

ChemComm

Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: A. Das, L. Kloene, S. Chandra, R. M. Koenigs and S. Murarka, *Chem. Commun.*, 2026, DOI: 10.1039/D6CC01889K.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

COMMUNICATION

Visible-Light Palladium Catalysis for Alkylated and Difluoroalkylated Pyrazolones

Anindya Das^a, Lennard Kloene,^b Sneha Chandra,^a Rene M. Koenigs^{*b}, and Sandip Murarka^{*a}Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

We report a photoinduced palladium-catalyzed protocol for the synthesis of biologically relevant alkylated and difluoroalkylated pyrazolones via a radical cascade between *N'*-arylidene-*N*-acryloylphenylhydrazides and unactivated alkyl and difluoroalkyl halides. Mechanistic studies support a Pd-mediated radical generation and capture pathway, accommodating both electrophilic and nucleophilic carbon-centered radicals. The protocol exhibits broad substrate scope, good functional group tolerance, and applicability to complex drug and natural product-derived fragments, providing a practical platform for late-stage molecular diversification.

In the context of drug discovery, incorporating three-dimensional aliphatic frameworks into heterocyclic cores is highly desirable, as it often enhances molecular diversity and improves pharmacokinetic properties.¹ Given the pervasiveness of Csp³-rich drug molecules in pharmaceutical research, the development of facile strategies for the efficient synthesis of alkylated molecular architectures is highly essential. Among them, radical cascades have attracted considerable attention as step-economic strategies for the construction of alkylated heterocycles. Although numerous alkylating surrogates have been reported in the literature,² most require preactivation or synthesis, generating substantial amounts of waste. Among alkyl sources, unactivated, commercially available alkyl halides are attractive precursors due to their abundance and structural versatility.³ However, traditional transition-metal-catalyzed reactions with alkyl halides are often hindered by slow oxidative addition and competing β -hydride elimination pathways (Scheme 1A).⁴ Recent advances in excited-state palladium catalysis have provided elegant solutions to these challenges. Visible-light-mediated palladium catalysis has emerged as a powerful and sustainable platform for enabling transformations that are challenging under conventional thermal conditions.⁵ In such systems, the palladium catalyst serves a dual function, acting both as a photosensitizer that harvests photon energy and as a transition-metal catalyst that mediates bond-forming and bond-cleaving events, thereby eliminating the need for an exogenous photosensitizer. In such systems, oxidative addition proceeds via a

single-electron transfer (SET) pathway, generating hybrid Pd–radical intermediates that enable various radical transformations under mild conditions.⁶ Computational studies have further supported that these inner-sphere SET processes proceed with low activation barriers, highlighting their mechanistic efficiency (Scheme 1B).⁷

Meanwhile, 2-pyrazoline-5-one derivatives represent an important class of nitrogen-containing heterocycles with broad pharmacological significance, including analgesic, antipyretic, antitumor, antibacterial, and antidepressant activities. Beyond their biological importance, pyrazoline-5-ones serve as versatile building blocks for the synthesis of functionalized pyrazolones and pyrazoles (Scheme 1C).⁸ Consequently, the development of efficient, modular synthetic routes for their structural diversification remains an active area of research. In 2024, our group reported a visible-light-driven radical cascade cyclization strategy that enabled the construction of functionalized pyrazolones via a novel *N'*-arylidene-*N*-acryloyltosylhydrazide scaffold.⁹ Building on this concept, other groups have subsequently developed photo-induced radical annulation methods employing related frameworks.¹⁰ Despite notable progress, most reported methods either depend on preactivated redox reagents bearing bulky leaving groups, which diminish atom economy and require additional preparation steps, or are restricted to electrophilic radical precursors, thereby limiting their overall practicality.

To address these limitations, we envisioned a cost-effective photoinduced Pd-catalyzed strategy employing readily available alkyl halides and *N'*-arylidene-*N*-acryloylphenylhydrazides for the direct synthesis of alkylated pyrazoline-5-ones. Furthermore, given the pharmacological relevance of *gem*-difluoroalkyl motifs as bioisosteres that can enhance lipophilicity, metabolic stability, and overall drug-like properties, we sought to extend this strategy to incorporate such groups.¹¹ As part of our program on photoinduced alkylative radical cascades^{9a, 12} and palladium photocatalysis,^{3, 6c, 13} herein, we report a visible-light-driven Pd-catalyzed (difluoro)alkylation/annulation involving *N'*-arylidene-*N*-acryloylphenylhydrazides, providing an efficient and versatile route to diversely functionalized pyrazolones.

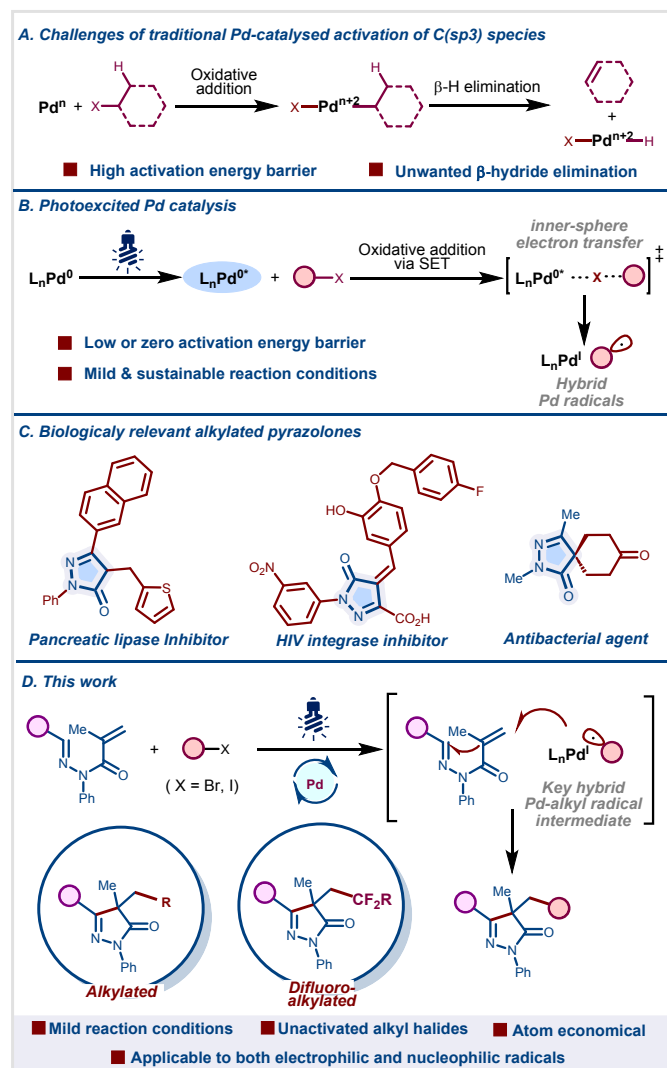
^a Department of Chemistry, Indian Institute of Technology Jodhpur, Karwar-342037, Rajasthan, India.

^b University of Bayreuth, D-52074 Bayreuth, Germany

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Electronic Supplementary Information (ESI) available: [details of any supplementary





Scheme 1 (A) Challenges of Traditional Pd-Catalyzed activation of C(sp³) species. (B) Photoexcited Pd Catalysis. (C) Biologically Relevant Alkylated Pyrazolones. (D) This Work: Pd Photocatalysis to Synthesize Functionalized Pyrazolones.

To realize the feasibility of the conceived approach, (*E*)-*N*-benzylidene-*N*-phenylmethacrylohydrazone (**1a**) and 1-Boc-4-bromopiperidine (**2a**) were taken as model substrates and optimization studies were carried out (Table 1, see Table S1 in SI for complete optimization studies). We were pleased to observe that the reaction between **1a** (1.0 equiv.), **2a** (1.5 equiv.), in the presence of Pd(PPh₃)₂Cl₂ (5.0 mol%) as a catalyst, PPh₃ (1.0 equiv.) as a ligand and Cs₂CO₃ (2.0 equiv.) as a base in toluene (1 mL) provided **3aa** in 78% yield after irradiation with blue LEDs (456 nm) for 12 h (Table 1, entry 1). Screening of various Pd catalysts did not improve the yield (entry 2). Altering the ligand loading (6 mol%) or replacing PPh₃ with other ligands (6 mol%) such as Xantphos, and RuPhos proved ineffective (entry 3). Evaluation of other bases, both organic and inorganic (Et₃N, K₃PO₄, Na₂CO₃), resulted in diminished yields (entry 4). Changing the solvent either reduced the yield or completely suppressed product formation (entry 5). Replacing the alkyl bromide with its iodide congener did not improve reaction efficiency (entry 6). Control experiments confirmed that the catalyst, base, and visible light are all essential for the transformation (entry 7).

Table 1 Optimization of the reaction conditions^a

View Article Online
DOI: 10.1039/D6CC01889K

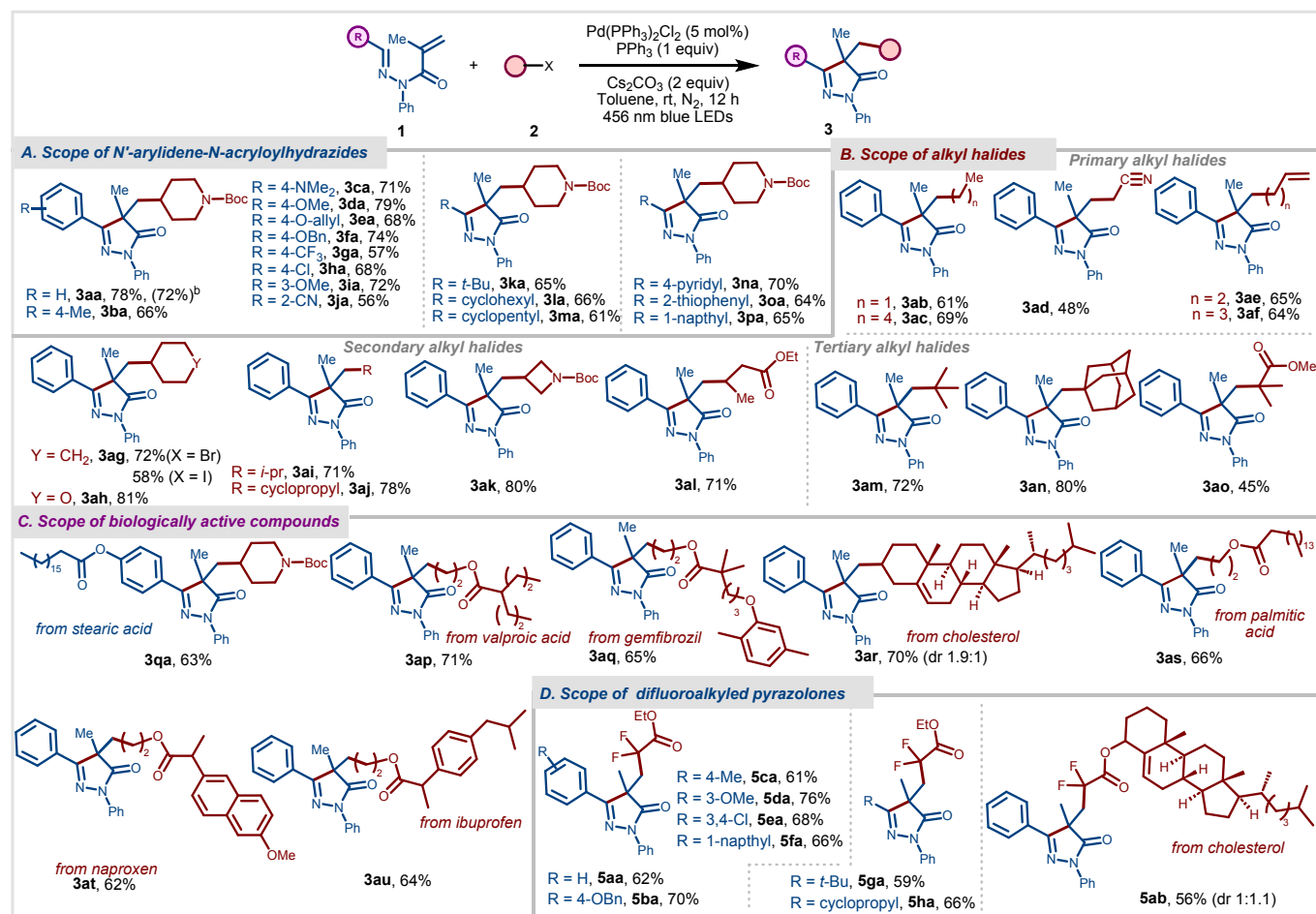
entry	deviation from standard condition	yield (%) ^b
1	none	78
2	Pd-Cat: Pd(PPh ₃) ₄ , Pd(OAc) ₂ , Pd(Ptol ₃) ₂ Cl ₂	67, 65, N.D.
3	Ligand (6 mol%): Xantphos, RuPhos, PPh ₃	36, N.D., 31
4	Base: K ₃ PO ₄ , Na ₂ CO ₃ , Et ₃ N	34, 21, N.D.
5	Solvent: ACN, DMF, Benzene	41, 28, 71
6	Alkyl iodide instead of alkyl bromide	58
7	No Pd-Cat, No Base, No Irradiation	N.D., N.D., N.D.

^aReaction conditions: **1a** (0.1 mmol, 1 equiv), **2a** (1.5 equiv), Pd(PPh₃)₂Cl₂ (5 mol%), PPh₃ (1.0 equiv) and Cs₂CO₃ (2 equiv) in toluene (1 mL), irradiated at 456 nm blue LEDs at room temperature under N₂ atmosphere for 12 h. ^bIsolated yields. N.D. = Not Detected.

With the optimized reaction conditions in hand, we next explored the substrate scope of the cascade manifold by reacting a series of *N*-acyl aldehyde hydrazones (**1**) with alkyl bromide **2a** (Scheme 2A). A diverse range of aryl aldehyde-derived *N*-methacryloyl hydrazones bearing electron-donating (Me, NMe₂, OMe, OAllyl, OBn) and electron-withdrawing (CF₃, Cl) substituents at the *para*-position of the aromatic ring participated smoothly in the reaction, affording the corresponding alkylated pyrazolones (**3ba-3ha**) in moderate to good yields (57-79%). Substituents at the *meta*- and sterically demanding *ortho*-positions were also well tolerated, furnishing products **3ia** and **3ja** in 72% and 56% yields, respectively. The methodology further accommodated hydrazones derived from structurally diverse aliphatic aldehydes, including pivaldehyde, cyclopentane- and cyclohexanecarbaldehyde, delivering the corresponding products (**3ka-3ma**) in 61-65% yields. Moreover, heteroaromatic substrates such as pyridine and thiophene were well tolerated, affording **3na** and **3oa** in 70% and 64% yields, respectively. Notably, polycyclic aromatic substrates, such as naphthyl derivatives, were also compatible, delivering the corresponding yielding **3pa** in 65% yield. Next, the generality of the protocol with respect to alkyl halides (**2**) was examined by reacting with **1a** under the optimized conditions (Scheme 2B). Primary alkyl bromides bearing long alkyl chains or functional groups, such as nitriles and alkenes, were compatible, affording desired products (**3ab-3af**) in appreciable yields (48-69%). Furthermore, both cyclic and acyclic secondary alkyl halides underwent smooth transformation, delivering respective products (**3ag-3al**) in good to excellent yields (58-81%). Notably, heterocyclic secondary alkyl bromides provided the best results, further underscoring the broad applicability and efficiency of the method. A range of tertiary such as *tert*-butyl, 1-adamantyl, and methyl 2-bromo-2-methylpropanoate, readily participated in the reaction to furnish the corresponding products (**3am-3ao**) in 45-80% yields, demonstrating that the reactive ester functionality was well tolerated. Furthermore, the reaction was successfully extended to densely functionalized *N*-methacryloyl aldehyde hydrazones derived from complex molecules, such as stearic acid, affording **3qa** in 63% yield. Likewise, alkyl halides functionalized with valproic acid, gemfibrozil, cholesterol, palmitic acid, naproxen and ibuprofen moieties underwent smooth transformation to furnish products **3ap-3au** in 64-71% yields (Scheme 2C).



COMMUNICATION



Scheme 2. Reaction conditions: **1a** (0.25 mmol, 1 equiv), **2a** (1.5 equiv), Pd(PPh₃)₂Cl₂ (5 mol%), PPh₃ (1 equiv), and toluene (2.5 mL) under nitrogen atmosphere using blue LEDs (456 nm) for 12 h. ^bGram-scale synthesis using optimized conditions.

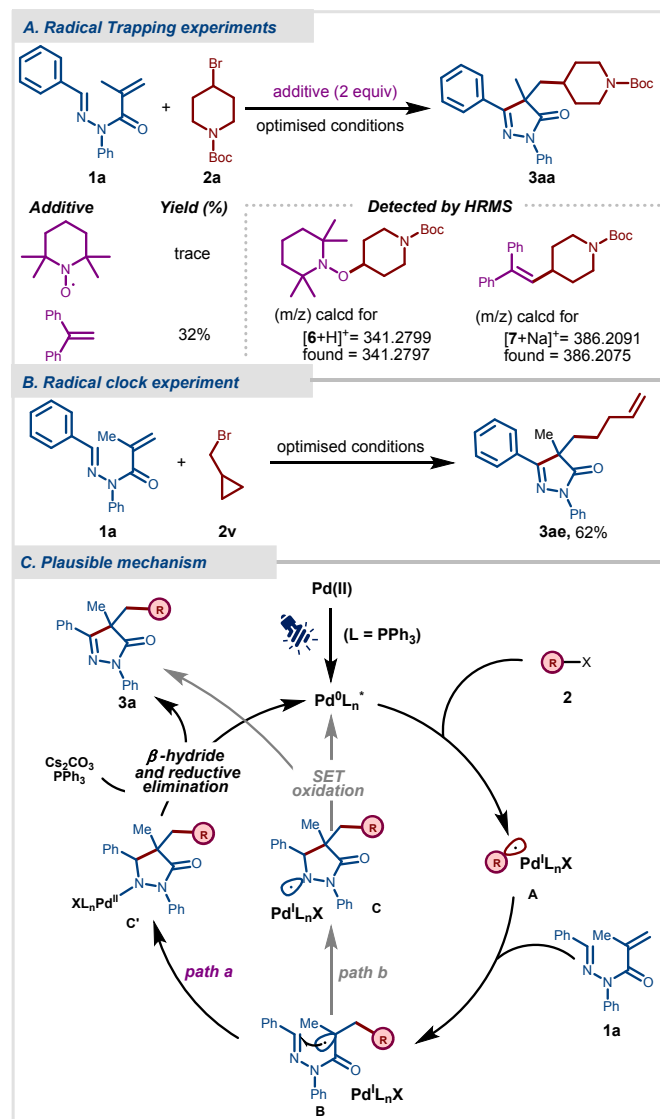
These results further highlight the robustness, scalability, and excellent functional group tolerance of the developed methodology. Encouraged by the success of the alkylation process, we sought to further expand the synthetic utility of the developed protocol. Considering the beneficial role of *gem*-difluoroalkyl groups in enhancing the physicochemical and pharmacokinetic profiles of bioactive molecules, we envisioned a divergent extension of this strategy toward the synthesis of *gem*-difluoroalkylated 2-pyrazoline-5-ones. Gratifyingly, the optimized reaction conditions could be directly applied to achieve this transformation, affording a diverse array of *gem*-difluoroalkylated pyrazolones with substitution either at the aldehyde or alkyl halide terminus of the scaffold (**5aa–5ha** and **5ab**) (scheme 2D). In these reactions, the corresponding difluoroalkyl bromides (**4**) served efficiently as radical precursors, delivering the desired products in good yields (56–76%). The practicality of the method was demonstrated on a 1 g scale, where **1a** reacted with **2a** to afford **3aa** in 72% yield (Scheme 2A). These findings highlight the broad adaptability, scalability and versatility of the method.

Radical-trapping experiments revealed that the reaction was completely or partially suppressed in the presence of TEMPO (trace) and 1,1-diphenylethylene (32% yield), and corresponding adducts (**6** and **7**) were detected by HRMS (Scheme 3A). Additionally, a radical-clock experiment using **2r** yielded the ring-opened product **3ae** in 62%, supporting a radical-mediated pathway (Scheme 3B). The light-dark experiment, combined with quantum yield ($\Phi = 0.212$) measurements, indicated the necessity of continuous irradiation and ruled out the possibility of a radical chain mechanism (See SI, fig. S2).

Based on control experiments and documented literature,^{6c–e} a plausible mechanism involving an alkyl radical palladium hybrid species is shown in (Scheme 3C).^{6b, 6d} Initially Single electron reduction of alkyl-X (X = Br, I) by excited-state Pd(0) affords alkyl-Pd(I)-X radical hybrid species **A** under visible light irradiation. The addition of the nucleophilic alkyl radical to the activated double bond of the *N*-acryloyl hydrazone **1a** delivers the carbon-centred radical intermediate **B**, which subsequently undergoes regioselective intramolecular 5-*endo-trig* cyclization,¹⁴ leading to intermediate **C** or



C'. Intermediate **C** furnishes the product via β -hydride elimination followed by reductive elimination (*path a*), while intermediate **C'** undergoes single-electron oxidation followed by base-assisted deprotonation to furnish **3** (*path b*). In both pathways, the reduced Pd(0) species is regenerated, thereby completing the photoredox catalytic cycle. Notably, PPh₃ serves a dual role in the catalytic cycle, both as a ligand as well as a reductant to regenerate the active Pd species from Pd(II).^{6k}



Scheme 3 (A) Radical trapping experiments. (B) Radical clock experiment. (C) Plausible mechanism.

In summary, we have disclosed a visible-light-mediated, excited-state palladium-catalyzed radical cascade enabling the synthesis of alkylated and difluoroalkylated 2-pyrazoline-5-ones from unactivated alkyl halides and *N*-acryloyl aldehyde hydrazones in good to excellent yields. The reaction accommodates a broad array of diverse hydrazones and primary, secondary, tertiary, and sterically hindered alkyl halides as reacting partners under mild conditions, demonstrating high tolerance to various functional groups. This method is robust, scalable, and compatible with densely functionalized substrates derived from natural products and pharmaceuticals. Detailed mechanistic studies support a hybrid alkyl-Pd radical pathway and confirm the proposed mechanism.

SM acknowledges ANRF [CRG/2022/000470] for funding and DST-FIST [SR/FST/CS-II/2019/119(C)] for the HRMS facility at IIT Bombay. RMK thanks the German Science Foundation (Grant no: KO5659/6-1) for financial support. AD, SC thanks UGC for the fellowship.

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.

Notes and references

- (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752-6756; (b) D.-H. Liu, P. M. Pflüger, A. Outlaw, L. Lückemeier, F. Zhang, C. Regan, H. Rashidi Nodeh, T. Cernak, J. Ma and F. Glorius, *J. Am. Chem. Soc.*, 2024, **146**, 11866-11875; (c) W. F. Zhu, C. Empel, S. Pelliccia, R. M. Koenigs, E. Proschak and V. Hernandez-Olmos, *J. Med. Chem.*, 2024, **67**, 4322-4345.
- (a) C.-R. Wang, W.-Y. Zhang, C. Yu, Y. Li and J.-H. Li, *Chinese Journal of Chemistry*, 2025, **43**, 3676-3698; (b) S. K. Parida, T. Mandal, S. Das, S. K. Hota, S. De Sarkar and S. Murarka, *ACS Catal.*, 2021, **11**, 1640-1683.
- S. Senapati, S. Kumar Hota, L. Kloene, C. Empel, S. Murarka and R. M. Koenigs, *Angew. Chem. Int. Ed.*, 2025, **64**, e202417107.
- (a) I. D. Hills, M. R. Netherton and G. C. Fu, *Angew. Chem. Int. Ed.*, 2003, **42**, 5749-5752; (b) A. Ariafard and Z. Lin, *Organometallics*, 2006, **25**, 4030-4033; (c) A. Kaga and S. Chiba, *ACS Catal.*, 2017, **7**, 4697-4706.
- (a) S. Sarkar, K. P. S. Cheung and V. Gevorgyan, *Angew. Chem. Int. Ed.*, 2024, **63**, e202311972; (b) K. P. S. Cheung and V. Gevorgyan, *Acc. Chem. Res.*, 2025, **58**, 861-876.
- (a) G. C. Upreti, T. Singh, K. Khanna and A. Singh, *J. Org. Chem.*, 2023, **88**, 4422-4433; (b) J. Du, X. Wang, H. Wang, J. Wei, X. Huang, J. Song and J. Zhang, *Org. Lett.*, 2021, **23**, 5631-5635; (c) H. Fang, C. Empel, I. Atodiresei and R. M. Koenigs, *ACS Catal.*, 2023, **13**, 6445-6451; (d) K. Muralirajan, R. Kancherla, A. Gimn Khan and M. Rueping, *Org. Lett.*, 2021, **23**, 6905-6910; (e) W.-J. Zhou, G.-M. Cao, G. Shen, X.-Y. Zhu, Y.-Y. Gui, J.-H. Ye, L. Sun, L.-L. Liao, J. Li and D.-G. Yu, *Angew. Chem. Int. Ed.*, 2017, **56**, 15683-15687; (f) M. Parasram, P. Chuentragool, Y. Wang, Y. Shi and V. Gevorgyan, *J. Am. Chem. Soc.*, 2017, **139**, 14857-14860; (g) M. Parasram, P. Chuentragool, D. Sarkar and V. Gevorgyan, *J. Am. Chem. Soc.*, 2016, **138**, 6340-6343; (h) N. Kvasovs and V. Gevorgyan, *Org. Lett.*, 2022, **24**, 4176-4181; (i) D. Kurandina, M. Parasram and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2017, **56**, 14212-14216; (j) N. Kvasovs, V. Iziumchenko, V. Palchykov and V. Gevorgyan, *ACS Catal.*, 2021, **11**, 3749-3754; (k) S. Yang, H. Hu, J.-h. Li and M. Chen, *ACS Catal.*, 2023, **13**, 15652-15662.
- (a) B. Zhao, R. Shang, G.-Z. Wang, S. Wang, H. Chen and Y. Fu, *ACS Catal.*, 2020, **10**, 1334-1343; (b) R. Kancherla, K. Muralirajan, B. Maity, C. Zhu, P. E. Krach, L. Cavallo and M. Rueping, *Angew. Chem. Int. Ed.*, 2019, **58**, 3412-3416; (c) C. Pei, Z. Yang and R. M. Koenigs, *Tetrahedron*, 2022, **123**, 132939.



8. (a) V. Hadi, Y.-H. Koh, T. W. Sanchez, D. Barrios, N. Neamati and K. W. Jung, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6854-6857; (b) X. Sheng, K. Hua, C. Yang, X. Wang, H. Ji, J. Xu, Z. Huang and Y. Zhang, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 3535-3540; (c) J. Zhang, Y. Yang, X.-K. Qian, P.-F. Song, Y.-S. Zhao, X.-Q. Guan, L.-W. Zou, X. Bao and H. Wang, *ChemMedChem*, 2021, **16**, 1600-1604; (d) Z. Zhao, X. Dai, C. Li, X. Wang, J. Tian, Y. Feng, J. Xie, C. Ma, Z. Nie, P. Fan, M. Qian, X. He, S. Wu, Y. Zhang and X. Zheng, *Eur. J. Med. Chem.*, 2020, **186**, 111893; (e) B. Borah, K. D. Dwivedi and L. R. Chowhan, *Arkivoc*, 2021, **2021**, 273-328.
9. (a) S. P. Panda, R. Dash, S. K. Hota and S. Murarka, *Org. Lett.*, 2024, **26**, 3667-3672; (b) K. R. Thombare, S. K. Parida, P. Meher and S. Murarka, *Chem. Commun.*, 2024, **60**, 13907-13910.
10. (a) S. Yu, Y. Cheng, C. Pan and J.-T. Yu, *Chem. Commun.*, 2025, **61**, 1196-1199; (b) C. Pan, Y. Gong and M. Zeng, *J. Org. Chem.*, 2025, **90**, 9457-9467; (c) C.-H. Liu, Z.-W. Zhang, Z.-J. Zhao, J. Jiang, Z. Yang, Z.-L. Wang and W.-M. He, *J. Org. Chem.*, 2025, **90**, 11982-11989; (d) Y. Xia, W. Xu, X. Wu, T. Yin, S. Wu, Z. Chen, B. Wang, Y. Zhang and C. Liu, *J. Org. Chem.*, 2025, **90**, 14429-14438; (e) Y. Zeng, Q. Yan, L. Tu, Z. Zhang, L. Li and Z. Li, *Chem. Commun.*, 2025, **61**, 16408-16411; (f) E. F. Pissinati, M. Azizzade, T. Opatz and M. W. Paixão, *Adv. Synth. Catal.*, 2025, **367**, e70118.
11. (a) C. Zhang, K. Yan, C. Fu, H. Peng, C. J. Hawker and A. K. Whittaker, *Chem. Rev.*, 2022, **122**, 167-208; (b) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432-2506; (c) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529-2591; (d) Z. Feng, Y.-L. Xiao and X. Zhang, *Acc. Chem. Res.*, 2018, **51**, 2264-2278.
12. (a) S. K. Hota, S. P. Panda, S. Das, S. K. Mahapatra, L. Roy, S. De Sarkar and S. Murarka, *J. Org. Chem.*, 2023, **88**, 2543-2549; (b) R. Dash, K. R. Thombare, A. Das and S. Murarka, *Chem. Commun.*, 2025, **61**, 17368-17371.
13. S. Senapati, S. Chandra, L. Kloene, C. Poehner, C. Empel, S. Murarka and R. M. Koenigs, *JACS Au*, 2026, **6**, 1249-1255.
14. C. Chatgililoglu, C. Ferreri, M. Guerra, V. Timokhin, G. Froudakis and T. Gimisis, *J. Am. Chem. Soc.*, 2002, **124**, 10765-10772.

View Article Online
DOI: 10.1039/D6CC01889K



View Article Online
DOI: 10.1039/D6CC01889K

The data supporting this article have been included as part of the Supplementary Information.

