


 Cite this: *Chem. Commun.*, 2024, 60, 6268

 Received 18th April 2024,
 Accepted 22nd May 2024

DOI: 10.1039/d4cc01837k

rsc.li/chemcomm

Direct C–H alkylation of 3,4-dihydroquinoline-2-ones with *N*-(acyloxy)phthalimides via radical–radical cross coupling†

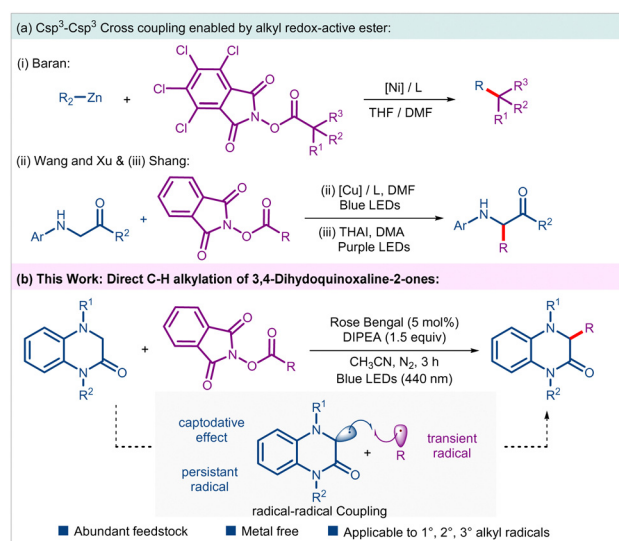
 Sudhir Kumar Hota, Gulshan Singh and Sandip Murarka *

We present an organophotoredox-catalyzed direct Csp³–H alkylation of 3,4-dihydroquinoline-2-ones employing *N*-(acyloxy)phthalimides to provide corresponding products in good yields. A broad spectrum of NHPI esters (1°, 2°, 3°, and sterically encumbered) participates in the photoinduced alkylation of a variety of 3,4-dihydroquinoline-2-ones. In general, mild conditions, broad scope with good functional group tolerance, and scalability are the salient features of this direct alkylation process.

The C–C bond forming reactions have revolutionized organic synthesis, particularly in pharmaceutical industry and materials science. To improve the prospect of clinical success, there is a growing demand in medicinal chemistry to synthesize sp³-enriched drug candidates.¹ However, despite substantial progress, Csp³–Csp³ coupling remains a significant challenge and has attracted attention of numerous synthetic chemists.² In this regard, *N*-(acyloxy)phthalimides (NHPI esters) that can readily be prepared from feedstock carboxylic acids have emerged as a surrogate of alkyl halides in a variety of radical cross-couplings (RCC) under thermal, photochemical and electrochemical conditions.³ In 2016, the Baran group documented a nickel-catalyzed alkyl–alkyl cross coupling between NHPI esters and alkyl zinc reagents under non-photoinduced conditions (Scheme 1a(i)).⁴ The last decade has witnessed revolutionary impact of photoinduced synthetic transformations in the advancement of organic synthesis and catalysis.⁵ Accordingly, several photoinduced approaches involving NHPI esters have been developed for the generation and subsequent Giese-type addition of resulting alkyl radicals on a variety of activated/unactivated alkenes leading to the construction of alkyl–alkyl bonds.^{3b} Nevertheless, examples of Csp³–Csp³ couplings through direct alkylation of Csp³–H bonds with alkyl NHPI esters are scarcely explored.⁶ Noteworthy examples include, Wang, Xu, and coworkers visible-light-induced Cu-catalyzed Csp³–H alkylation

of glycines and peptides, and Shang's photoinduced ammonium iodide-catalyzed C–H alkylation of glycines (Scheme 1a(ii) and (iii)).^{6a,d} Additionally, Cong and Zhang group in their independent reports documented alkylation of benzylic Csp³–H bonds of *N*-aryl tetrahydroisoquinolines with NHPI esters using either dye-sensitized semiconductor or through electron donor–acceptor (EDA) approach, respectively.^{6b,c} Considering such limited examples, it is of utmost importance to develop novel and sustainable methods enabling Csp³–H functionalizations on a variety of other important substrate classes using NHPI esters as alkyl progenitors.

3,4-Dihydroquinoline-2-ones are a unique class of nitrogen-containing heterocycles that have garnered significant interest from synthetic organic chemists owing to their rich medicinal properties. Compounds embedded with such motifs have shown antiviral, anti-inflammatory, anticancer and other pharmacological properties.⁷ Accordingly, direct C–H functionalization of this class of compounds enabling tapping of



Scheme 1 Csp³–Csp³ cross coupling of alkyl *N*-(acyloxy)phthalimides and proposed work.

Department of Chemistry, Indian Institute of Technology Jodhpur, Karwar-342037, Rajasthan, India. E-mail: sandipmurarka@iitj.ac.in

 † Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4cc01837k>

unchartered territory of chemical space have been explored.⁸ To the best of our knowledge, Csp³-H functionalization of such motifs with an unactivated alkyl group leading to direct Csp³-Csp³ coupling has not been realized till date. These facts inspired us to examine the feasibility of an alkyl-alkyl cross coupling between 3,4-dihydroquinoxalin-2-ones and alkyl NHPI esters under mild photoinduced conditions. In this envisaged process, the transient alkyl radical generated through reductive disintegration of alkyl NHPI esters should undergo radical-radical coupling with the α -amino radical generated from 3,4-dihydroquinoxalin-2-ones under suitable conditions (Scheme 1b). Notably, heteroselectivity in such diffusion-controlled radical-radical couplings is steered by a kinetic phenomenon called persistent radical effect.⁹ Nevertheless, such an intriguing direct Csp³-H functionalization strategy allowing alkyl-alkyl coupling would be efficient and rewarding from the perspective of sustainable synthesis, especially if carried out under organophotoredox-catalyzed conditions. Accordingly, as part of our program on the photoinduced synthetic transformations involving NHPI esters,¹⁰ we report an organophotoredox-catalyzed alkylation of 3,4-dihydroquinoxalin-2-ones leading to the synthesis of an array of hitherto unexplored alkylated 3,4-dihydroquinoxalin-2-ones in an efficient fashion.

After initial studies, we realized that the reaction was best conducted when a solution of 4-benzyl-3,4-dihydroquinoxalin-2(1H)-one **1a** (0.1 mmol, 1 equiv.), NHPI ester **2a** (1.5 equiv.), *N,N*-diisopropylethylamine (DIPEA, 1.5 equiv.), and rose bengal (RB, 5 mol%) in acetonitrile (CH₃CN) was irradiated using blue LEDs (440 nm) under nitrogen atmosphere (entry 1, Table 1, see Table S1 in the ESI† for complete optimization). Gratifyingly, under these conditions the reaction was completed in 3 h to provide the desired *tert*-butylated 3,4-dihydroquinoxalin-2(1H)-one **3aa** in 90% yield (entry 1). Replacing rose bengal with other commonly employed photocatalysts, such as eosin Y, and Ru(bpy)₃Cl₂·6H₂O failed to better the yield (entry 2). A quick screening of solvents and bases established CH₃CN and DIPEA as the optimal combination (entries 3 and 4). Control

experiments indicated the indispensable role of the base, photocatalyst, and visible light irradiation towards the success of this alkyl-alkyl coupling process (entries 5–7).

Having optimized the reaction conditions, we set out to explore the scope of the process. Other than pivaloyl radical, tertiary alkyl radicals derived from 1-methyl-1-cyclohexanecarboxylic acid and 2,2-dimethylbutanoic acid underwent smooth transformation to provide respective products (**3ab–3ac**) in good yields (80–85%) (Scheme 2). Pleasingly, several secondary alkyl NHPI esters derived from acyclic, such as isopropyl carboxylic acid, as well as cyclic, such as cyclopentyl and cyclohexyl carboxylic acids, 4,4-difluorocyclohexanecarboxylic acid, and *N*-*boc*-4-peridincarboxylic acid successfully engaged in the process to provide corresponding products (**3ad–3ah**) in moderate to good yields (68–78%). To our delight, more challenging primary alkyl radicals were found to be equally efficient. A palette of primary NHPI esters derived from various carboxylic acids afforded the desired products (**3ai–3an**) in moderate to excellent yields (60–90%). Notably, primary NHPI esters with terminal alkyne (**3am**, 62%), as well as derived from α -heteroatom-substituted carboxylic acid (**3an**, 74%) were compatible under the reaction conditions. A wide range of natural products and pharmaceuticals bearing primary, secondary, and tertiary carboxylic acids, such as stearic acid (**3ao**, 66%), palmitic acid (**3ap**, 64%), oleic acid (**3aq**, 65%), isoxepac (**3ar**, 72%), ibuprofen (**3as**, 74%), and gemfibrozil (**3at**, 82%) were amenable to the C-H alkylation process.

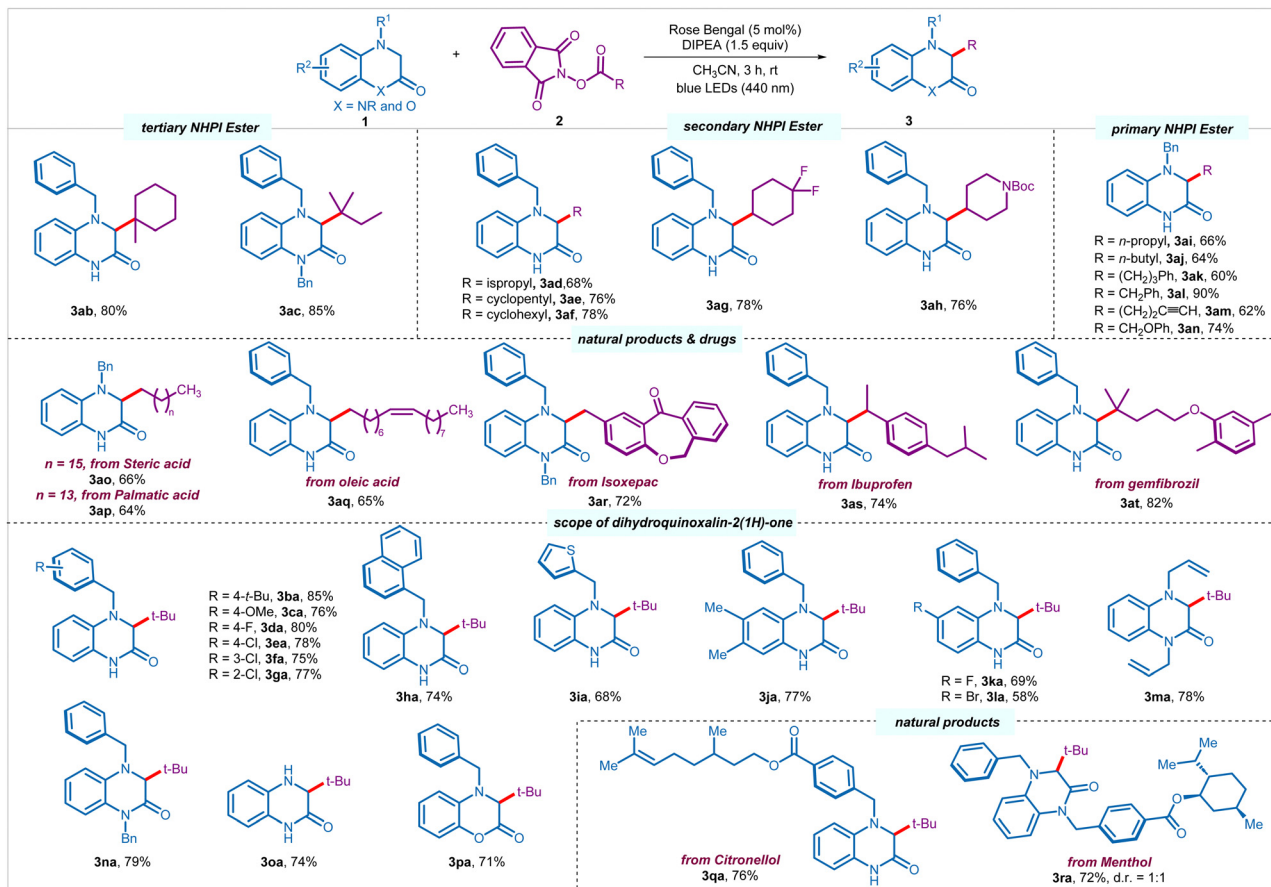
Subsequently, we investigated the scope of 3,4-dihydroquinoxalin-2-ones **1** by reacting with alkyl NHPI ester **2a** under the optimized conditions (Scheme 2). Several *N*₄-benzylated 3,4-dihydroquinoxalin-2-ones with diverse electron-donating (4-*t*-Bu, 4-OMe), and electron-withdrawing (4-F, 4-Cl, 3-Cl, 2-Cl) substituents on the phenyl ring of benzyl moiety underwent facile transformation to the desired products (**3ba–3ga**) in good yields (75–85%), regardless of the position of the substituents. Pleasingly, the aryl functionality at the *N*₄-position could also be replaced with naphthyl (**3ha**, 74%) and thiophenyl (**3ia**, 68%) group without affecting the efficacy of the process. Moreover, the core aromatic ring of the heterocycle could also be orchestrated with electron-donating and electron-withdrawing substitution pattern, such as 6,7-di-Me, 6-F, and 6-Br, furnishing desired products (**3ja–3la**) in good yields (58–77%). To our delight, 1,4-disubstituted (allyl and benzyl) 3,4-dihydroquinoxalin-2-ones were also tolerated to give corresponding products **3ma** and **3na** in 78% and 79% yields in a respective manner. Notably, unprotected 3,4-dihydroquinoxalin-2(1H)-one with synthetic handle for further modifications was compatible under the reaction conditions to provide **3oa** in 74% yield. Interestingly, other heterocycles, such as 4-benzyl-3,4-dihydro-2H-benzo[*b*][1,4]oxazin-2-one participated in the direct alkylation to provide the corresponding product **3pa** in 71% yield. Moreover, 3,4-dihydroquinoxalin-2-ones stitched with various natural products and pharmaceuticals provided desired products (**3qa** and **3ra**) in good yields (76% and 72%).

The scalability and robustness of the method was demonstrated by reacting 1 g of 3,4-dihydroquinoxalin-2-one **1a** with NHPI ester **2a** under the optimized conditions to afford desired

Table 1 Optimization of the reaction conditions^a

Entry	Variation from optimized conditions	Yield ^b (%)
1	None	90
2	Eosin Y, Ru(bpy) ₃ Cl ₂ ·6H ₂ O instead of RB	66, 85
3	THF, CH ₂ Cl ₂ instead of CH ₃ CN	71, 61
4	TMEDA, Et ₃ N instead of DIPEA	64, 46
5	Without DIPEA	N.D.
6	Without rose bengal	N.D.
7	Without irradiation	N.D.

^a Reaction conditions: **1a** (0.1 mmol, 1 equiv.), **2a** (1.5 equiv.), rose bengal (5 mol%), DIPEA (1.5 equiv.), and CH₃CN (1 mL) under nitrogen atmosphere using blue LEDs (440 nm) for 3 h. ^b Isolated yield. N.D. = not detected.



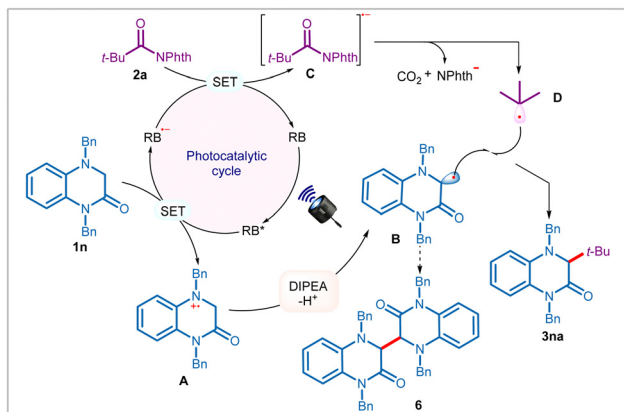
Scheme 2 Scope of the photoinduced C–H alkylation process.^a Reaction conditions: **1** (0.25 mmol, 1 equiv.), **2** (0.375 mmol, 1.5 equiv.), rose bengal (5 mol%), DIPEA (0.375 mmol, 1.5 equiv.), and CH₃CN (2.5 mL) under nitrogen atmosphere using blue LEDs (440 nm) for 3 h.

3aa in 79% yield (see Scheme S1 in the ESI[†]). To understand the intermediacy of radicals in these transformations, **1a** and **2a** were reacted in the presence of radical scavengers, such as TEMPO (2,2,6,6-tetramethyl-1-piperidine-1-oxyl) (see Scheme S1 in the ESI[†]). Expectedly, product formation was not recorded under these conditions, rather, radical trapping adducts **4** and **5** were identified through high-resolution mass spectrometry (HRMS) (Scheme S1 in the ESI[†]). To further our understanding of the mechanism, we carried out in-depth photophysical investigations. The “light-on-off” experiment in combination with quantum yield ($\Phi = 0.11$) measurements concluded that the desired product **3aa** was formed only during the steady irradiation of light and the reaction did not proceed through radical chain mechanism (please see ESI[†]).¹¹ In the steady-state Stern–Volmer experiments, significant quenching of the fluorescence emission band of rose bengal with 3,4-dihydroquinoxalin-2-one **1a**, rather than with **2a** or DIPEA was observed (see Scheme S1 in the ESI[†]). These quenching studies implied that the reaction was initiated through a reductive quenching of the photocatalyst.

Based on the above findings and literature precedence,^{5f,6a,d,8c,d,12} we propose that the reaction is initiated through photoexcitation of the catalyst to generate an excited state RB*, which upon reductive quenching with 3,4-dihydroquinoxalin-2-ones, such as **1n**

affords reduced photocatalyst (RB^{•-}) and radical–cation species **A** (Scheme 3). The intermediate **A** upon DIPEA-assisted deprotonation provides persistent α -amino radical **B**. Notably, in the absence of NHPI ester **2a**, formation of dimer **6** was detected, thereby reaffirming the existence of α -amino radical **B** in the reaction. On the other hand, RB^{•-} reduces NHPI esters **2a** through SET to generate radical–anion **C**, thereby completing the photocatalytic cycle. **C** then undergoes disintegration with concomitant elimination of phthalimide anion and carbon dioxide to produce transient alkyl radical **D**. Finally, radical–radical coupling between **B** and **D** results in the formation of cross-coupling product **3na**.

In summary, we have described a visible light photoredox-catalyzed direct C–H alkylation of 3,4-dihydroquinoxalin-2-ones using alkyl NHPI esters as alkyl radical surrogates. The method exhibits mild conditions, broad scope, and appreciable functional group tolerance. A broad variety of NHPI esters participated in the alkylation of an array of 3,4-dihydroquinoxalin-2-ones to provide corresponding products in good to excellent yields. Detailed mechanistic studies provided explicit insight into the reaction mechanism. Our ongoing research activities focus on developing novel photoinduced synthetic transformation involving redox-active esters enabling tapping of uncharted territory of chemical space.



Scheme 3 Proposed reaction mechanism.

SM acknowledges SERB [CRG/2022/000470], and CSIR [02(0426)/21/EMR-II] for funding and DST-FIST [SR/FST/CS-II/2019/119(C)] for the HRMS facility at IIT Jodhpur.

Conflicts of interest

“There are no conflicts to declare”.

Notes and references

- (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756; (b) F. Lovering, *Med. Chem. Commun.*, 2013, **4**, 515–519.
- (a) M. S. Kharasch, J. K. Hambling and T. P. Rudy, *J. Org. Chem.*, 1959, **24**, 303–305; (b) V. D. Parker, L. H. Piette, R. M. Salinger and C. R. Noller, *J. Am. Chem. Soc.*, 1964, **86**, 1110–1112; (c) J. K. Kochi and M. Tamura, *J. Am. Chem. Soc.*, 1971, **93**, 1485–1487; (d) J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu and N. Kambe, *J. Am. Chem. Soc.*, 2002, **124**, 4222–4223; (e) K. B. Urkalan and M. S. Sigman, *J. Am. Chem. Soc.*, 2009, **131**, 18042–18043; (f) O. Vechorkin and X. Hu, *Angew. Chem., Int. Ed.*, 2009, **48**, 2937–2940; (g) J. Choi and G. C. Fu, *Science*, 2017, **356**, eaaf7230.
- (a) S. K. Parida, S. K. Hota, R. Kumar and S. Murarka, *Chem. – Asian J.*, 2021, **16**, 879–889; (b) S. K. Parida, T. Mandal, S. Das, S. K. Hota, S. De Sarkar and S. Murarka, *ACS Catal.*, 2021, **11**, 1640–1683; (c) S. Murarka, *Adv. Synth. Catal.*, 2018, **360**, 1735–1753; (d) X. Zhu and H. Fu, *Chem. Commun.*, 2021, **57**, 9656–9671; (e) K. Okada, K. Okamoto and M. Oda, *J. Am. Chem. Soc.*, 1988, **110**, 8736–8738; (f) K. Okada, K. Okamoto, N. Morita, K. Okubo and M. Oda, *J. Am. Chem. Soc.*, 1991, **113**, 9401–9402.
- T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate and P. S. Baran, *Science*, 2016, **352**, 801–805.
- (a) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102–113; (b) S. Kumar Hota, D. Jinan, S. Prakash Panda, R. Pan, B. Sahoo and S. Murarka, *Asian J. Org. Chem.*, 2021, **10**, 1848–1860; (c) I. K. Sideri, E. Voutyritsa and C. G. Kokotos, *Org. Biomol. Chem.*, 2018, **16**, 4596–4614; (d) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363; (e) M. H. Shaw, J. Twilton and D. W. C. MacMillan, *J. Org. Chem.*, 2016, **81**, 6898–6926; (f) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–10166.
- (a) G.-Z. Wang, M.-C. Fu, B. Zhao and R. Shang, *Sci. China: Chem.*, 2021, **64**, 439–444; (b) P. Ma, Y. Liu, L. Chen, X. Zhao, B. Yang and J. Zhang, *Org. Chem. Front.*, 2021, **8**, 2473–2479; (c) L. Ren and H. Cong, *Org. Lett.*, 2018, **20**, 3225–3228; (d) C. Wang, M. Guo, R. Qi, Q. Shang, Q. Liu, S. Wang, L. Zhao, R. Wang and Z. Xu, *Angew. Chem., Int. Ed.*, 2018, **57**, 15841–15846.
- (a) Y. Yang, L. Zhao, B. Xu, L. Yang, J. Zhang, H. Zhang and J. Zhou, *Bioorg. Chem.*, 2016, **68**, 236–244; (b) D. J. Hayes, T. M. Mosher and A. J. Greenshaw, *Behav. Brain Res.*, 2009, **197**, 323–330; (c) J. Ren, C. E. Nichols, P. P. Chamberlain, K. L. Weaver, S. A. Short, J. H. Chan, J.-P. Kleim and D. K. Stammers, *J. Med. Chem.*, 2007, **50**, 2301–2309; (d) J. J. Chen, W. Qian, K. Biswas, V. N. Viswanadhan, B. C. Askew, S. Hitchcock, R. W. Hungate, L. Arik and E. Johnson, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4477–4481.
- (a) J. Rostoll-Berenguer, F. J. Sierra-Molero, G. Blay, J. R. Pedro and C. Vila, *Adv. Synth. Catal.*, 2022, **364**, 4054–4060; (b) J. Rostoll-Berenguer, V. García-García, G. Blay, J. R. Pedro and C. Vila, *ACS Org. Inorg. Au*, 2023, **3**, 130–135; (c) W. Xiong, W.-B. Qin, Y.-S. Zhao, K.-Z. Fu and G.-K. Liu, *Org. Chem. Front.*, 2022, **9**, 2141–2148; (d) J. Rostoll-Berenguer, G. Blay, J. R. Pedro and C. Vila, *Org. Lett.*, 2020, **22**, 8012–8017; (e) J. Rostoll-Berenguer, M. Martín-López, G. Blay, J. R. Pedro and C. Vila, *J. Org. Chem.*, 2022, **87**, 9343–9356.
- (a) D. Leifert and A. Studer, *Angew. Chem., Int. Ed.*, 2020, **59**, 74–108; (b) L. Zhang, Y. Li, Z. Guo, Y. Li, N. Li, W. Li, C. Zhu and J. Xie, *Chin. J. Catal.*, 2023, **50**, 215–221; (c) M. Miao, L.-L. Liao, G.-M. Cao, W.-J. Zhou and D.-G. Yu, *Sci. China: Chem.*, 2019, **62**, 1519–1524; (d) X.-Y. Chen, X. Kuang, Y. Wu, J. Zhou and P. Wang, *Chin. J. Chem.*, 2023, **41**, 1979–1986; (e) J. Xie, H. Jin and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2017, **46**, 5193–5203; (f) W. Li, Y. Duan, M. Zhang, J. Cheng and C. Zhu, *Chem. Commun.*, 2016, **52**, 7596–7599; (g) J. Xie, J. Yu, M. Rudolph, F. Rominger and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2016, **55**, 9416–9421.
- (a) S. Das, S. K. Parida, T. Mandal, S. K. Hota, L. Roy, S. De Sarkar and S. Murarka, *Org. Chem. Front.*, 2021, **8**, 2256–2262; (b) 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; (c) S. P. Panda, S. K. Hota, R. Dash, L. Roy and S. Murarka, *Org. Lett.*, 2023, **25**, 3739–3744; (d) S. Das, A. Azim, S. K. Hota, S. P. Panda, S. Murarka and S. De Sarkar, *Chem. Commun.*, 2021, **57**, 13130–13133; (e) S. Das, S. K. Parida, T. Mandal, L. Sing, S. De Sarkar and S. Murarka, *Chem. – Asian J.*, 2020, **15**, 568–572.
- M. A. Cismesia and T. P. Yoon, *Chem. Sci.*, 2015, **6**, 5426–5434.
- (a) H. Xue, M. Guo, C. Wang, Y. Shen, R. Qi, Y. Wu, Z. Xu and M. Chang, *Org. Chem. Front.*, 2020, **7**, 2426–2431; (b) W. Ding, L.-Q. Lu, J. Liu, D. Liu, H.-T. Song and W.-J. Xiao, *J. Org. Chem.*, 2016, **81**, 7237–7243; (c) C.-M. Chan, Q. Xing, Y.-C. Chow, S.-F. Hung and W.-Y. Yu, *Org. Lett.*, 2019, **21**, 8037–8043; (d) M. Hari Babu and J. Sim, *Eur. J. Org. Chem.*, 2022, e202200859; (e) J. Rostoll-Berenguer, G. Blay, J. R. Pedro and C. Vila, *ChemCatChem*, 2023, **15**, e202300177.