

RESEARCH ARTICLE

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Cite this: *Org. Chem. Front.*, 2024, **11**, 7037 δ -Amination of alkyl alcohols *via* energy transfer photocatalysis†Christian Cristóbal,^a Inés Alonso,^{a,b,d} Francisco Tato,^{a,c} María J. Cabrera-Afonso,^{a,*} Javier Adrio,^{a,b,d} and Maria Ribagorda,^{a,b}

Amino alcohols play a crucial role in the realm of biologically active compounds due to their functional diversity. In this study, we introduce a metal-free energy transfer photocatalytic method for the preparation of 1,4-aminoalcohols from readily available alcohol feedstocks. The key feature of this transformation is the simultaneous generation of a persistent iminyl radical and a transient carbon-centered radical through σ -homolytic cleavage of the O–N bond *via* energy transfer (EnT). The process involves fragmentation/decarboxylation/1,5-HAT (hydrogen atom transfer), leading to the formation of a C(sp³)-hybridized radical, which undergoes selective radical–radical cross-coupling or a radical chain event to yield the desired products. In addition, the protocol was also found to be suitable for *N*-tosyl amines, giving rise to 1,4-diamines. Our approach combines experimental mechanistic investigations with detailed computational studies using density functional theory (DFT) to provide insights into the reaction mechanism. This innovative method provides a new approach for preparing δ -amino alkyl alcohols and amines.

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Introduction

The generation of radicals under mild visible light photocatalyzed conditions has emerged as a powerful tool that has expanded the repertoire of synthetic transformations, enabling new ways to access complex molecules.¹ For instance, the functionalization of a carbon centered radical generated by 1,5-hydrogen atom transfer (HAT) from a heteroatom radical is exceptionally interesting since it allows remote selective functionalization of inert C–H bonds.² Consequently, diverse approaches have been developed for this remote functionalization (Scheme 1A).³

The most common strategy involves the preactivation of the O–H bond using a redox auxiliary (Scheme 1A, O-RP, RP = radical precursor) such as *N*-alkoxyphthalimides,⁴ *N*-alkoxy-pyridinium salts⁵ or α -oxime acids or esters,⁶ among others. These radical precursors are easy to prepare and produce the desired alkoxy radical, and consequently the δ -C

(sp³)-centered radical, under photoredox conditions. Strategies for the formation of alkoxy radicals from free alcohols have also been recently developed using stoichiometric amounts of organohypervalent iodine^{7a-c} or sulfoxide reagents^{7d} (Scheme 1A, O-[A]), coordination of the alcohol with metals by ligand-to-metal charge transfer (LMCT, Ce or Fe catalyst)⁸ or direct hydrogen atom transfer of the O–H bond by proton coupled electron transfer (PCET).⁹ However, to the best of our knowledge, methods to functionalize δ -C(sp³)-H bonds of aliphatic alcohols *via* energy transfer (EnT) mechanism have not yet been reported.

Recently, different research groups have described the simultaneous generation of a persistent iminyl radical and a transient O-centered radical *via* σ -homolytic bond cleavage through EnT activation (Scheme 1B).¹⁰ In 2021, the groups of Glorius¹¹ and Han¹² independently reported the generation of both alkoxy-carbonyloxy radicals from oxime carbonates to synthesize 1,2-amino carbonates (Scheme 1B, R = OR). Huo's group described the synthesis of 1,2-amino alkoxy-carbonyl compounds *via* the formation of an alkoxy-carbonyl radical intermediate from oxime esters.¹³ Recently, Glorius *et al.* reported the generation of an alkoxy radical to prepare 1,3-amino alcohols *via* N–O bond homolysis, followed by a radical Brook rearrangement (Scheme 1B).¹⁴

Amino alcohols are valuable compounds in organic synthesis, medicinal chemistry, and materials science. In particular, 1,4-amino alcohol subunits are present in many biologically active compounds, act as flexible building blocks in synthetic chemistry and have been used as ligands in asymmetric

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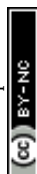
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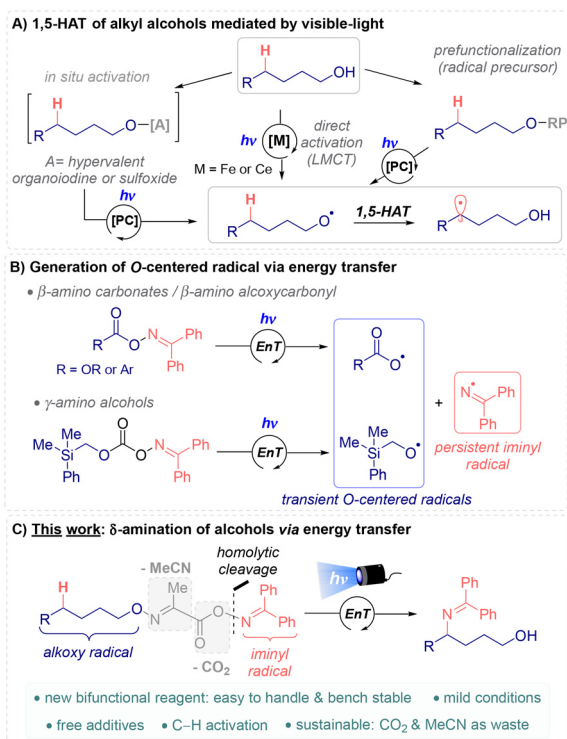
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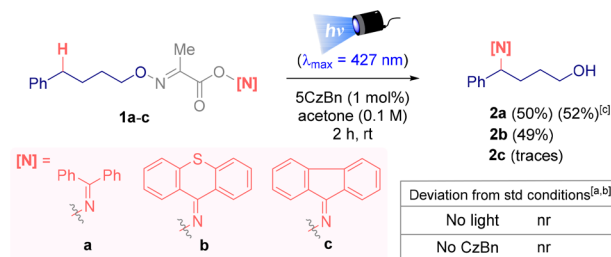


Scheme 1 (A) Different visible-light-assisted strategies to generate δ -C-centered radical from alkyl alcohols. (B) Bifunctional reagents to achieve O-centered radicals by energy transfer photocatalysis. (C) Merging of alkoxy radical reactivity with energy transfer activation.

catalysis.¹⁵ Due to the great importance of this motif, and inspired by the inherent reactivity of the alkoxy radical and the advantages that the energy transfer presents, we envisaged a δ -imination reaction of alkyl alcohols *via* EnT photocatalysis (Scheme 1C). The selective insertion of the protected amino group at this remote position of an alkyl alcohol will be achieved by the use of a novel bifunctional reagent. This new reagent has to carry both the iminyl and the alkoxy fragments in its structure, must be bench stable and easy to handle, and produce minimal waste after its activation.

Results and discussion

To investigate the feasibility of the proposed δ -amination protocol from alcohols, the bifunctional reagent **1a** was used as the model substrate.¹⁶ This starting material is bench stable and easily accessible from the corresponding alcohol after three synthetic steps. After screening several reaction conditions (different photocatalyst, solvent, catalyst loading, concentration and sources of light), the best results were obtained using 5CzBn (1 mol%) as the organo photocatalyst in acetone (0.1 M) under blue light irradiation ($\lambda_{max} = 427$ nm), yielding the δ -amino alcohol **2a** in 50% isolated yield (Scheme 2).¹⁶ Additionally, as part of the structural design of the new bifunctional reagent, different iminyl fragments were evaluated. The



Scheme 2 Structure optimization of **1** and control experiments. ^a Std conditions: **1** (0.10 mmol), 5CzBN (1 mol%), in dry degassed acetone (0.1 M) under blue Kessil irradiation ($\lambda_{max} = 427$ nm) for 2 h at rt, inert atmosphere. ^b Starting material **1a**. ^c Open-to-air conditions. Abbreviation: std, standard; nr, no reaction.

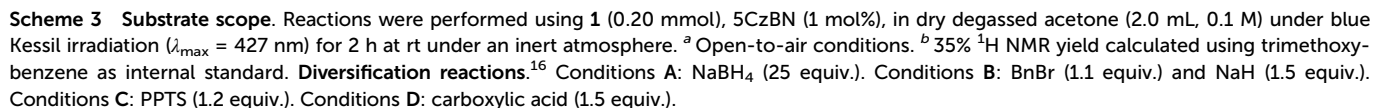
derivative from thioxanthone afforded the corresponding desired product **2b** in a similar yield. However, the 9-fluorenone derivative was unreactive, with only a trace amount of **2c** detected by ¹H NMR analysis (Scheme 2). Given the advantages offered by reagent **1a**, the synthesis of its oxime is well described and it is easy to prepare and cost effective (benzophenone ~€0.02 per g vs. thioxanthone ~€0.80 per g),¹⁷ benzophenone was chosen as the optimal iminyl precursor. Control experiments performed in the absence of light or the photocatalyst confirmed that both conditions are essential to enable the δ -imination of aliphatic alcohols (Scheme 2).¹⁶ The reactions can be performed under open air conditions with similar yields being obtained.

With the structure of the optimal bifunctional reagent established and the best reaction conditions in hand, the scope of this amination reaction was explored (Scheme 3A.1). The desired δ -imination product from primary alkyl alcohols, both non-functionalized (**2d-g**) and functionalized (**2h-q**), was achieved. Hence, the products resulting from a secondary C-centered radical intermediate (**2e-f**, **2q-s**) and a non-stabilized primary C-centered radical (**2d**) were obtained, whereas product **2g** derived from a stabilized tertiary C-centered radical intermediate was obtained in 6% yield. We hypothesized that the low yields observed in certain examples may be attributed to unfavourable pathways involving the iminyl and alkoxy radicals, as the starting alcohol was detected in most cases.¹⁸

Terminal alkyne (**2h**), chlorine (**2k**) and azide (**2l**) functional groups were tolerated under the standard reaction conditions. This protocol also allowed the synthesis of α - and β -amino esters (**2i** and **2j**) containing a free alcohol in moderate yields. The phenolic ether **2m** (from *thymol*), electron-poor and electron-rich heterocycles (**2n** and **2o**) and the δ -lactam moiety **2p** were also suitable for this transformation (Scheme 3A.1). Using secondary alcohols, no β -fragmentation product was detected and the corresponding product **2r** was obtained in 21% yield.

Interestingly, the reaction using the 4-pentenyl derivative **1t** afforded the iminated tetrahydrofuran product **2t** after an intramolecular 5-*exo-trig* cyclization event¹⁹ followed by imine insertion. In certain cases (**2a**, **2h**, **2j** and **2l**), the reactions





Next, we investigated a Hoffman-Löffler-Freytag-type (HLF) reaction using alkyl *N*-tosyl amines **1** (X = NTos).^{20,21} The synthesis of these reagents was inspired by Yu's seminal work on the δ -halogenation of alkyl *N*-tosyl amines from hydrazonyl carboxylic acid precursors.²² To our delight, the desired 5-iminyl alkylamines (**2u-y**) were obtained under the standard

Furthermore, the scale-up of this transformation was achieved using a continuous-flow photoreactor.²³ This technology enabled the complete conversion of 1.0 gram of **1a** to the desired product **2a** after only 5 h of irradiation ($t_R = 15$ min), yielding 50% of the isolated product (Scheme 3A.3). This con-

tinuous flow process was optimized using **2a** as the model substrate at 0.25 mmol scale, and the yield obtained under batch conditions was not improved.¹⁶

Some diversification reactions were performed using products **2a** and **2h** (Scheme 3B). The treatment of **2a** with NaBH₄ afforded the 1,4-amino alcohol **3** in good yield by reduction of the imine moiety. The 1,4-amino ether **4** was obtained *via* Williamson etherification followed by the hydrolysis of the imine group, while an esterification and deprotection reaction with PPTS yielded 1,4-amino esters **5** and **6** from biotin and indomethacin, respectively. These transformations showed the synthetic utility of the 1,4-imino alcohol motifs **2** in the construction of more complex molecules.

Some mechanistic investigations were carried out to shed light on the reaction mechanism. The addition of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) under the standard conditions completely inhibited the reaction, resulting in the complete recovery of the starting material **1a**. Furthermore, the direct excitation of **1a** in the absence of the photocatalyst, using a purple Kessil lamp ($\lambda_{\text{max}} = 390$ nm), yielded the desired product **2a** in 30% yield. Both results ruled out the possibility of a redox process and indicated that this trans-

formation proceeded through an energy transfer event between the photocatalyst and substrate **1a**.¹⁶

In addition, dispersion corrected density functional theory (DFT) calculations were performed. Fig. 1 shows the mechanistic energetic profile of **2a** from **1a**. The excited state **1a*** (44.9 kcal mol⁻¹) can be accessed by the triple-triplet state 5CzBn* (58.2 kcal mol⁻¹). Then, the N–O homolytic cleavage happens from **1a*** to TS1* with a small energy barrier ($\Delta\Delta G_{\text{rel}}^{\ddagger} = 4.8$ kcal mol⁻¹), forming the persistent ambiphilic iminyl radical **B** and the transient O-centered radical **A**. The highly reactive alkoxy radical **C** ($\ddagger$ 64.5 kcal mol⁻¹ downhill in energy from **1a***) is generated after spontaneously extrusion of CO₂ and MeCN *via* TSA. Then, **C'** can undergo an irreversible 1,5-HAT event *via* TSC' to afford the transient δ -C(sp³)-centered radical **D** (downhill in energy by 14.5 kcal mol⁻¹ from **C'**). Afterward, **D** can undergo a selective radical–radical cross coupling with the iminyl radical **B** to generate the 1,4-amino alcohol **2a**. However, **D** can also follow a radical chain pathway to form **2a**, as suggested by the experimentally measured quantum yield value ($\Phi \approx 3$) and the lower relative concentration of the iminyl radical **B** *versus* the precursor **1a**. **D** upon addition to reagent **1a** *via* TSD-**1a** forms the radical intermedi-

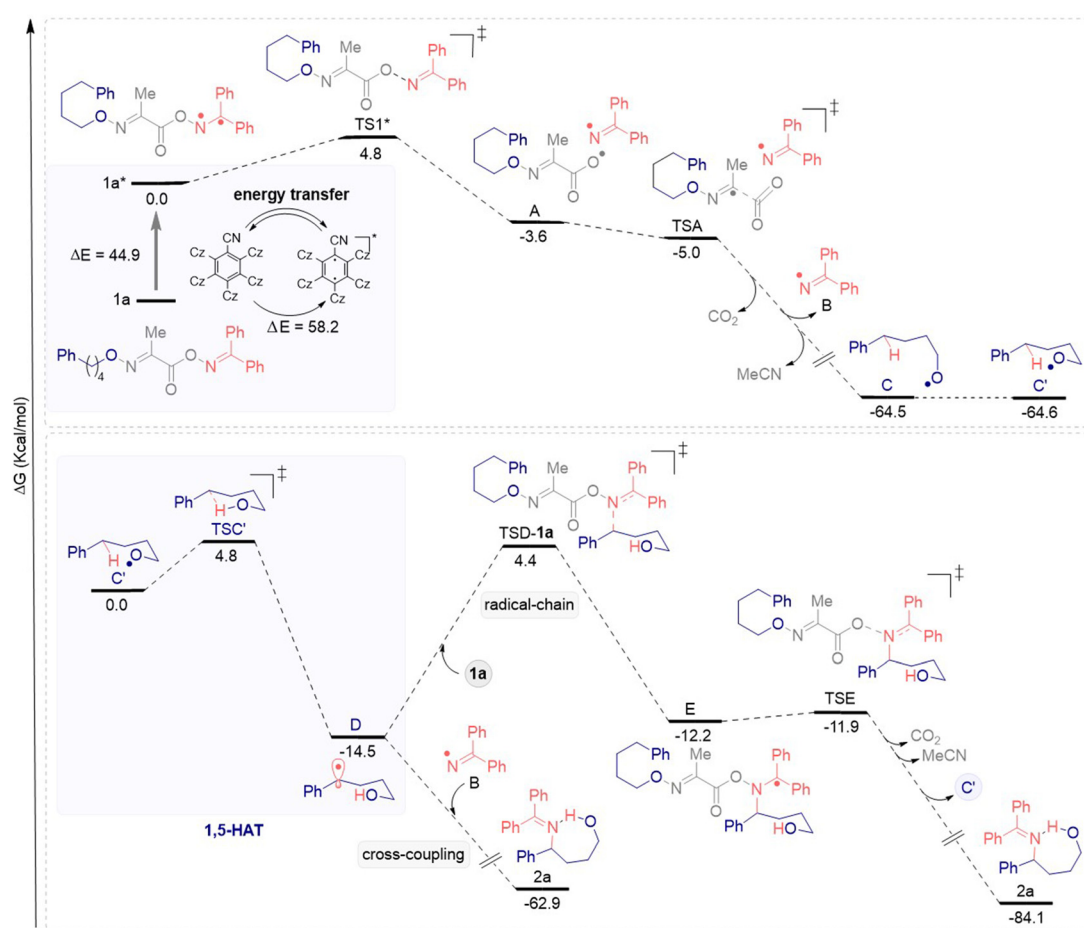


Fig. 1 Proposed mechanism supported by computational studies to transform **1a** into **2a**. Calculated free Gibbs energy (*G*) values at 298 K (kcal mol⁻¹) [CPCM(acetone) UB3LYP-D3/def2-svp].¹⁶



ate **E** ($\epsilon_{\text{rel}}^{\ddagger}$ 2.3 kcal mol⁻¹ uphill in energy from **D**). Finally, intermediate **E** affords the desired 1,4-amino alcohol **2a** via TSE (energy barrier of 0.3 kcal mol⁻¹) through the release of CO₂, MeCN and **C'**, regenerating the cycle. These findings are in agreement with previous reports similar to this transformation^{14,24} and with the results of the light on/off experiment.¹⁶

Conclusions

In summary, an operationally simple δ -insertion of protected amines into the skeleton of aliphatic alcohols was developed from bifunctional reagents. These reagents were designed to carry both radical partners, a transient alkoxy radical and a persistent iminyl radical formed through an energy transfer (EnT) photocatalytic process. This protocol was used in the synthesis of tetrahydrofuran **2t** and in the δ -amination of alkyl *N*-tosyl amines. The scale-up of this photoinduced transformation was conveniently realized via a continuous-flow system, maintaining reactivity and reducing reaction time compared to batch conditions. Furthermore, the synthetic potential of the constructed δ -imino alcohols was demonstrated through some derivatization reactions incorporating this motif into pharmaceuticals such as indomethacin. Although the photochemical quantum yield suggested a radical chain mechanism, its low value and computational studies do not entirely rule out the catalytic cycle pathway.

Author contributions

All authors have given approval to the final version of the manuscript.

Data availability

Experimental procedures and analytical data (NMR, MS and melting points) can be found in the ESI.† Copies of the NMR spectra are also provided.

Conflicts of interest

There are no conflicts to declare.

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References

- (a) Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards, L. I. Frye, O. L. Garry, M. N. Lavagnino, B. X. Li, Y. Liang, E. Mao, A. Millet, J. V. Oakley, N. L. Reed, H. A. Sakai, C. P. Seath and D. W. C. MacMillan, Metallaphotoredox: The Merger of Photoredox and Transition Metal Catalysis, *Chem. Rev.*, 2022, **122**, 1485–1542; (b) L. Candish, K. D. Collins, G. C. Cook, J. J. Douglas, A. Gómez-Suárez, A. Jolit and S. Keess, Photocatalysis in the Life Science Industry, *Chem. Rev.*, 2022, **122**, 2907–2980; (c) N. Holmberg-Douglas and D. A. Nicewicz, Photoredox-Catalyzed C–H Functionalization Reactions, *Chem. Rev.*, 2022, **122**, 1925–2016; (d) J. D. Bell and J. A. Murphy, 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; (e) N. A. Romero and D. A. Nicewicz, Organic Photoredox Catalysis, *Chem. Rev.*, 2016, **116**, 10075–10166.
- Selective δ -C(sp³)-H bond functionalization of alkyl alcohols relies on the formation of a stronger O–H bond (BDE $\approx$ 105 kcal mol⁻¹) versus an intramolecular 1,5-hydrogen atom transfer (HAT) of the weaker aliphatic C–H bond (BDE $\approx$ 98–102 kcal mol⁻¹) by the alkoxy radical. See: L. Capaldo, D. Ravelli and M. Fagnoni, Direct Photocatalyzed Hydrogen Atom Transfer (HAT) for Aliphatic C–H Bonds Elaboration, *Chem. Rev.*, 2022, **122**, 1875–1924.
- Selected reviews: (a) L. Chang, Q. An, L. Duan, K. Feng and Z. Zuo, Alkoxy Radicals See the Light: New Paradigms of Photochemical Synthesis, *Chem. Rev.*, 2022, **122**, 2429–2486; (b) W. Guo, Q. Wang and J. Zhu, Visible light photoredox-catalysed remote C–H functionalisation enabled by 1,5-hydrogen atom transfer (1,5-HAT), *Chem. Soc. Rev.*, 2021, **50**, 7359–7377; (c) E. Tsui, H. Wang and R. R. Knowles, Catalytic generation of alkoxy radicals from unfunctionalized alcohols, *Chem. Sci.*, 2020, **11**, 11124–11141.
- (a) Y. Li, J. Zhang, D. Li and Y. Chen, Metal-Free C(sp³)-H Allylation via Aryl Carboxyl Radicals Enabled by Donor–Acceptor Complex, *Org. Lett.*, 2018, **20**, 3296–3299; (b) C. Wang, K. Harms and E. Meggers, Catalytic Asymmetric Csp³-H Functionalization under Photoredox Conditions by Radical Translocation and Stereocontrolled Alkene Addition, *Angew. Chem.*, 2016, **128**, 13693–13696; (c) J. Zhang, Y. Li, F. Zhang, C. Hu and Y. Chen, Generation of Alkoxy Radicals by Photoredox Catalysis Enables Selective C(sp³)-H Functionalization under Mild Reaction Conditions, *Angew. Chem.*, 2016, **128**, 1904–1907.
- Some examples: (a) X. Bao, Q. Wang and J. Zhu, Remote C(sp³)-H Arylation and Vinylation of *N*-Alkoxy pyridinium



- Salts to δ -Aryl and δ -Vinyl Alcohols, *Chem. – Eur. J.*, 2019, **25**, 11630–11634; (b) X. Bao, Q. Wang and J. Zhu, Dual Photoredox/Copper Catalysis for the Remote C(sp³)-H Functionalization of Alcohols and Alkyl Halides by N-Alkoxyppyridinium Salts, *Angew. Chem., Int. Ed.*, 2019, **58**, 2139–2143; (c) I. Kim, B. Park, G. Kang, J. Kim, H. Jung, H. Lee, M. Baik and S. Hong, Visible-Light-Induced Pyridylation of Remote C(sp³)-H Bonds by Radical Translocation of N-Alkoxyppyridinium Salts, *Angew. Chem., Int. Ed.*, 2018, **57**, 15517–15522.
- 6 (a) A. N. Herron, D. Liu, G. Xia and J.-Q. Yu, δ -C-H Mono- and Dihalogenation of Alcohols, *J. Am. Chem. Soc.*, 2020, **142**, 2766–2770; (b) X.-L. Luo, S.-S. Li, Y.-S. Jiang, F. Liu, S.-H. Li and P.-J. Xia, Photocatalytic 1,2-Iminosulfonylation and Remote 1,6-Iminosulfonylation of Olefins, *Org. Lett.*, 2023, **25**, 1742–1747; (c) Y. Zheng, Z. Liao, Z. Xie, H. Chen, K. Chen, H. Xiang and H. Yang, Photochemical Alkene Trifluoromethylimination Enabled by Trifluoromethylsulfonylamide as a Bifunctional Reagent, *Org. Lett.*, 2023, **25**, 2129–2133.
- 7 (a) Z. Liu, Y. Pan, P. Zou, H. Huang and Y. Chen, Hypervalent Iodine Reagents Enable C-H Alkynylation with Iminophenylacetic Acids via Alkoxy Radicals, *Org. Lett.*, 2022, **24**, 5951–5956; (b) G. Li, X. Hu, G. He and G. Chen, Photoredox-mediated remote C(sp³)-H heteroarylation of free alcohols, *Chem. Sci.*, 2019, **10**, 688–693; (c) X. Wu, H. Zhang, N. Tang, Z. Wu, D. Wang, M. Ji, Y. Xu, M. Wang and C. Zhu, Metal-free alcohol-directed regioselective heteroarylation of remote unactivated C(sp³)-H bonds, *Nat. Commun.*, 2018, **9**, 3343; (d) D. S. Finis and D. A. Nicewicz, Alkoxy Radical Generation Mediated by Sulfoxide Cation Radicals for Alcohol-Directed Aliphatic C-H Functionalization, *J. Am. Chem. Soc.*, 2024, **146**, 16830–16837.
- 8 Some examples: (a) Z. Jue, Y. Huang, J. Qian and P. Hu, Visible Light-Induced Unactivated δ -C(sp³)-H Amination of Alcohols Catalyzed by Iron, *ChemSusChem*, 2022, **15**, e202201241; (b) A. Hu, J. Guo, H. Pan, H. Tang, Z. Gao and Z. Zuo, δ -Selective Functionalization of Alkanols Enabled by Visible-Light-Induced Ligand-to-Metal Charge Transfer, *J. Am. Chem. Soc.*, 2018, **140**, 1612–1616.
- 9 Some examples: (a) M. Wang, L. Huan and C. Zhu, Cyanohydrin-Mediated Cyanation of Remote Unactivated C(sp³)-H Bonds, *Org. Lett.*, 2019, **21**, 821–825; (b) X. Wu, M. Wang, L. Huan, D. Wang, J. Wang and C. Zhu, Tertiary-Alcohol-Directed Functionalization of Remote C(sp³)-H Bonds by Sequential Hydrogen Atom and Heteroaryl Migrations, *Angew. Chem., Int. Ed.*, 2018, **57**, 1640–1644.
- 10 Some reviews: (a) S. Dutta, J. E. Erchinger, F. Strieth-Kalthoff, R. Kleinmans and F. Glorius, Energy transfer photocatalysis: exciting modes of reactivity, *Chem. Soc. Rev.*, 2024, **53**, 1068–1089; (b) F. Strieth-Kalthoff, M. J. James, M. Teders, L. Pitzer and F. Glorius, Energy transfer catalysis mediated by visible light: principles, applications, directions, *Chem. Soc. Rev.*, 2018, **47**, 7190–7202.
- 11 T. Patra, M. Das, C. G. Daniliuc and F. Glorius, Metal-free photosensitized oxyimination of unactivated alkenes with bifunctional oxime carbonates, *Nat. Catal.*, 2021, **4**, 54–61.
- 12 S. Lai, B. Wei, J. Wang, W. Yu and B. Han, Photocatalytic Anti-Markovnikov Radical Hydro- and Aminoxyoxygenation of Unactivated Alkenes Tuned by Ketoxime Carbonates, *Angew. Chem., Int. Ed.*, 2021, **60**, 21997–22003.
- 13 J. Li, Y. Yuan, X. Bao, T. Sang, J. Yang and C. Huo, Visible-Light-Induced Intermolecular Oxyimination of Alkenes, *Org. Lett.*, 2021, **23**, 3712–3717.
- 14 R. Laskar, S. Dutta, J. C. Spies, P. Mukherjee, A. Rentería-Gómez, R. E. Thuelemann, C. G. Daniliuc, O. Gutierrez and F. Glorius, γ -Amino Alcohols via Energy Transfer Enabled Brook Rearrangement, *J. Am. Chem. Soc.*, 2024, **146**, 10899–10907.
- 15 Some examples: (a) D. J. Diaz, K.-G. Hylton and L. McElwee-White, Selective Catalytic Oxidative Carbonylation of Amino Alcohols to Ureas, *J. Org. Chem.*, 2006, **71**, 734–738; (b) D. Scarpi, F. Lo Galbo and A. Guarna, Synthesis of a new 1,4-aminoalcohol and its use as catalyst in the enantioselective addition of organozinc to aldehydes, *Tetrahedron: Asymmetry*, 2006, **17**, 1409–1414; (c) J.-C. Zhong, M.-G. Wang, H.-C. Guo, M.-M. Yin, Q.-H. Bian and M. Wang, Design and Synthesis of 1,4-Amino Alcohol Ligands with a Chiral Cyclopropane Backbone for Asymmetric Diethylzinc Addition to Aromatic Aldehydes, *Synlett*, 2006, 1667–1670; (d) M. Sugiura, H. Hagio, R. Hirabayashi and S. Kobayashi, Lewis Acid-Catalyzed Ring-Opening Reactions of Semicyclic N, O-Acetals Possessing an Exocyclic Nitrogen Atom: Mechanistic Aspect and Application to Piperidine Alkaloid Synthesis, *J. Am. Chem. Soc.*, 2001, **123**, 12510–12517; (e) N. Hanyu, T. Mino, M. Sakamoto and T. Fujita, Facile synthesis of amino bicyclo[2.2.1]heptyl alcohol and its application for enantioselective additions of diethylzinc to aldehydes, *Tetrahedron Lett.*, 2000, **41**, 4587–4590.
- 16 See the ESI† for further details.
- 17 Information obtained from ChemoSapiens chemical suppliers' platform.
- 18 1,4-Imino alcohol **2g** was formed in 35% ¹H NMR yield; the crude mixture was analysed using trimethoxybenzene as the internal standard.
- 19 Y. Kim, K. Lee, G. R. Mathi, I. Kimab and S. Hong, Visible-light-induced cascade radical ring-closure and pyridylation for the synthesis of tetrahydrofurans, *Green Chem.*, 2019, **21**, 2082–2087.
- 20 Some reviews: (a) X. Teng, T. Yu, J. Shi, H. Huang, R. Wang, W. Peng, K. Sun, S. Yang and X. Wang, Recent Advances in the Functionalization of Remote C-H Bonds by Hofmann-Löffler-Freytag-type Reactions, *Adv. Synth. Catal.*, 2023, **365**, 3211–3226; (b) N. Goswami and D. Maiti, An Update on Distal C(sp³)-H Functionalization Involving 1,5-HAT Emerging from Nitrogen Radicals, *Isr. J. Chem.*, 2020, **60**, 303–312; (c) C. Pratley, S. Fenner and J. A. Murphy, Nitrogen-Centered Radicals in Functionalization of sp²



- Systems: Generation, Reactivity, and Applications in Synthesis, *Chem. Rev.*, 2022, **122**, 8181–8260; (d) M. D. Kärkäs, Photochemical Generation of Nitrogen-Centered Amidyl, Hydrazonyl, and Imidyl Radicals: Methodology Developments and Catalytic Applications, *ACS Catal.*, 2017, **7**, 4999–5022.
- 21 (a) S.-P. Hu, C.-H. Gao, T.-M. Liu, B.-Y. Miao, H.-C. Wang, W. Yu and B. Han, Integrating Olefin Carboamination and Hofmann-Löffler-Freytag Reaction by Radical Deconstruction of Hydrazonyl N–N Bond, *Angew. Chem., Int. Ed.*, 2024, **63**, e202400168; (b) S.-S. Li, Y.-S. Jiang, X.-L. Luo, C.-X. Pan and P.-J. Xia, Photoinduced Remote C(sp³)-H Imination Enabled by Vinyl Radical-Mediated 1,5-Hydrogen Atom Transfer, *Org. Lett.*, 2023, **9**, 1595–1599; (c) Q. Guo, X. Ren and Z. Lu, Controllable Intramolecular Unactivated C(sp³)-H Amination and Oxygenation of Carbamates, *Org. Lett.*, 2019, **21**(4), 880–884; (d) X. Ren, Q. Guo, J. Chen, H. Xie, Q. Xu and Z. Lu, Visible-Light Promoted Distereodivergent Intramolecular Oxyamidation of Alkenes, *Chem. – Eur. J.*, 2016, **22**, 18695–18699.
- 22 A. N. Herron, C. Hsu and J.-Q. Yu, δ-C–H Halogenation Reactions Enabled by a Nitrogen-Centered Radical Precursor, *Org. Lett.*, 2022, **24**, 3652–3656.
- 23 R. I. Rodríguez, M. Sicignano, M. J. García, R. G. Enríquez, S. Cabrera and J. Alemán, Taming photocatalysis in flow: easy and speedy preparation of α-aminoamide derivatives, *Green Chem.*, 2022, **24**, 6613–6618.
- 24 J. Majhi, R. K. Dhungana, Á. Rentería-Gómez, M. Sharique, L. Li, W. Dong, O. Gutierrez and G. A. Molander, Metal-Free Photochemical Imino-Alkylation of Alkenes with Bifunctional Oxime Esters, *J. Am. Chem. Soc.*, 2022, **144**, 15871–15878.

