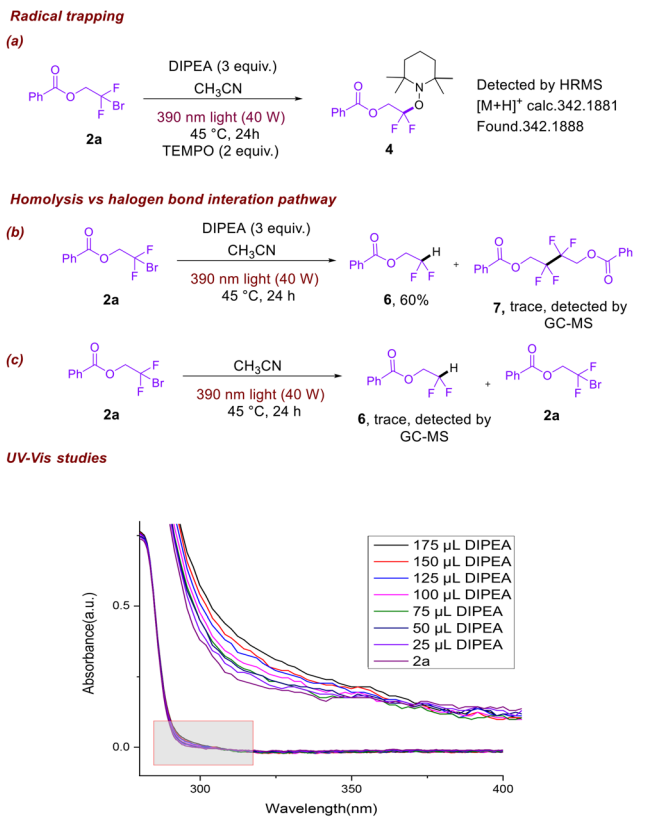
Additionally, a scale-up reaction on a 1 mmol scale produced **3k** with a 42% yield. To demonstrate the potential applications of this methodology, late-stage modification of the bioactive molecules was investigated (Scheme 3). Successful diversification of amines, aryl sulfonyl motifs and difluoroalkyl bromides was achieved with compounds such as leelamine, sildenafil, dansyl chloride, naproxen and ciprofibrate. Under our reaction conditions, these molecules afforded the corresponding products in moderate to good yields (**3ab–3af**, 52–69%).

Next, in order to elucidate the reaction mechanism, a series of mechanistic studies were conducted (Scheme 4). Initially, a radical-trapping experiment was performed using TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl). Analysis of the crude reaction mixture by high-resolution mass spectrometry (HRMS) identified a TEMPO-trapped adduct **4** (Scheme 4a), revealing the radicaloid nature of the mechanism. HRMS analysis also revealed that the secondary amine ^{n}Bu$_2$NH was formed under our reaction conditions (see the SI), indicating that the α-aminoalkyl radical is formed under our reaction conditions. The difluoroalkyl radical was also trapped with 1-phenyl styrene and characterised (see the SI). Control experiments (Scheme 4b and c) revealed that the presence of DIPEA was crucial for radical generation and that DIPEA was a likely HAT donor under the reaction conditions.

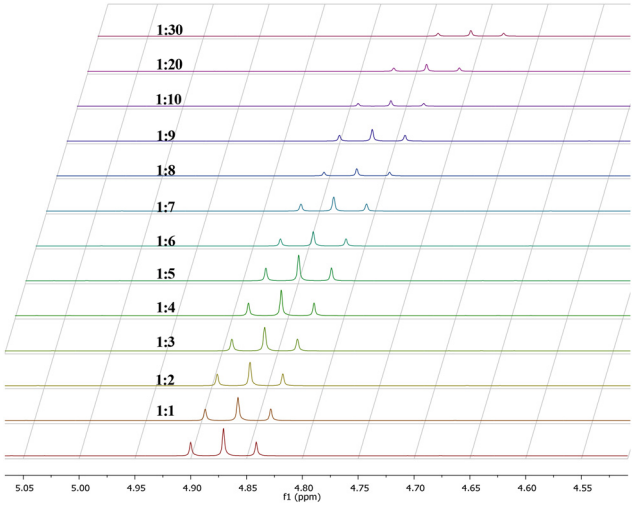
Furthermore, UV-Vis absorption experiments were performed with each individual reaction partner and with the combined reaction mixture (Scheme 4). Analysis of the absorption spectrum of the **2a** + DIPEA mixture showed a slight red shift, and furthermore, Job's plot analysis suggested the formation of a 1 : 1 halogen-bonded complex between **2a** and DIPEA (see the SI). Additionally, ^{1}H (Scheme 5) and ^{19}F NMR titrations, DOSY NMR analysis, CV studies and DFT studies (see the SI) revealed an interaction between **2a** and DIPEA,



Scheme 3 Substrate scope of pharmaceutically relevant molecules. **1** (0.1 mmol), **2** (0.2 mmol), DIPEA (0.3 mmol), CH_3CN (1 mL) and water (40 μL) at 45 °C for 24 h. Light source placed 3 cm away from the reaction vial. Isolated yields, average of at least two independent runs.



Scheme 4 Preliminary mechanistic studies.

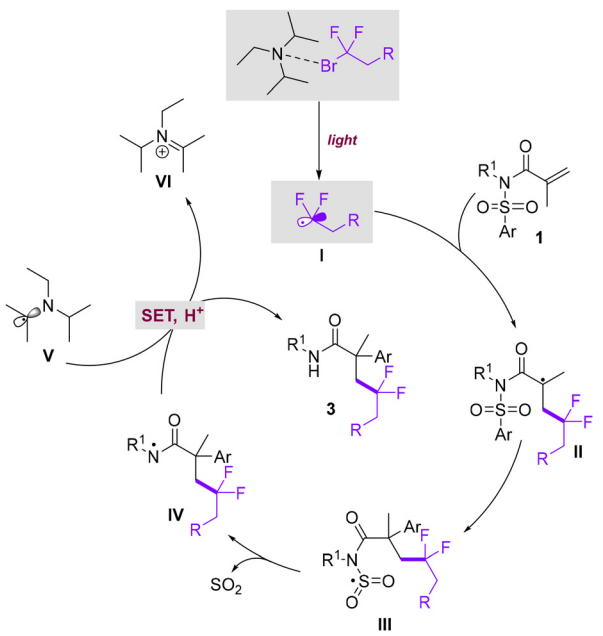


Scheme 5 ^{1}H NMR titration studies of **2a** with DIPEA.

similar to previous reports.[12] The binding constant for the complex was evaluated and found to be 0.56 M^{-1} (see the SI). Light-on/off experiments (see the SI) revealed that constant irradiation was necessary for reaction progress. During optimization studies, we observed the formation of a cyclized by-product (**3k′**) in the absence of water (see the SI), whereas only trace amounts of **3k′** were detected in its presence. The role of water in this mechanism is presently unclear, and studies to elucidate the same are ongoing.

Based on our control experiments and literature precedents,[8,11,12] we propose the following tentative reaction mechanism (Scheme 6). We believe that the photoexcitation of the halogen bond complex between DIPEA and **2a** generates the difluoroethyl phenylcarboxylate radical (**I**), which undergoes addition to substrate **1** to yield alkyl radical **II**. Subsequently, a concerted Truce–Smiles rearrangement leads to intermediate **III**, which undergoes desulfonylation, yielding the resultant amidyl radical **IV**. **IV** is then reduced by the α-aminoalkyl radical **V** and protonated to deliver the product.[13]

In summary, we have developed a sustainable and catalyst-free protocol for the photoinduced carboarylation of sulfonyl acrylamides. This protocol offers several advantages, including the use of simple starting materials, a broad substrate scope and potential applications in the synthesis of pharmaceutically relevant molecules. Furthermore, computational and experimental studies show that radical upconversion enables the dual role of amines as both XB and SET activators. Our laboratory is exploring additional photoinduced halogen-bonding-enabled transformations.



Scheme 6 Mechanistic hypothesis.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental and computational details and data on compounds. See DOI: https://doi.org/10.1039/d6ob01060a.

Acknowledgements

Financial support from MHRD-STARS (MoE-STARS/STARS-2/2023-0092) is greatly acknowledged. V. K. thanks UGC for the SRF fellowship.

References

1 (*a*) F. Juliá, T. Constantin and D. Leonori, *Chem. Rev.*, 2022, **122**, 2292–2352; (*b*) G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati and G. Terraneo, *Chem. Rev.*, 2016, **116**, 2478–2601; (*c*) L. C. Gilday, S. W. Robinson, T. A. Barendt, M. J. Langton, B. R. Mullaney and P. D. Beer, *Chem. Rev.*, 2015, **115**, 7118–7195; (*d*) R. L. Sutar and S. M. Huber, *ACS Catal.*, 2019, **9**, 9622–9639; (*e*) H. Wang, W. Wang and J. W. Jin, *Chem. Rev.*, 2016, **116**, 5072–5104; (*f*) A. Mukherjee, S. Tothadi and G. R. Desiraju, *Acc. Chem. Res.*, 2014, **47**, 2514–2524; (*g*) T. M. Beale, M. G. Chudzinski, M. G. Sarwar and M. S. Taylor, *Chem. Soc. Rev.*, 2013, **42**, 1667–1680; (*h*) R. Wilcken, M. O. Zimmermann, A. Lange, A. C. Joerger and F. M. Boeckler, *J. Med. Chem.*, 2013, **56**, 1363–1388; (*i*) P. Metrangolo, F. Meyer, T. Pilati, G. Resnati and G. Terraneo, *Angew. Chem., Int. Ed.*, 2008, **47**, 6114–6127; (*j*) P. Politzer, J. S. Murray and T. Clark, *Phys. Chem. Chem.*

Phys., 2013, **15**, 11178–11189; (*k*) P. Politzer, J. Murray, T. Clark and G. Resnati, *Phys. Chem. Chem. Phys.*, 2017, **19**, 32166–32178.

2 (*a*) S. Kozuch and J. M. L. Martin, *J. Chem. Theory Comput.*, 2013, **9**, 1918–1931; (*b*) J. Řezáč and A. De La Lande, *Phys. Chem. Chem. Phys.*, 2017, **19**, 791–803; (*c*) M. H. Kolář and P. Hobza, *Chem. Rev.*, 2016, **116**, 5155–5187; (*d*) L. N. Anderson, F. W. Aquino, A. E. Raeber, X. Chen and B. M. Wong, *J. Chem. Theory Comput.*, 2018, **14**, 180–190; (*e*) R. Miao, D. Wang, J. Xiao, J. Ma, D. Xue, F. Liu and Y. Fang, *Phys. Chem. Chem. Phys.*, 2020, **22**, 10212–10218.

3 (*a*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330; (*b*) Q. A. Huchet, B. Kuhn, B. Wagner, N. A. Kratochwil, H. Fischer, M. Kansy, D. Zimmerli, E. M. Carreira and K. Müller, *J. Med. Chem.*, 2015, **58**, 9041–9060; (*c*) Y. Zafrani, G. Sod-Moriah, D. Yeffet, A. Berliner, D. Amir, D. Marciano, S. Elias, S. Katalan, N. Ashkenazi and M. Madmon, *J. Med. Chem.*, 2019, **62**, 5628–5637; (*d*) H. Mei, J. Han, K. D. Klika, K. Izawa, T. Sato, N. A. Meanwell and V. A. Soloshonok, *Eur. J. Med. Chem.*, 2020, **186**, 111826; (*e*) N.-A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529–2591; (*f*) Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov and S. Saphier, *J. Med. Chem.*, 2017, **60**, 797–804; (*g*) C. D. Sessler, M. Rahm, S. Becker, J. M. Goldberg, F. Wang and S. J. Lippard, *J. Am. Chem. Soc.*, 2017, **139**, 9325–9332; (*h*) N. A. Meanwell, *J. Med. Chem.*, 2018, **61**, 5822–5880.

4 (*a*) D.-Q. Dong, H. Yang, J.-L. Shi, W.-J. Si, Z.-L. Wang and X.-M. Xu, *Org. Chem. Front.*, 2020, **7**, 2538–2575; (*b*) A. Lemos, C. Lemaire and A. Luxen, *Adv. Synth. Catal.*, 2019, **361**, 1500–1537; (*c*) J. B. I. Sap, C. F. Meyer, N. J. W. Straathof, N. Iwumene, C. W. am Ende, A. A. Trabanco and V. Gouverneur, *Chem. Soc. Rev.*, 2021, **50**, 8214–8247; (*d*) L. Shi, D. Ana and G.-J. Mei, *Org. Chem. Front.*, 2022, **9**, 4192–4208; (*e*) Y. Lu, C. Liu and Q.-Y. Chen, *Curr. Org. Chem.*, 2015, **19**, 1638–1650; (*f*) J. Hu, W. Zhang and F. Wang, *Chem. Commun.*, 2009, **48**, 7465–7478.

5 (*a*) Y. Arai, R. Tomita, G. Ando, T. Koike and M. Akita, *Chem. – Eur. J.*, 2016, **22**, 1262–1265; (*b*) R. I. Rodriguez, M. Sicignano and J. Aleman, *Angew. Chem., Int. Ed.*, 2022, **61**, e202112632; (*c*) A. Cai, W. Yan, X. Zeng, S. B. Zacate, T.-H. Chao, J. A. Krause, M.-J. Cheng and W. Liu, *Nat. Commun.*, 2021, **12**, 3272; (*d*) C. Palasetty, S. Vinjamuri, G. Surbhi and S. Devarajulu, *Org. Lett.*, 2023, **25**, 2857–2862; (*e*) J. Yang, S. Zhu, F. Wang, F.-L. Qing and L. Chu, *Angew. Chem., Int. Ed.*, 2021, **60**, 4300–4306; (*f*) X.-J. Tang and W. R. Dolbier Jr, *Angew. Chem., Int. Ed.*, 2015, **54**, 4246–4249; (*g*) V. R. Yatham, Y. Shen and R. Martin, *Angew. Chem., Int. Ed.*, 2017, **56**, 10915–10919; (*h*) H. Wang, J. Zhang, J. Shi, F. Li, S. Zhang and K. Xu, *Org. Lett.*, 2019, **21**, 5116–5120; (*i*) A. K. Jha, V. Kumar, S. K. Perumandla and V. R. Yatham, *ChemPhotoChem*, 2024, **8**, e202300288; (*j*) R. Huang, D. Duan, N. Fu and S. Lu, *Org. Lett.*, 2025, **27**, 12337–12342; (*k*) Z. He, P. Tan, C. Ni and J. Hu, *Org. Lett.*, 2015, **17**, 1838–1841; (*l*) S.-P. Zhang, J.-X. Lan, M.-L. Yang, J.-Y. Cao, Y. Zhang and W.-C. Yang, *Org. Lett.*, 2024, **26**, 9990–9995.

6 For recent reviews: (*a*) Z.-Y. Wang, Z. Zhang, W. Chen, Y. Liu, A. Sun and R. Xia, *Org. Biomol. Chem.*, 2025, DOI: 10.1039/d5ob01027f. Advance Article. (*b*) F. Jiaxu, J. Xiaodong, Z. Shuyue, L. Kui and C. Dominique, *Org. Chem. Front.*, 2022, **9**, 3598–3623; (*c*) T. Koike, *Asian J. Org. Chem.*, 2020, **9**, 529–537.

7 For selected reviews on photoredox catalysis: (*a*) L. Marzo, S. K. Pagire, O. Reiser and B. König, *Angew. Chem., Int. Ed.*, 2018, **57**, 10034; (*b*) M. D. Kärkäs, J. A. Porco Jr and C. R. Stephenson, *J. Chem. Rev.*, 2016, **116**, 9683; (*c*) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075; (*d*) M. H. Shaw, J. Twilton and D. W. C. MacMillan, *J. Org. Chem.*, 2016, **81**, 6898.

8 (*a*) K. Mondal and M. Baidya, *Adv. Synth. Catal.*, 2024, **366**, 148–153; (*b*) D. M. Whalley, H. A. Duong and M. F. Greaney, *Chem. – Eur. J.*, 2019, **25**, 1927–1930; (*c*) L. Huang, C. Wang, Z. Chen, Q. Jin, S. Song, J. Zhou and J. Li, *Chem. – Eur. J.*, 2025, **31**, e202403286; (*d*) C.-H. Qu, R. Huang, Y. Liu, T. Liu and G.-T. Song, *Org. Chem. Front.*, 2022, **9**, 4135–4145; (*e*) C.-H. Qu, X. Yan, S.-T. Li, J.-B. Liu, Z.-G. Xu, Z.-Z. Chen, D.-Y. Tang, H.-X. Liu and G.-T. Song, *Green Chem.*, 2023, **25**, 3453–3461; (*f*) S. Song, C. Luo, G. Wang, J. Guo, Z. Chena and J. Li, *Chem. Commun.*, 2024, **60**, 11323–11326; (*g*) N. Kato, T. Nanjo and Y. Takemoto, *ACS Catal.*, 2022, **12**, 7843–7849.

9 W.-J. Yue, C. S. Day, A. J. B. Rucinski and R. Martin, *Org. Lett.*, 2022, **24**, 5109–5114.

10 (*a*) V. Kumar, A. Bisoyi, V. F. Beevi and V. R. Yatham, *J. Org. Chem.*, 2024, **89**, 16964–16968; (*b*) A. Bisoyi, A. R. Tripathy, G. S. Yedase, S. P. Shifana, U. Choudhury and V. R. Yatham, *J. Org. Chem.*, 2023, **88**, 2631–2641; (*c*) A. Bisoyi, A. R. Tripathy, R. Poolamanna and V. R. Yatham, *Org. Lett.*, 2025, **27**(32), 9042–9048; (*d*) V. Kumar, A. Kumar, A. Panuganti and V. R. Yatham, *Chem. Commun.*, 2026, **62**, 9006–9010; (*e*) V. K. Simhadri, A. Bisoyi, R. Sur, A. Panuganti and V. R. Yatham, *J. Org. Chem.*, 2026, **91**(19), 6751–6756; (*f*) A. K. Jha, G. S. Kana, A. Panuganti, K. L. Gayathri and V. R. Yatham, *Adv. Synth. Catal.*, 2026, e70443, DOI: 10.1002/adsc.70443; (*g*) A. R. Tripathy, A. Bisoyi, S. V. Kumar, A. Panuganti and V. R. Yatham, *Adv. Synth. Catal.*, 2026, e70526, DOI: 10.1002/adsc.70526.

11 (*a*) E. M. Alvarez, T. Karl, F. Berger, L. Torkowski and T. Ritter, *Angew. Chem., Int. Ed.*, 2021, **60**, 13609–13613; (*b*) I. V. Alabugin, P. Eckhardt, K. M. Christopher and T. Opatz, *J. Am. Chem. Soc.*, 2024, **146**, 27233–27254; (*c*) M. A. Syroeshkin, F. Kuriakose, E. A. Saverina, V. A. Timofeeva, M. P. Egorov and I. V. Alabugin, *Angew. Chem., Int. Ed.*, 2018, **58**, 5532–5550.

12 (*a*) Y. Wang, J. Wang, G.-X. Li, G. He and G. Chen, *Org. Lett.*, 2017, **19**, 1442–1445; (*b*) K.-Y. Zhang, Y.-L. Wang, C. L. He, Y.-K. Zhou, D.-N. Wang, M.-Y. Hu, X.-H. Duan and L. Liu, *Org. Chem. Front.*, 2022, **9**, 5599–5605.

13 An initial version of this work was deposited in ChemRxiv on September 19, 2025; V. Kumar, A. Panuganti, V. F. Beevi, A. Kumar, R. Kuniyil and V. R. Yatham, *ChemRxiv*, 2025, preprint, DOI: 10.26434/chemrxiv-2025-htsst.