


 Cite this: *RSC Adv.*, 2026, **16**, 17005

 Received 2nd February 2026
 Accepted 12th March 2026

DOI: 10.1039/d6ra00901h

rsc.li/rsc-advances

Selective Functionalization of 1-substituted-3-arylquinoxalin-2(1*H*)-ones via C–H activation

 Prashant Kumar,^{ID}*^a Priya,^a Sriparna Dutta,^{*b} Deepak Mishra^a and Naresh Kumar^a

Over the past few decades, transition-metal-catalyzed selective functionalization of C–H bonds has fascinated the scientific community by offering striking advantages in comparison to traditional methods, such as high atom economy, a reduced number of reaction steps, and milder reaction conditions. Moreover, directing-group-assisted C–H activation enhances the significance of transition-metal catalysis further by enabling precise and site-selective functionalization. This mini-review outlines recent advancements in the imine-directed, transition-metal-catalyzed selective functionalization of *N*-alkyl-3-phenylquinoxalin-2(1*H*)-ones, highlighting C–C, C–O, C–X (X = Cl, Br, and I), C–S, and C–Se bond formation reactions and mechanistic aspects of these transformations.

1. Introduction

Quinoxalin-2(1*H*)-ones are highly privileged scaffolds belonging to the quinoxalinone family and are widely distributed in nature as well as pharmaceuticals. Amongst the various derivatives of quinoxalin-2(1*H*)-ones, 3-phenylquinoxalin-2(1*H*)-ones have garnered significant interest from the scientific fraternity due to their broad applications in agriculture, medicinal chemistry and materials science.^{1–8} Their ability to regulate various biochemical pathways has positioned them as potential drug candidates for treating neurological disorders,^{9–11} cardiovascular ailments¹² and diabetes-like diseases.^{13,14} Besides, 3-substituted quinoxalin-2(1*H*)-ones demonstrate a wide range of biological activities, including anti-tumor activity,¹⁵ anti-viral

activity,^{16,17} anti-microbial activity,¹⁸ anti-cancer activity,¹⁹ and anti-inflammatory activity.²⁰ Furthermore, a few 3-phenylquinoxalin-2(1*H*)-one derivatives display enzyme-inhibiting properties such as stearyl-CoA desaturase inhibition,²¹ aldose reductase inhibition,²² serine/threonine-protein kinase inhibition,²³ STK33 inhibition and FXa coagulation inhibition.²⁴ Fig. 1 presents some examples of bioactive molecules containing 3-phenylquinoxalin-2(1*H*)-one as a key motif. Considering the importance of quinoxalin-2(1*H*)-one derivatives, several transition-metal-catalyzed and chelating group-assisted methodologies have been developed for the selective and direct functionalization of quinoxalin-2(1*H*)-ones via C–H activation.^{25–29} These strategies enable the efficient formation of C–C and C–heteroatom bonds at the C-3 position of quinoxalin-2(1*H*)-one, thereby facilitating access to structurally complex and biologically relevant derivatives. These transition-metal-mediated approaches are widely favoured due to their broad substrate scope, high catalytic activity, and well-developed

^aDepartment of Chemistry, SRM University Delhi-NCR Sonapat, Haryana-131029, India. E-mail: prashant.kumar@srmuniversity.ac.in; prashanttomar972@gmail.com

^bDepartment of Chemistry, Hindu College, University of Delhi, Delhi-110007, India


Prashant Kumar

Prashant Kumar is currently an Assistant Professor at SRM University, Delhi-NCR, Sonapat, India. He completed his Ph.D. in 2018 from the Department of Chemistry, University of Delhi. Dr Kumar has good expertise in organic chemistry. He has worked extensively on metal-catalyzed and metal-free C–H activation reactions, and microwave-assisted synthesis of biologically active molecules.


Priya

Priya is currently pursuing her Master's degree at SRM University Delhi-NCR, Sonapat. She completed her Bachelor of Science with Honors in Chemistry in 2023 from SRMUH. She has been a hardworking and sincere student throughout her career.



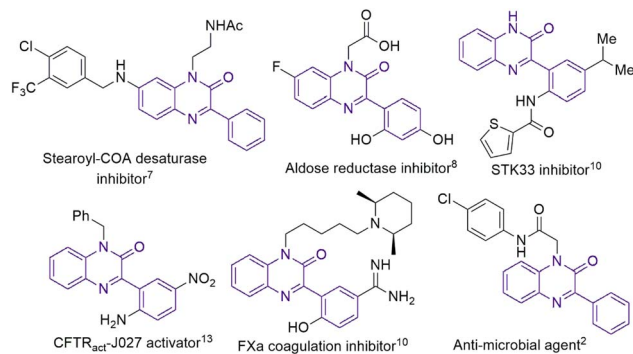


Fig. 1 Examples of bioactive molecules containing 3-phenylquinoxalin-2(1H)-one as a key motif.

mechanistic understanding, which collectively ensure predictable outcomes in complex molecule synthesis.^{30,31} However, despite the effectiveness of transition-metal-catalyzed approaches, growing environmental concerns and sustainability requirements have prompted a shift towards the development of robust and more sustainable alternatives. Consequently, in recent years, visible-light-induced transformations and heterogeneous catalytic systems have emerged



Sriparna Dutta

Dr. Sriparna Dutta is currently a faculty member at Hindu College, University of Delhi, a treasurer of the Royal Society of Chemistry, and a member of Green Chemistry Network Centre, University of Delhi. She has a doctorate in chemistry, and her research focuses on the design of novel nanoengineered catalysts for industrially significant organic transformations.



Deepak Mishra

Deepak Mishra is currently working as an Assistant Professor at SRM University, Delhi-NCR, Sonapat. He obtained his PhD in Organic Chemistry from Delhi Technical University in 2018. His research work includes synthetic organic chemistry, medicinal chemistry and heterocyclic chemistry. He has published various research papers in highly reputed international journals.

as powerful tools for the direct functionalization of quinoxalin-2(1H)-ones.^{32,33}

The past decades have witnessed an escalating interest in transition-metal-catalyzed direct C–H functionalization reactions for the introduction of desirable functional groups into targeted organic molecules.^{34–44} However, the achievement of regioselective C–H activation remains a considerable challenge in synthetic chemistry owing to the pervasive nature of C–H bonds.^{45–47} Therefore, the emergence of transition-metal-catalyzed, directing-group-assisted selective C–H bond functionalization has attracted significant attention in recent years. This approach enables the efficient and regioselective formation of C–C and C–heteroatom bonds, as the directing group coordinates with the metal center, positioning it in close proximity to the target C–H bond and thereby facilitating its activation.^{48–57} A directing group often contains a heteroatom that binds the substrate with a transition metal *via* an agostic interaction, leading to the formation of a kinetically and thermodynamically stable cyclometallated intermediate.^{58–63} A directing-group-assisted, transition-metal-catalyzed selective *ortho*-C–H bond functionalization of the C-3 aryl ring in quinoxalin-2(1H)-ones was reported by Carrer *et al.* in 2013.⁶⁴ Since the initial discovery of this reactivity, significant efforts have been focused on introducing diverse functional groups at the *ortho*-position of the 3-aryl ring in 1-substituted-3-arylquinoxalin-2(1H)-ones. In this mini-review, we present an overview of the recent progress in transition-metal-catalyzed, chelating-group-assisted selective functionalization of 1-substituted-3-phenylquinoxalin-2(1H)-ones, emphasizing the scope, mechanistic aspects, and synthetic utility of these transformations.

2. Scope of review

There is a need to disseminate how wondrously *N*-alkyl-3-phenylquinoxalin-2(1H)-ones have been selectively functionalized using the C–H activation approach. Although there are several reviews on C–H bond activation and transition metal-catalyzed reactions, to the best of our knowledge, there is no review that sheds light on the selective functionalization of the



Naresh Kumar

Naresh Kumar obtained his PhD from Guru Nanak Dev University, Amritsar, India in 2013. Later, he joined PPSM, Université Paris Saclay as a Post-doctoral Fellow. He was a JSPS researcher at Osaka University from 2016 to 2018. He currently holds the position of Assistant Professor at SRM University, Delhi-NCR, Sonapat, India. His research includes fluorescence-based molecular recognition and imaging.



ortho-C–H bond of the 3-phenyl ring, resulting in the formation of valuable C–C, C–O, C–X (X = Cl, Br, and I), C–S, and C–Se bonds *via* C–H activation. This review comprehensively highlights some of the exciting accomplishments achieved in past few years in the development of novel catalytic systems, and modern synthetic strategies such as photocatalysis and spiro annulation. The role of substituent effects on the electronic and steric properties of the quinoxalinone core, which govern the reactivity and product distribution, and mechanistic aspects that will enable researchers to think creatively and work in this exciting area are briefly discussed. Overall, this review intends to serve as a comprehensive guide for researchers working on quinoxaline chemistry, catalysis, and heterocyclic functionalization, and to inspire the development of novel synthetic strategies for constructing complex heterocyclic architectures.

3. C–H functionalization of *N*-alkyl-3-phenylquinoxalin-2(1*H*)-ones

3.1. Acetoxylation

Selective C–H acetoxylation reactions are of great importance, as the resulting acetoxyated products find wide applications in the chemical industry.⁶⁵ Moreover, the acetoxy group can be readily converted into a hydroxy group and also serves as a versatile functional group for numerous organic transformations, highlighting its broad synthetic utility.^{66,67}

Carrer *et al.*, in 2013, reported the Pd-catalyzed oxidative C-3 arylation of quinoxalin-2(1*H*)-ones with arylboronic acids. To explore the versatility of the developed method, the authors carried out the regioselective C–H functionalization of the synthesized C-3 arylated products.⁶⁴ Delightfully, two desired

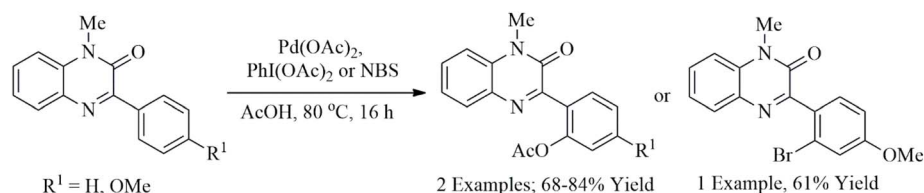
ortho-acetoxyated and one *ortho*-brominated *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones could be obtained in 84%, 68% and 61% yield, respectively, *via* Pd-catalyzed *N*-assisted C–H functionalization (Scheme 1).

3.2. Acylation

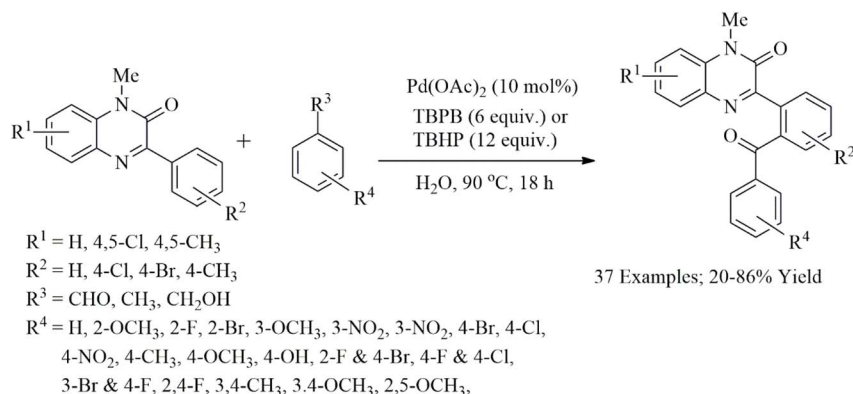
Ketones serve as fundamental building blocks in the synthesis of various bioactive molecules,⁶⁸ pharmaceuticals,^{69–73} dyes,⁷⁴ and electronic materials.⁷⁵ Over the past decade, cross-coupling strategies have emerged as powerful tools for the direct synthesis of ketones *via* the selective acylation of organic substrates.^{76–82} The direct acylation approach offers several advantages over classical methods, including fewer reaction steps, improved selectivity, and higher atom economy.

In 2022, Singh *et al.* developed a green and sustainable method for the regioselective acylation of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones with benzaldehydes using water as the solvent.⁸³ Upon screening various catalysts such as Cu, Ni and several Pd-salt, Pd(OAc)₂ was found to be the best catalyst. The optimization of oxidants revealed TBPB as a suitable oxidant and the reaction provides the best results using water as the solvent. The developed methodology tolerated electron-rich and electron-deficient benzaldehydes, and a library of 29 acylated products was developed by reacting several aromatic aldehydes with 1-methyl-3-phenylquinoxalin-2-(1*H*)-ones (Scheme 2). Notably, when 1-methyl-3-phenylquinoxalin-2-(1*H*)-one was reacted with 1*H*-indole-3-carbaldehyde, the corresponding product was obtained in 64% yield.

To propose a plausible reaction mechanism, the authors conducted several control experiments, as depicted in Scheme 3. The mechanism starts with cyclopalladation of 1-methyl-3-

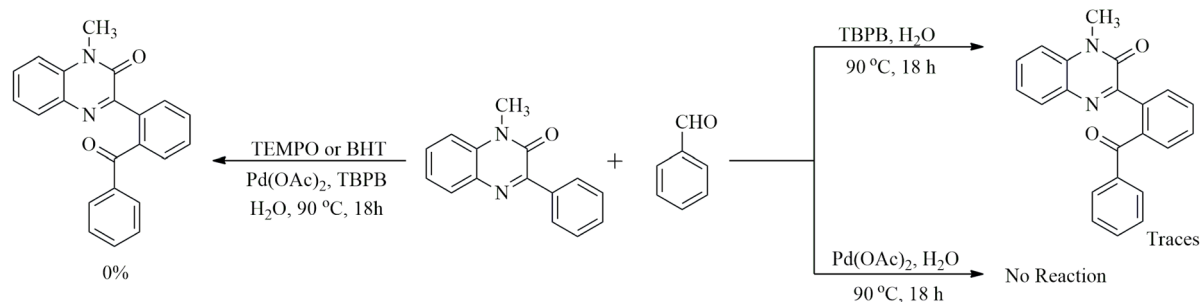


Scheme 1 Pd-catalyzed *N*-assisted C–H acetoxylation/bromination of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones.

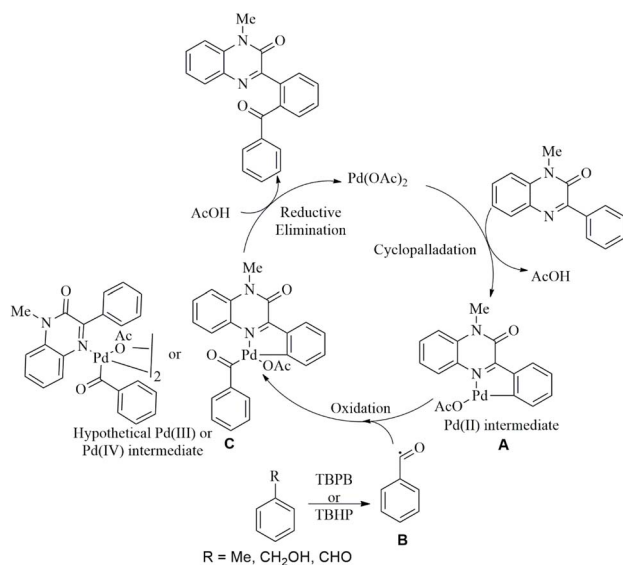


Scheme 2 Pd-catalyzed regioselective acylation of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones in water.

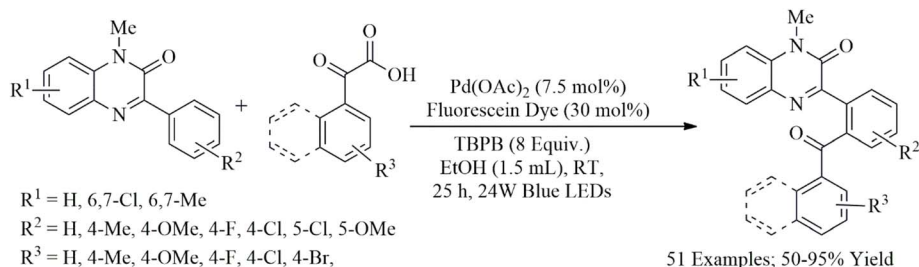




Scheme 3 Control experiments.

Scheme 4 Proposed reaction mechanism for the Pd-catalyzed regioselective acylation of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones.

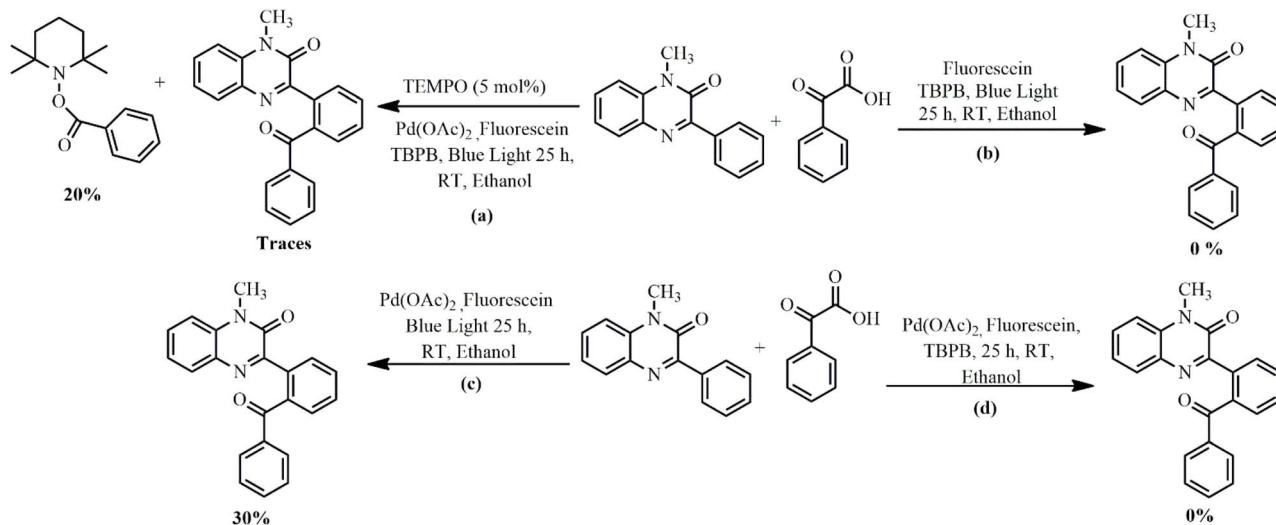
phenylquinoxalin-2(1*H*)-one to generate Pd(II) intermediate **A**. Simultaneously, an acyl radical (**B**) is generated by the action of TBPB on aldehyde/benzyl alcohol and TBHP on toluene. Then, intermediate **A** undergoes oxidation with the acyl radical (**B**) to generate Pd(IV) or dimeric Pd(III) intermediate **C**. Lastly, reductive elimination from intermediate **C** yields the corresponding acylated compound and the Pd(II) catalyst is regenerated to continue the catalytic cycle (Scheme 4).

Scheme 5 Pd-catalyzed regioselective decarboxylative C–H acylation of *N*-methyl 3-phenylquinoxalin-2(1*H*)-ones using α -oxo-2-phenylacetic acids.

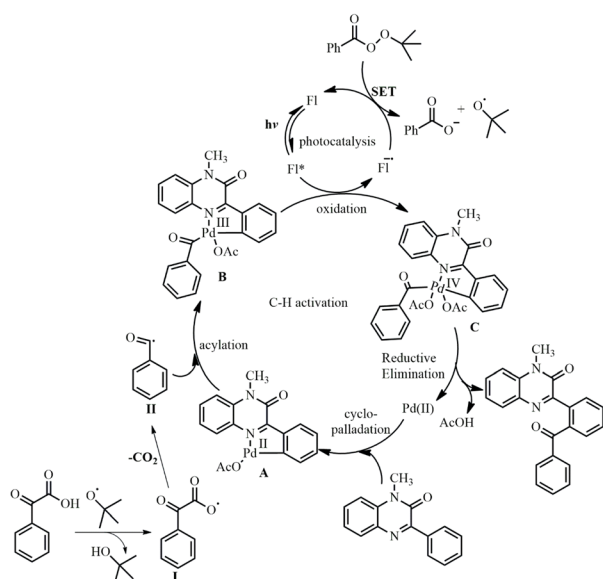
Later in 2024, Singh and co-workers reported the regioselective decarboxylative C–H acylation of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones using α -oxo-2-phenylacetic acids as effective acylating agents under visible light *via* dual palladium-photoredox catalysis.⁸⁴ A fluorescent dye was used as a photocatalyst and Pd(OAc)₂ as a transition-metal-catalyst to develop a dual photocatalytic system. The established protocol tolerated a wide range of functional groups on α -oxo-2-phenylacetic and *N*-methyl-3-phenylquinoxalin-2(1*H*)-one, irrespective of the position and nature of the functional group, and delivered the corresponding products in good yields under photocatalytic conditions (Scheme 5). Notably, heterocyclic analogues of *N*-methylquinoxalin-2(1*H*)-one, such as 3-thiophene derivative on reaction with α -oxo-2-phenylacetic acid and 2-(naphthalen-2-yl)-2-oxoacetic acid on reaction with 3-(4-fluorophenyl)-1,6,7-trimethylquinoxalin-2(1*H*)-one, also furnished the targeted products in 70% and 60% yield, respectively. Further, several controlled experiments were conducted to elucidate the reaction mechanism, including (a) a reaction in the presence of the radical scavenger TEMPO and (b–d) without Pd-catalyst, oxidant TBPB, and LED light, respectively (Scheme 6).

Based on the outcomes of these controlled experiments and other literature facts, a plausible mechanism was established by the authors (Scheme 7). The catalytic mechanism initiated by visible-light irradiation, which promotes fluorescein (FI) to its excited state (FI^{*}). Concurrently, cyclopalladation of *N*-methyl-3-phenylquinoxalin-2(1*H*)-one with the Pd(II) catalyst generates palladacyclic intermediate **A**. Intermediate **A** undergoes reaction with acyl radical **II**, generated *in situ*, to afford Pd(III) species **B**. Single-electron oxidation of **B** leads to the formation of Pd(IV)





Scheme 6 Control experiments.



Scheme 7 Plausible reaction mechanism.

complex **C**, accompanied by reductive quenching of FI^* to the fluorescein radical anion ($\text{FI}^{\bullet-}$). The $\text{FI}^{\bullet-}$ species then participates in a back-electron transfer process to generate a *tert*-butoxide radical, which undergoes decarboxylation to generate acyl radical **II**. Finally, reductive elimination from $\text{Pd}(\text{IV})$ complex **C** delivers the desired halogenated product and regenerates the $\text{Pd}(\text{II})$ catalyst.

3.3. Halogenation

Halogenation of aromatic compounds is an essential transformation in modern synthetic chemistry, as aromatic halides represent one of the most fundamental classes of organic molecules and serve as highly versatile electrophilic partners in transition-metal-catalyzed cross-coupling reactions.^{85–94}

Therefore, from classical methodologies to modern catalytic strategies, significant efforts have been directed toward the efficient and selective preparation of aromatic halides.^{95–104}

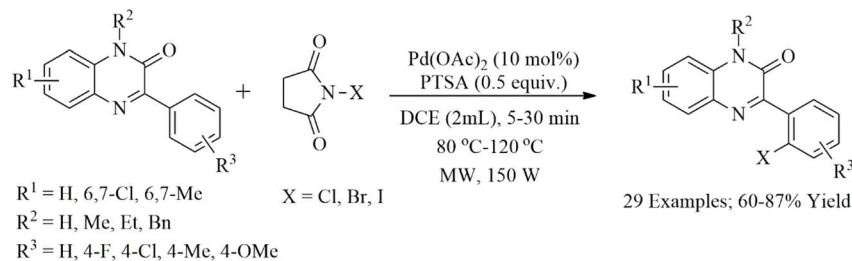
In 2023, Singh *et al.* established a Pd-catalyzed microwave-assisted methodology for the regioselective *ortho*-monohalogenation of 3-phenylquinoxalin-2(1*H*)-one derivatives.¹⁰⁵ The optimal results were obtained using $\text{Pd}(\text{OAc})_2$ (10 mol%) as the catalyst and NXS (X = Cl, Br, and I; 1.2 equiv.) as the halogen source, in the presence of PTSA (0.5 equiv.) as an additive in DCE solvent under MW irradiation (150 W). To extend the utility of this protocol, several 1-alkyl/benzyl-3-phenylquinoxalin-2(1*H*)-ones were reacted with *N*-bromosuccinimide and the reaction proceeded smoothly, providing good product yields. 1-Methyl-3-phenylquinoxalin-2(1*H*)-one containing electron-withdrawing as well as electron-releasing groups on either of its aryl ring afforded the corresponding products. To demonstrate the generality of this method, chlorination and iodination of 1-alkyl/benzyl-3-phenylquinoxalin-2(1*H*)-ones were also accomplished using NCS and NIS as the halogenating agents, respectively (Scheme 8).

A plausible reaction mechanism for this transformation is outlined in Scheme 9. The catalytic cycle is initiated by the reaction of $\text{Pd}(\text{OAc})_2$ and PTSA to generate active $\text{Pd}(\text{OTf})_2$ species. Subsequent directed C–H activation of 1-alkyl- or 1-benzyl-3-phenylquinoxalin-2(1*H*)-one affords cyclopalladated intermediate **A**. Oxidative addition of *N*-halosuccinimide to intermediate **A** then furnishes $\text{Pd}(\text{IV})$ intermediate **B**. Finally, reductive elimination from intermediate **B** delivers the corresponding halogenated product and regenerates the $\text{Pd}(\text{II})$ catalyst, thereby completing the catalytic cycle.

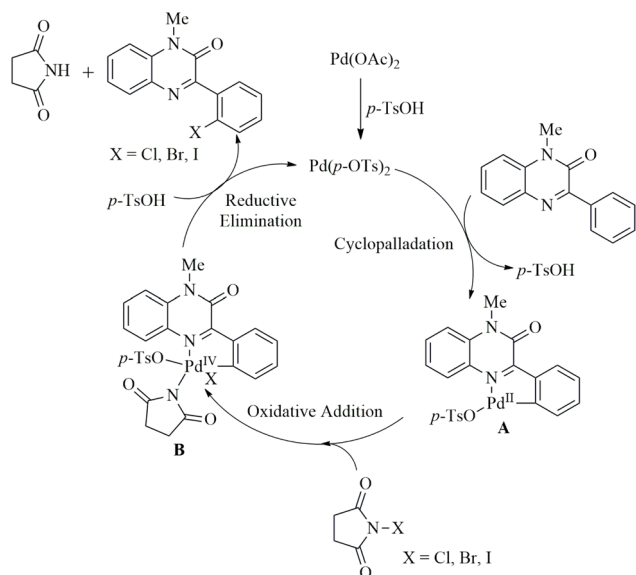
3.4. Selenylation and sulfenylation

Organosulfur and organoselenium compounds have emerged as indispensable entities in modern organic synthesis owing to their structural diversity and broad applications in agrochemicals,^{106–109} pharmaceuticals,^{110–115} and functional





Scheme 8 Pd-catalyzed, regioselective *ortho*-monohalogenation of 3-phenylquinoxalin-2(1*H*)-one derivatives using *N*-halosuccinimides (NXS).



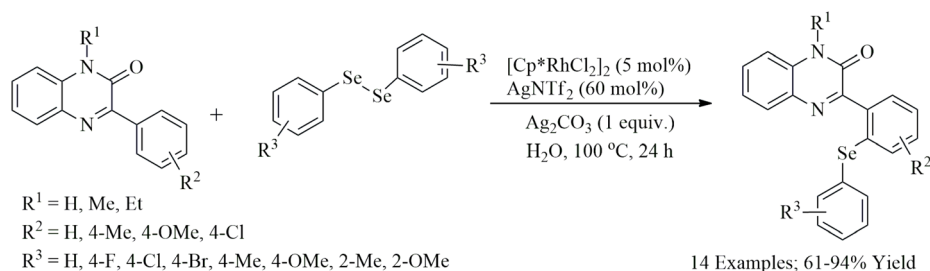
Scheme 9 Plausible reaction mechanism for *ortho*-monohalogenation of 3-phenylquinoxalin-2(1*H*)-one.

materials.^{116–118} Notably, nearly one-fourth of the top 200 FDA-approved drugs contain organosulfur motifs, underscoring their profound medicinal significance.¹¹⁹ These organochalcogenides exhibit diverse biological activities^{120–127} and their incorporation often enhances the photophysical and electronic properties of organic frameworks.^{128–131} Consequently, the development of innovative and efficient strategies for constructing C–S and C–Se bonds has become a focal point of modern synthetic research.^{132–136}

Lalji and co-workers developed a rhodium-catalyzed approach for the regioselective selenylation and sulfenylation of *N*-substituted-3-phenylquinoxalin-2(1*H*)-ones via *N*-directed C–H activation in aqueous medium.¹³⁷ The compatibility of the developed protocol towards C–Se bond formation was first evaluated through the selenylation of various *N*-ethyl- and *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones with diphenyl diselenides (Scheme 10). Both *N*-alkyl-phenylquinoxalin-2(1*H*)-ones and diphenyl diselenide having electron-releasing (Me and OMe) groups and electron-withdrawing (F, Cl, and Br) groups were allowed to react and 14 selenylated products were obtained in good to excellent yields.

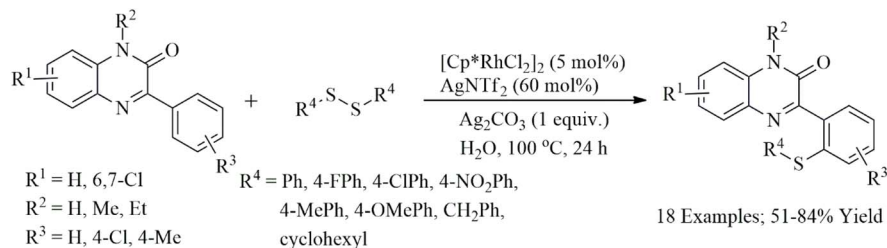
Besides, the developed protocol was extended to dialkyl disulfides for the C–S functionalization of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones, enabling the synthesis of 18 thioether derivatives in good yields (Scheme 11). Substrates having electron-donating (Me and OMe) groups delivered higher yields compared to those containing electron-withdrawing (F and Cl) groups. Similarly, *N*-methyl-3-phenylquinoxalin-2(1*H*)-one with a methyl group could afford a higher product yield relative to its chloro-substituted counterparts. Furthermore, dialkyl disulfides were also compatible reaction partners, providing the corresponding products in good yields.

Two mechanistic pathways were proposed for these transformations (Scheme 12). The mechanism is initiated by the reaction of dimeric [Cp*RhCl₂]₂ with silver triflimide, resulting in the *in situ* generation of active rhodium(III) species X. The newly generated catalyst X subsequently undergoes cyclo-metallation with *N*-ethyl-3-phenylquinoxalin-2(1*H*)-one via directed C–H activation to afford rhodacyclic intermediate A. Thereafter, intermediate A engages in a nucleophilic substitution reaction with diphenyl diselenide or diphenyl disulfides,

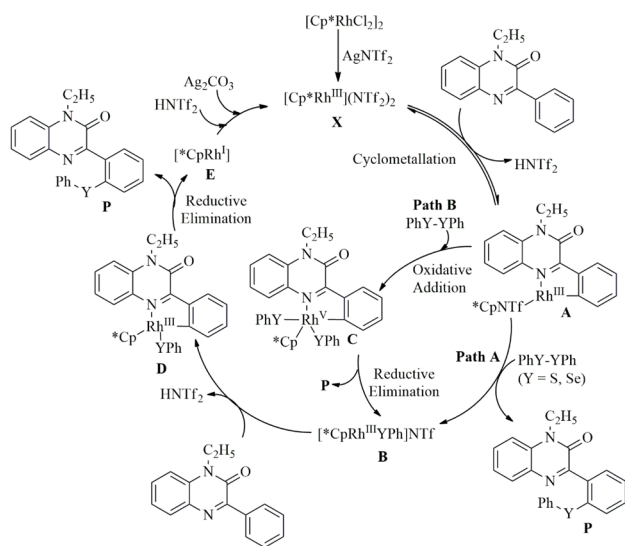


Scheme 10 Rh-catalyzed regioselective selenylation of *N*-substituted-3-phenylquinoxalin-2(1*H*)-ones.





Scheme 11 Rh-catalyzed regioselective sulfenylation of *N*-substituted-3-phenylquinoxalin-2(1*H*)-ones.



Scheme 12 Plausible reaction mechanism for Rh-catalyzed, regioselective selenylation/sulfenylation of *N*-substituted-3-phenylquinoxalin-2(1*H*)-ones.

leading to the formation of the desired product **P** along with rhodium intermediate **B** (Scheme 12, path A).

The authors also proposed an alternative mechanistic pathway (Scheme 12, path B), wherein cyclometalated intermediate **A** undergoes oxidative addition with diphenyl diselenide or diphenyl sulfide to generate high-valent rhodium(v) complex **C**. Subsequent, reductive elimination from **C** furnishes the desired product **P** and Rh(III) intermediate **B**. Thereafter, coordination and C–H activation of another molecule of *N*-alkyl-3-phenylquinoxalin-2(1*H*)-one by intermediate **B** leads to the formation of cyclometalated intermediate **D**. Reductive elimination from **D** produces Rh(I) complex **E** and the desired product **P**.

3.5. Alkylation and alkenylation

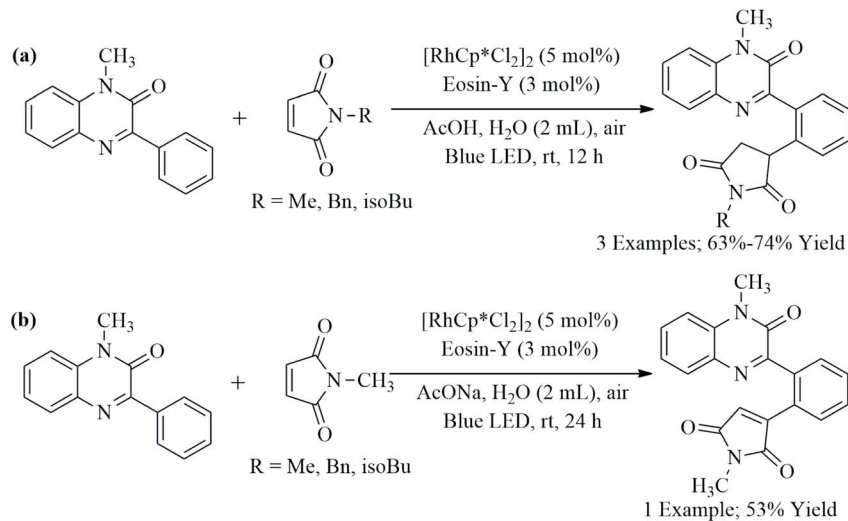
Transition-metal-catalyzed C–H alkylation and alkenylation reactions have emerged as powerful tools in contemporary synthetic chemistry, offering direct and atom-economical routes to functionalized organic molecules.^{138–140} More recently, the merger of visible-light photoredox catalysis with transition-metal catalysis has further expanded their scope, enabling sustainable and highly selective C–H functionalization

under mild or ambient conditions.^{141–145} The versatility of these methodologies has been elegantly demonstrated in the late-stage modification of complex bioactive molecules and natural products, underscoring their growing significance in pharmaceutical and materials research.¹⁴⁶ Recently, Bhawale and co-workers (2025) reported a visible-light-enabled dual catalytic strategy for the regioselective C–H alkylation and alkenylation of 2-aryl heteroarenes using maleimides under aqueous conditions.¹⁴⁷ The combination of [RhCp*Cl₂]₂ as a transition metal catalyst and Eosin Y as an organic photocatalyst efficiently promoted C–H functionalization under blue LED irradiation in air. To assess the scope and versatility of this photocatalytic system toward selective *ortho*-C–H alkylation of the 2-aryl ring in *N*-substituted-3-phenylquinoxalin-2(1*H*)-ones, reactions between *N*-methyl-3-phenylquinoxalin-2(1*H*)-one and various *N*-alkyl maleimides were performed using AcOH as an additive under the optimized dual catalytic conditions. The transformations proceeded smoothly at room temperature under blue LED irradiation for 12 h, affording the corresponding alkylated products in 63–74% yield (Scheme 13a).

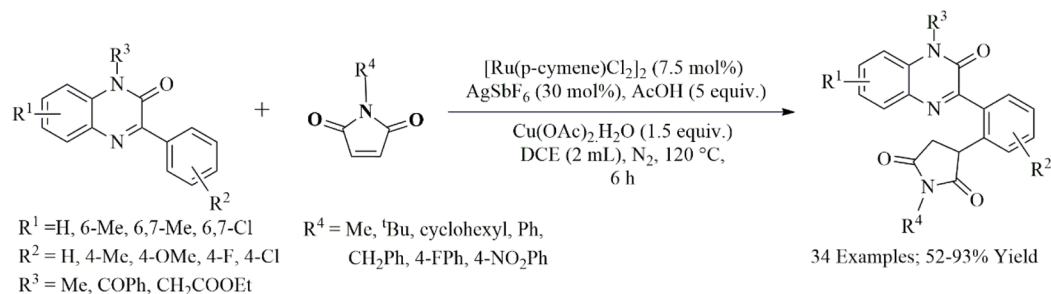
Moreover, selective alkenylation was accomplished by replacing AcOH with AcONa as the additive and extending the reaction time to 24 h, resulting in the desired alkenylated product in 53% yield (Scheme 13b).

Later, in 2025, Monika and co-workers reported the Ru(II)-catalyzed *ortho* C–H alkylation of the 3-phenyl ring of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones.¹⁴⁸ To alkylate the desired 1-alkyl-3-phenylquinoxalin-2(1*H*)-ones, various *N*-alkyl maleimides were used as alkylating agents using [Ru(*p*-cymene)Cl₂]₂/AgSbF₆/AcOH/Cu(OAc)₂·H₂O as an effective catalytic system. The reactions were carried out in 1,2-dichloroethane solvent at 120 °C under an N₂ atmosphere, and the corresponding *ortho*-alkylated products were obtained in excellent yields. The systematic optimization of the reaction conditions showed that the concentration of catalyst, additives and oxidant has significant impact on the reaction yield as a deviation from the optimum amount of these species resulted in a lower product yield. Furthermore, the generality of the developed reaction conditions for *ortho*-alkylation was evaluated by reacting structurally and electronically distinct 1-alkyl-3-phenylquinoxalin-2(1*H*)-ones with several *N*-substituted maleimides (Scheme 14). The screening of quinoxalin-2(1*H*)-ones revealed that 1,6-dimethyl-3-phenylquinoxalin-2(1*H*)-one delivered better product yields in comparison to 1,6,7-trimethyl-3-phenylquinoxalin-2(1*H*)-one. Moreover, 6,7-dichloro-1-methyl-





Scheme 13 Selective C–H (a) alkylation and (b) alkenylation of *N*-methyl-3-phenylquinoxalin-2(1*H*)-one with maleimides through a dual-catalysis approach.

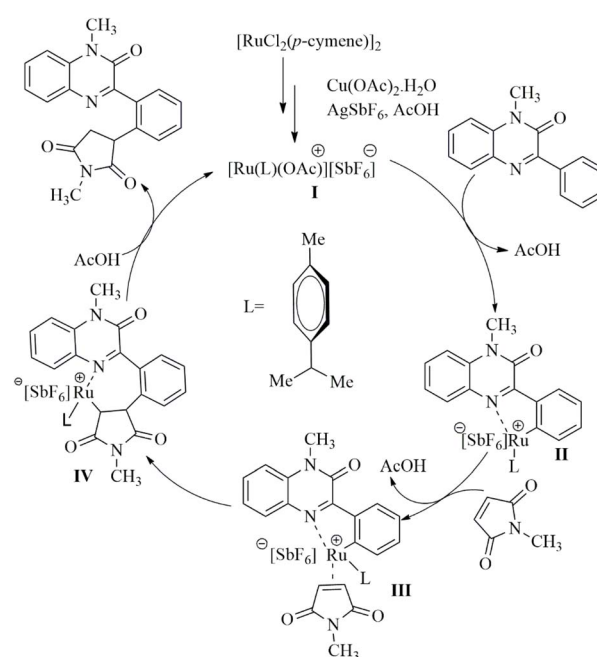


Scheme 14 Ru-catalyzed *ortho* C–H alkylation of 3-phenyl ring of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones with maleimides.

3-phenylquinoxalin-2(1*H*)-one could afford the products in 60–62% yield. The scope of various *N*-substituted maleimides was also examined for this transformation, and all the tested maleimides furnished the targeted alkylated products in good to excellent yields. The authors also proposed a plausible reaction mechanism, as shown in Scheme 15. Initially, a catalytically active cationic ruthenium species (**A**) is generated from [Ru(*p*-cymene)Cl₂]₂ in the presence of AgSbF₆, AcOH and Cu(OAc)₂·H₂O. Subsequent coordination of species **A** with 1-methyl-3-phenylquinoxalin-2(1*H*)-one results in the formation of five-membered cycloruthenated intermediate **B**. Coordination of maleimide to it affords complex **C**, which undergoes migratory insertion to generate heptacyclic intermediate **D**. Finally, β-hydride elimination from intermediate **D** furnishes the desired alkylated product and regenerates cationic ruthenium species **A**.

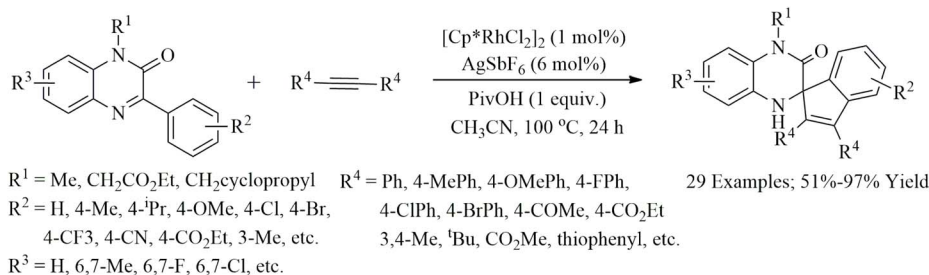
3.6. Spiro annulation

Spiro compounds constitute a distinctive class of three-dimensional molecular architectures that have garnered considerable attention in synthetic and medicinal chemistry.^{149,150} Their rigid, non-planar frameworks endow them with unique physicochemical characteristics, often improving the



Scheme 15 Plausible reaction mechanism for the Ru-catalyzed *ortho* C–H alkylation of the 3-phenyl ring of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones with maleimides.





Scheme 16 Rh(III)-catalyzed synthesis of spiro-quinoxalinone derivatives of 3-arylquinoxalin-2(1H)-ones.

metabolic stability, receptor selectivity, and bioavailability of drug molecules. Consequently, spiroannulation reactions have emerged as powerful synthetic strategies for the efficient assembly of these architecturally complex scaffolds. Recent years have witnessed remarkable progress in transition-metal-catalyzed, organocatalytic, and photoredox-mediated spiroannulation methodologies, providing streamlined access to spirocyclic systems with high levels of regio- and stereo-control.¹⁵¹ Collectively, these advancements have greatly enriched the synthetic toolbox for the rational design of spirocyclic molecules with tailored structures and biological significance. Notably, Zhang and co-workers, in 2020, developed an efficient Rh(III)-catalyzed tandem C–H functionalization/[3 + 2] annulation strategy for the synthesis of spiro-quinoxalinone derivatives from 3-arylquinoxalin-2(1H)-ones and internal alkynes.¹⁵² This method provided a practical and atom-economical route to a library of 27 spiro[1,2'-quinoxalin]-3'-ones, employing only 1 mol% [Cp*RhCl₂]₂ as the catalyst.

To begin with the development of this approach, *N*-methyl-3-phenylquinoxalin-2(1H)-one and 1,2-diphenylethyne were allowed to stir at 100 °C for 24 h in the presence of 1 mol% [Cp*RhCl₂]₂ in combination with 4 mol% AgSbF₆ as the catalytic system. This delivered the spiro compound in 62% yield; however, the addition of 1 equiv. of PivOH accelerated

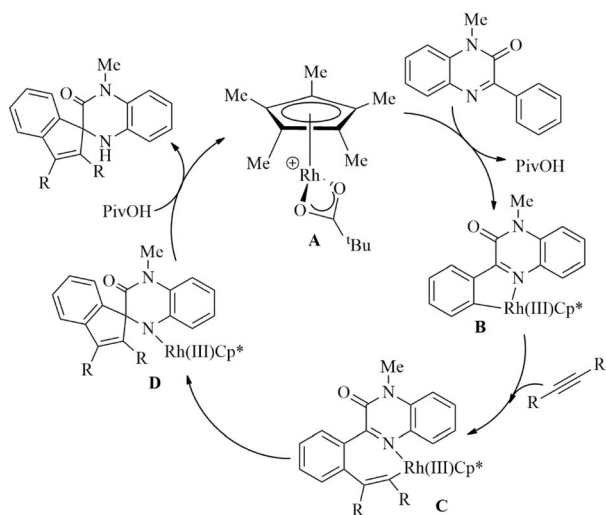
the C–H activation process, resulting in 86% product yield. This protocol was compatible with various substituted 3-phenylquinoxalin-2(1H)-ones. Substrates bearing electron-donating groups (Me and *i*Pr) at the *para*-position of the 3-aryl ring furnished the desired products in higher yields compared to those containing electron-withdrawing substituents (Cl, Br, CF₃, CN, and CO₂Et) (Scheme 16).

All symmetrical alkynes employed participated efficiently in the annulation reaction, delivering the desired products in high yields. Interestingly, the reaction of the unsymmetrical alkyne prop-1-yn-1-ylbenzene afforded two separable isomeric products in excellent overall yield but with moderate selectivity. Terminal alkynes such as phenylacetylene and ethyl propiolate failed to furnish the corresponding annulated products.

The catalytic cycle for this reaction begins with the coordination of quinoxalinone to cationic rhodium species **A**, followed by electrophilic C–H activation to form rhodacyclic intermediate **B**. Subsequent alkyne insertion into the Rh–C bond generates intermediate **C**, which undergoes intramolecular nucleophilic addition of the Rh–C bond to the imine moiety, affording intermediate **D**. Finally, protonation by PivOH releases the spiroquinoxalinone product and regenerates the Rh(III) catalyst, thereby completing the catalytic cycle (Scheme 17).

4. Conclusion and future perspectives

Recent years have witnessed the versatility of the transition-metal-catalyzed chelating-group-assisted selective functionalization of C(sp²)-H bonds for the formation of C–C and C–X (X = halogens, C, O, N, *etc.*) bonds and late-stage functionalization. This review provides an overview of Pd-, Ru-, and Rh-catalyzed regioselective functionalization of the *ortho*-C(sp²)-H bond of the 3-phenyl ring of *N*-alkyl-3-phenylquinoxalin-2(1H)-ones. Mechanistic insights are also elucidated to deepen the understanding required for the rational design of these methodologies. Ru(II)-catalysts have been shown to promote regioselective *ortho*-alkyl C–H activation through a cycloruthenated intermediate, offering good substrate tolerance and practical reaction conditions. Cp*Rh(III) systems exhibit enhanced reactivity in annulation, chalcogenation and photoredox transformations *via* well-defined rhodacycles, generally affording high yields and regioselectivity. In contrast, Pd(II)-catalyzed protocols offer



Scheme 17 Plausible reaction mechanism for Rh(III)-catalyzed tandem C–H functionalization/[3 + 2] annulation.



complementary reactivity, enabling C–H acylation and halogenation of the quinoxalinone framework through Pd(II)/Pd(IV) catalytic cycles, thereby expanding diversification strategies. Collectively, these metal-specific reactivity profiles provide a versatile platform for the site-selective functionalization of *N*-alkyl-3-phenylquinoxalin-2(1*H*)-ones.

Although momentous growth has been achieved in the regioselective functionalization of *N*-alkyl-3-phenylquinoxalin-2(1*H*)-one via transition-metal-catalyzed C–H activation, several critical areas still remained unexplored. There is a need to develop greener synthetic protocols by replacing toxic solvents with biomass-derived solvents or other environmentally benign alternatives. Furthermore, the use of photocatalysts, heterogenized metal–organic framework (MOF)-based catalysts, and direct transformations including alkenylation, alkylation, and amination warrants further investigation to extend the scope and applicability of selective C–H functionalization of *N*-alkyl-3-phenylquinoxalin-2(1*H*)-ones.

Author contributions

Prashant Kumar conducted the literature survey, prepared the manuscript, and contributed to editing, formatting and overall supervision throughout the manuscript preparation. Piya prepared the manuscript. Deepak Mishra and Naresh Kumar contributed to proof reading and editing of the manuscript. Sriparna Dutta contributed to editing, formatting and overall supervision throughout the manuscript preparation.

Conflicts of interest

There are no conflicts to declare.

Data availability

No new data were generated; hence, data sharing is not applicable to this article.

Acknowledgements

The authors are grateful to the SRM University, Delhi-NCR, Sonapat, and Hindu College, University of Delhi, for extending all the possible support for this research.

Notes and references

- 1 L. Shi, W. Hu, J. Wu, H. Zhou, H. Zhou and X. Li, Quinoxalinone as a privileged platform in drug development, *Mini-Rev. Med. Chem.*, 2018, **18**, 392, DOI: [10.2174/1389557517666171101111134](https://doi.org/10.2174/1389557517666171101111134).
- 2 A. Carta, S. Piras, G. Loriga and G. Paglietti, Chemistry, biological properties and SAR analysis of quinoxalinones, *Mini-Rev. Med. Chem.*, 2006, **6**, 1179, DOI: [10.2174/138955706778742713](https://doi.org/10.2174/138955706778742713).
- 3 X. Li, K.-H. Yang, W.-L. Li and W.-F. Xu, Recent advances in the research of quinoxalinone derivatives, *Drugs Future*, 2006, **31**, 979, DOI: [10.1358/dof.2006.031.11.1037128](https://doi.org/10.1358/dof.2006.031.11.1037128).

- 4 D. Chen and W. Bao, An efficient domino synthesis of quinoxalin-2(1*H*)-ones via an oxidative C–C bond formation reaction, *Adv. Synth. Catal.*, 2010, **352**, 955, DOI: [10.1002/adsc.200900859](https://doi.org/10.1002/adsc.200900859).
- 5 M. S. Goma, A. H. A. Ahmed, S. M. El Rayes, I. A. I. Ali, W. Fathalla, M. S. Alturki, A. H. Al Khzem, A. H. Almalki, M. F. Aldawsari, F. H. Pottoo, F. A. Khan and M. Amir, Synthesis and antiproliferative activity of 2-oxo-3-phenylquinoxaline derivatives and related compounds against colon cancer, *RSC Adv.*, 2024, **14**, 35679, DOI: [10.1039/D4RA06822J](https://doi.org/10.1039/D4RA06822J).
- 6 J. Quinn, C. Guo, L. Ko, B. Sun, Y. He and Y. Li, Pyrazino[2,3-*g*]quinoxaline-2,7-dione based π -conjugated polymers with affinity towards acids and semiconductor performance in organic thin film transistors, *RSC Adv.*, 2016, **6**, 22043, DOI: [10.1039/C5RA26227E](https://doi.org/10.1039/C5RA26227E).
- 7 X.-H. Liu, W. Yu, L.-J. Min, D. E. Wedge, C. X. Tan, J. Q. Weng, H.-K. Wu, C. L. Cantrell, J. Bajsa-Hirschel, X.-W. Hua and S. O. Duke, Synthesis and pesticidal activities of new quinoxalines, *J. Agric. Food Chem.*, 2020, **68**, 7324, DOI: [10.1021/acs.jafc.0c01042](https://doi.org/10.1021/acs.jafc.0c01042).
- 8 R. Liu, Z. Huang, M. G. Murray, X. Guo and G. Liu, Quinoxalin-2(1*H*)-One Derivatives As Inhibitors Against Hepatitis C Virus, *J. Med. Chem.*, 2011, **54**, 5747, DOI: [10.1021/jm200670t](https://doi.org/10.1021/jm200670t).
- 9 P. K. Singh and B. N. Choudhary, Exploring the Neuroprotective Effects of Some New Quinoxalines: A Novel Approach to Alzheimer's Disease Management, *Asian J. Res. Biochem.*, 2025, **15**, 188, DOI: [10.9734/ajrb/2025/v15i3400](https://doi.org/10.9734/ajrb/2025/v15i3400).
- 10 S. Mahajan, N. Slathia, V. K. Nuthakki, S. B. Bharate and K. K. Kapoor, Malononitrile-activated synthesis and anti-cholinesterase activity of styrylquinoxalin-2 (1 H)-ones, *RSC Adv.*, 2020, **10**, 15966, DOI: [10.1039/D0RA02816A](https://doi.org/10.1039/D0RA02816A).
- 11 G. Olayiwola, C. A. Obafemi and F. O. Taiwo, Synthesis and neuropharmacological activity of some quinoxalinone derivatives, *Afr. J. Biotechnol.*, 2007, **6**, 777.
- 12 X. Jiang, K. Wu, R. Bai, P. Zhang and Y. Zhang, Functionalized quinoxalinones as privileged structures with broad-ranging pharmacological activities, *Eur. J. Med. Chem.*, 2022, **229**, 114085, DOI: [10.1016/j.ejmech.2021.114085](https://doi.org/10.1016/j.ejmech.2021.114085).
- 13 X. Hao, X. Wang, Q. Jiang, Y. Zhu, Y. Zhu, M. Chen, G. Qi, C. Zhu and Z. Han, Novel Multifunctional Aldose Reductase Inhibitors Based on Quinoxalin-2 (1*H*)-one Scaffold for Treatment of Diabetic Complications: Design, Synthesis, and Biological Evaluation, *Chem. Biodivers.*, 2025, **22**, e202402358, DOI: [10.1002/cbdv.202402358](https://doi.org/10.1002/cbdv.202402358).
- 14 W. Jia, J. Wang, C. Wei, M. Bian, S. Bao and L. Yu, Synthesis and hypoglycemic activity of quinoxaline derivatives, *Front. Chem.*, 2023, **11**, 1197124, DOI: [10.3389/fchem.2023.1197124](https://doi.org/10.3389/fchem.2023.1197124).
- 15 M. S. Ayoup, A. R. Rabee, H. Abdel-Hamid, A. Amer, M. M. Abu-Serie, S. Ashraf, D. A. Ghareeb, R. S. Ibrahim, M. B. Hawsawi and M. Negm, Design and Synthesis of Quinoxaline Hybrids as Modulators of HIF-1 α , VEGF, and



- p21 for Halting Colorectal Cancer, *ACS Omega*, 2024, **9**, 24643, DOI: [10.1021/acsomega.4c01075](https://doi.org/10.1021/acsomega.4c01075).
- 16 L. Yang, P. Wang, J.-F. Wu, L.-M. Yang, R.-R. Wang, W. Pang, Y.-G. Li, Y.-M. Shen, Y.-T. Zheng and X. Li, Design, synthesis and anti-HIV-1 evaluation of hydrazide-based peptidomimetics as selective gelatinase inhibitors, *Bioorg. Med. Chem.*, 2016, **24**, 2125, DOI: [10.1016/j.bmc.2016.03.043](https://doi.org/10.1016/j.bmc.2016.03.043).
- 17 R. Liu, Z. Huang, M. G. Murray, X. Guo and G. Liu, Quinoxalin-2(1H)-one derivatives as inhibitors against hepatitis c virus, *J. Med. Chem.*, 2011, **54**, 5747, DOI: [10.1021/jm200394x](https://doi.org/10.1021/jm200394x).
- 18 H. M. Refaat, A. A. Moneer and O. M. Khalil, Synthesis and antimicrobial activity of certain novel quinoxalines, *Arch Pharm. Res.*, 2004, **27**, 1093, DOI: [10.1007/BF02975110](https://doi.org/10.1007/BF02975110).
- 19 P. Sanna, A. Carta, M. Loriga, S. Zanetti and L. Sechi, Synthesis of substituted 2-ethoxycarbonyl- and 2-carboxyquinoxalin-3-ones for evaluation of antimicrobial and anticancer activity, *Il Farmaco*, 1998, **53**, 455, DOI: [10.1016/S0014-827X\(98\)00044-5](https://doi.org/10.1016/S0014-827X(98)00044-5).
- 20 O. I. El-Sabbagh, M. E. El-Sadek, S. M. Lashine, S. H. Yassin and S. M. El-Nabtity, Synthesis of new 2(1H)-quinoxalinone derivatives for antimicrobial and antiinflammatory evaluation, *Med. Chem. Res.*, 2009, **18**, 782, DOI: [10.1007/s00044-009-9203-y](https://doi.org/10.1007/s00044-009-9203-y).
- 21 D. O. Koltun, E. Q. Parkhill, N. I. Vasilevich, A. I. Glushkov, T. M. Zilbershtein, A. V. Ivanov, A. G. Cole, I. Henderson, N. A. Zautke, S. A. Brunn, N. Mollova, K. Leung, J. W. Chisholm and J. Zablocki, Novel, Potent, selective, and metabolically stable stearoyl-CoA desaturase (SCD) inhibitors, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2048, DOI: [10.1016/j.bmcl.2009.02.019](https://doi.org/10.1016/j.bmcl.2009.02.019).
- 22 X. Qin, X. Hao, H. Han, S. Zhu, Y. Yang, B. Wu, S. Hussain, S. Parveen, C. Jing, B. Ma and C. Zhu, Design and synthesis of potent and multifunctional aldose reductase inhibitors based on quinoxalinones, *J. Med. Chem.*, 2015, **58**, 1254, DOI: [10.1021/jm501484b](https://doi.org/10.1021/jm501484b).
- 23 M. Weiwer, J. Spoonamore, J. Wei, B. Guichard, N. T. Ross, K. Masson, W. Silkworth, S. Dandapani, M. Palmer, C. A. Scherer, A. M. Stern, S. L. Schreiber and B. Munoz, A potent and selective quinoxalinone-based STK33 inhibitor does not show synthetic lethality in KRAS-dependent cells, *ACS Med. Chem. Lett.*, 2012, **3**, 1034, DOI: [10.1021/ml300246r](https://doi.org/10.1021/ml300246r).
- 24 J. A. Willardsen, D. A. Dudley, W. L. Cody, L. Chi, T. B. McClanahan, T. E. Mertz, R. E. Potoczak, L. S. Narasimhan, D. R. Holland, S. T. Rapundalo and J. J. Edmunds, Design synthesis, and biological activity of potent and selective inhibitors of blood coagulation factor Xa, *J. Med. Chem.*, 2004, **47**, 4089, DOI: [10.1021/jm0497491](https://doi.org/10.1021/jm0497491).
- 25 Q. Ke, G. Yan, J. Yu and X. Wu, Recent advances in the direct functionalization of quinoxalin-2(1H)-ones, *Org. Biomol. Chem.*, 2019, **17**, 5863, DOI: [10.1039/C9OB00782B](https://doi.org/10.1039/C9OB00782B).
- 26 P. Ghosh and S. Das, Recent advances and perspectives on the synthesis and C-H bond functionalization of quinoxalin-2(1H)-one, *Synth. Commun.*, 2020, **50**, 2266, DOI: [10.1080/00397911.2020.1765257](https://doi.org/10.1080/00397911.2020.1765257).
- 27 Y. Tan, J. Wang, H. Y. Zhang, Y. Zhang and J. Zhao, The C₃-H bond functionalization of quinoxalin-2(1H)-ones with hypervalent iodine(III) reagents, *Front. Chem.*, 2020, **8**, 582, DOI: [10.3389/fchem.2020.00582](https://doi.org/10.3389/fchem.2020.00582).
- 28 K. Sun, F. Xiao, B. Yu and W.-M. He, Photo-/electrocatalytic functionalization of quinoxalin-2(1H)-ones, *Chin. J. Catal.*, 2021, **42**, 1921, DOI: [10.1016/S1872-2067\(21\)63850-0](https://doi.org/10.1016/S1872-2067(21)63850-0).
- 29 A. Corio, C. Gravier-Pelletier and P. Busca, Regioselective functionalization of quinolines through CH activation: a comprehensive review, *Molecules*, 2021, **26**, 5467, DOI: [10.3390/molecules26185467](https://doi.org/10.3390/molecules26185467).
- 30 Q. Ke, G. Yan, J. Yu and X. Wu, Recent advances in the direct functionalization of quinoxalin-2(1H)-ones, *Org. Biomol. Chem.*, 2019, **17**, 5863, DOI: [10.1039/C9OB00782B](https://doi.org/10.1039/C9OB00782B).
- 31 Q. Yang, B. Wang, M. Wu and Y. Z. Lei, Recent developments in direct C-H Functionalization of quinoxalin-2(1H)-ones via multi-component tandem reactions, *Molecules*, 2013, **28**, 2513, DOI: [10.3390/molecules28062513](https://doi.org/10.3390/molecules28062513).
- 32 H. Xin, Y. Guo, Y. Hu, Y. Chang, Y. Guo and L. Shi, Recent advancements in visible-light-induced direct C(3)-H functionalization of quinoxalin-2(1H)-ones, *Green Synth. Catal.*, 2024, **7**, 24, DOI: [10.1016/j.gresc.2024.12.003](https://doi.org/10.1016/j.gresc.2024.12.003).
- 33 Q. Yang, H. Wang, X. Wang and Y. Lei, Recent developments in direct C-H functionalization of quinoxalin-2(1H)-ones via heterogeneous catalysis reactions, *Molecules*, 2023, **28**, 5030, DOI: [10.3390/molecules28135030](https://doi.org/10.3390/molecules28135030).
- 34 C. Sambiagio, D. Schönbauer, R. Blicke, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, A comprehensive overview of directing groups applied in metal-catalysed C-H functionalisation chemistry, *Chem. Soc. Rev.*, 2018, **47**, 6603, DOI: [10.1039/C8CS00201K](https://doi.org/10.1039/C8CS00201K).
- 35 S. V. Kumar, S. Banerjee and T. Punniyamurthy, Transition metal-catalyzed coupling of heterocyclic alkenes via C-H functionalization: recent trends and applications, *Org. Chem. Front.*, 2020, **7**, 1527, DOI: [10.1039/D0QO00279H](https://doi.org/10.1039/D0QO00279H).
- 36 B. Liu, L. Yang, P. Li, F. Wang and X. Li, Recent advances in transition metal-catalyzed olefinic C-H functionalization, *Org. Chem. Front.*, 2021, **8**, 1085, DOI: [10.1039/D0QO01159B](https://doi.org/10.1039/D0QO01159B).
- 37 J.-P. Wan, L. Gan and Y. Liu, Transition metal-catalyzed C-H bond functionalization in multicomponent reactions: a tool toward molecular diversity, *Org. Biomol. Chem.*, 2017, **15**, 9031, DOI: [10.1039/C7OB02011B](https://doi.org/10.1039/C7OB02011B).
- 38 D. Basu, S. Kumar, V. Sai Sudhir and R. Bandichhor, Transition metal catalyzed C-H activation for the synthesis of medicinally relevant molecules: a review, *J. Chem. Sci.*, 2018, **130**, 71, DOI: [10.1007/s12039-018-1468-6](https://doi.org/10.1007/s12039-018-1468-6).
- 39 B. Li, A. I. M. Ali and H. Ge, Recent advances in using transition-metal-catalyzed C-H functionalization to build fluorescent materials, *Chem*, 2020, **6**, 2591, DOI: [10.1016/j.chempr.2020.08.017](https://doi.org/10.1016/j.chempr.2020.08.017).
- 40 T. Rogge, N. Kaplaneris, N. Chatani, J. Kim, S. Chang, B. Punji, L. L. Schafer, D. G. Musaev, J. Wencel-Delord,



- C. A. Roberts, R. Sarpong, Z. E. Wilson, M. A. Brimble, M. J. Johansson and L. Ackermann, C–H activation, *Nat. Rev. Methods Primers*, 2021, **1**, 41, DOI: [10.1038/s43586-021-00041-2](https://doi.org/10.1038/s43586-021-00041-2).
- 41 J. Zhang, X. Lu, C. Shen, L. Xu, L. Ding and G. Zhong, Recent advances in chelation-assisted site- and stereoselective alkenyl C–H functionalization, *Chem. Soc. Rev.*, 2021, **50**, 3263, DOI: [10.1039/D0CS00447B](https://doi.org/10.1039/D0CS00447B).
- 42 P. Kumar, S. Dutta, D. Batra, D. Mishra, D. Kumar, G. Bhalla and B. K. Singh, Selective functionalization of 2-phenyl-4H-benzo[d][1,3]oxazin-4-ones via C–H activation, *Tetrahedron*, 2025, **173**, 134466, DOI: [10.1016/j.tet.2025.134466](https://doi.org/10.1016/j.tet.2025.134466).
- 43 X.-J. Si, T.-C. Wang, T.-P. Loh and M.-Z. Lu, Recent advances in catalytic asymmetric alkenyl C(sp²)-H bond functionalizations, *Chem. Sci.*, 2025, **16**, 5836, DOI: [10.1039/D5SC00623F](https://doi.org/10.1039/D5SC00623F).
- 44 A. García-Viada, J. C. Carretero, J. Adrio and N. Rodríguez, Insights into the mechanism of 3d transition-metal-catalyzed directed C(sp³)-H bond functionalization reactions, *Chem. Soc. Rev.*, 2025, **54**, 4353, DOI: [10.1039/D4CS00657G](https://doi.org/10.1039/D4CS00657G).
- 45 G. Meng, N. Y. S. Lam, E. L. Lucas, T. G. Saint-Denis, P. Verma, N. Chekshin and J.-Q. Yu, Achieving site-selectivity for C–H activation processes based on distance and geometry: a carpenter's approach, *J. Am. Chem. Soc.*, 2020, **142**, 10571, DOI: [10.1021/jacs.0c04074](https://doi.org/10.1021/jacs.0c04074).
- 46 A. Dey, S. Maity and D. Maiti, Reaching the south: metal-catalyzed transformation of the aromatic *para*-position, *Chem. Commun.*, 2016, **52**, 12398, DOI: [10.1039/C6CC05235E](https://doi.org/10.1039/C6CC05235E).
- 47 A. Dey, S. K. Sinha, T. K. Achar and D. Maiti, Accessing Remote *meta*- and *para*-C(sp²)-H Bonds with covalently attached directing groups, *Angew. Chem., Int. Ed.*, 2019, **58**, 10820, DOI: [10.1002/anie.201812116](https://doi.org/10.1002/anie.201812116).
- 48 R. Giri, B. F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, Transition metal-catalyzed C–H activation reactions: diastereoselectivity and enantioselectivity, *Chem. Soc. Rev.*, 2009, **38**, 3242, DOI: [10.1039/b816707a](https://doi.org/10.1039/b816707a).
- 49 X. Chen, K. M. Engle, D. H. Wang and J.-Q. Yu, Palladium(II)-catalyzed CH activation/CC cross-coupling reactions: versatility and practicality, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094, DOI: [10.1002/anie.200806273](https://doi.org/10.1002/anie.200806273).
- 50 J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, Towards mild metal-catalyzed C–H bond activation, *Chem. Soc. Rev.*, 2011, **40**, 4740, DOI: [10.1039/C1CS15083A](https://doi.org/10.1039/C1CS15083A).
- 51 K. M. Engle, T. S. Mei, M. Wasa and J.-Q. Yu, Weak coordination as a powerful means for developing broadly useful C–H functionalization reactions, *Acc. Chem. Res.*, 2012, **45**, 788, DOI: [10.1021/ar200185g](https://doi.org/10.1021/ar200185g).
- 52 Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, Transition metal-catalyzed C–H bond functionalizations by the use of diverse directing groups, *Org. Chem. Front.*, 2015, **2**, 1107, DOI: [10.1039/C5QO00004A](https://doi.org/10.1039/C5QO00004A).
- 53 T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, Mild metal-catalyzed C–H activation: examples and concepts, *Chem. Soc. Rev.*, 2016, **45**, 2900, DOI: [10.1039/C6CS00075D](https://doi.org/10.1039/C6CS00075D).
- 54 P. Kumar, R. S. K. Lalji, M. Gupta, V. S. Parmar and B. K. Singh, Palladium-catalyzed decarboxylative synthesis of 5H-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6*aH*)-diones using 2-phenyl-4H-benzo[d][1,3]oxazin-4-ones and α -oxo carboxylic acids, *Adv. Synth. Catal.*, 2019, **362**, 552, DOI: [10.1002/adsc.201901142](https://doi.org/10.1002/adsc.201901142).
- 55 M. Gupta, S. Kumar, P. Kumar, A. K. Singh, V. Bahadur and B. K. Singh, *N*-directed Pd-catalyzed direct *ortho*-acetoxylation and *ortho*-*tert*-butoxylation of 2-phenyl-4H-benzo[d][1,3]oxazin-4-ones via C–H activation, *ChemistrySelect*, 2019, **4**, 13992, DOI: [10.1002/slct.201902755](https://doi.org/10.1002/slct.201902755).
- 56 J. Zhang, L. Yao, J.-Y. Su, Y.-Z. Liu, Q. Wang and W. P. Deng, Transition-metal-catalyzed aromatic C–H functionalization assisted by the phosphorus-containing directing groups, *Green Synth. Catal.*, 2023, **4**, 206, DOI: [10.1016/j.gresc.2023.02.001](https://doi.org/10.1016/j.gresc.2023.02.001).
- 57 S. R. Mohanty, N. Prusty, T. Nanda, P. S. Mahulkar and P. C. Ravikumar, Directing group-assisted selective C–H activation of six-membered *N*-heterocycles and benzo-fused *N*-heterocycles, *Org. Chem. Front.*, 2024, **11**, 540, DOI: [10.1039/D3QO01396K](https://doi.org/10.1039/D3QO01396K).
- 58 A. D. Ryabov, Cyclopalladated complexes in organic synthesis, *Synthesis*, 1985, 233, DOI: [10.1055/s-1985-31169](https://doi.org/10.1055/s-1985-31169).
- 59 O. Daugulis, H.-Q. Do and D. Shabashov, Palladium- and copper-catalyzed arylation of carbon-hydrogen bonds, *Acc. Chem. Res.*, 2009, **42**, 1074, DOI: [10.1021/ar9000058](https://doi.org/10.1021/ar9000058).
- 60 D. A. Colby, R. G. Bergman and J. A. Ellman, Rhodium-catalyzed c–c bond formation via heteroatom-directed C–H bond activation, *Chem. Rev.*, 2010, **110**, 624, DOI: [10.1021/cr900005n](https://doi.org/10.1021/cr900005n).
- 61 L. Ackermann, Carboxylate-assisted transition-metal-catalyzed c–h bond functionalizations: mechanism and scope, *Chem. Rev.*, 2011, **111**, 1315, DOI: [10.1021/cr100412j](https://doi.org/10.1021/cr100412j).
- 62 H. P. L. Gemoets, I. Kalvet, A. V. Nyuchev, N. Erdmann, V. Hessel, F. Schoenebeck and T. Noël, Mild and selective base-free C–H arylation of heteroarenes: experiment and computation, *Chem. Sci.*, 2017, **8**, 1046, DOI: [10.1039/C6SC02595A](https://doi.org/10.1039/C6SC02595A).
- 63 J. R. Hummel, J. A. Boerth and J. A. Ellman, Transition-metal-catalyzed C–H bond addition to carbonyls, imines, and related polarized π bonds, *Chem. Rev.*, 2017, **117**, 9163, DOI: [10.1021/acs.chemrev.6b00661](https://doi.org/10.1021/acs.chemrev.6b00661).
- 64 A. Carrer, J. D. Brion, S. Messaoudi and M. Alami, Synthesis of 3,4-disubstituted quinolin-2-(1*H*)-ones via palladium-catalyzed decarboxylative arylation reactions, *Org. Lett.*, 2013, **15**, 5606, DOI: [10.1002/adsc.201300299](https://doi.org/10.1002/adsc.201300299).
- 65 C. J. Mulligan, S. M. Bagale, O. J. Newton, J. S. Parker and K. K. M. Hii, Peracetic acid: an atom-economical reagent for Pd-catalyzed acetoxylation of C–H bonds, *ACS Sustain. Chem. Eng.*, 2019, **7**, 1611, DOI: [10.1021/acssuschemeng.8b05370](https://doi.org/10.1021/acssuschemeng.8b05370).
- 66 R. Sheng, X. Lin, J. Li, Y. Jiang, Z. Shang and Y. Hu, Design, synthesis, and evaluation of 2-phenoxy-indan-1-one derivatives as acetylcholinesterase inhibitors, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3834, DOI: [10.1016/j.bmcl.2005.05.132](https://doi.org/10.1016/j.bmcl.2005.05.132).



- 67 G. Martelli, M. Cirillo, V. Giraldi and D. Giacomini, Chemoenzymatic enantioselective route to get (+) and (–) 4-acetoxy-azetid-2-one by lipase-catalysed kinetic resolution and their applications, *Bioorg. Chem.*, 2022, **120**, 105580, DOI: [10.1016/j.bioorg.2021.105580](https://doi.org/10.1016/j.bioorg.2021.105580).
- 68 D. J. Foley and H. Waldmann, Ketones as strategic building blocks for the synthesis of natural product-inspired compounds, *Chem. Soc. Rev.*, 2022, **51**, 4094, DOI: [10.1039/D2CS00101B](https://doi.org/10.1039/D2CS00101B).
- 69 M. D. Barratt, J. V. Castell, M. A. Miranda and J. J. Langowski, Development of an expert system rulebase for the prospective identification of photoallergens, *J. Photochem. Photobiol., B*, 2000, **58**, 54, DOI: [10.1016/S1011-1344\(00\)00100-7](https://doi.org/10.1016/S1011-1344(00)00100-7).
- 70 E. A. Smith, J. G. Marshall, S. S. Selph, D. R. Barker and C. M. Sedgley, Nonsteroidal anti-inflammatory drugs for managing postoperative endodontic pain in patients who present with preoperative pain: a systematic review and meta-analysis, *J. Endod.*, 2017, **43**, 7, DOI: [10.1016/j.joen.2016.09.010](https://doi.org/10.1016/j.joen.2016.09.010).
- 71 V. Agarwal, M. Bajpai and A. Sharma, Patented and approval scenario of nanopharmaceuticals with relevancy to biomedical application, manufacturing procedure and safety aspects, *Recent Pat. Drug Delivery Formulation*, 2018, **12**, 40, DOI: [10.2174/1872211312666180105114644](https://doi.org/10.2174/1872211312666180105114644).
- 72 J. Zheng, Metabolic activation-based design of uricosuric benzofuran derivatives with low potential of hepatotoxicity, *Drug Metab. Pharmacokinet.*, 2018, **33**, S70, DOI: [10.1016/j.dmpk.2018.01.189](https://doi.org/10.1016/j.dmpk.2018.01.189).
- 73 S. C. Zimmermann, T. Tichý, J. Vávra, R. P. Dash, C. E. Slusher, A. J. Gadiano, Y. Wu, A. Jančařík, L. Tenora, L. Monincová, E. Prchalová, G. J. Riggins, P. Majer, B. S. Slusher and R. Rais, *N*-substituted prodrugs of mebendazole provide improved aqueous solubility and oral bioavailability in mice and dogs, *J. Med. Chem.*, 2018, **61**, 3918, DOI: [10.1021/acs.jmedchem.7b01792](https://doi.org/10.1021/acs.jmedchem.7b01792).
- 74 G. Ding, C. Jing, X. Qin, Y. Gong, X. Zhang, S. Zhang, Z. Luo, H. Li and F. Gao, Conjugated dyes carrying *N,N*-dialkylamino and ketone groups: One-component visible light Norrish type II photoinitiators, *Dyes Pigm.*, 2017, **137**, 456, DOI: [10.1016/j.dyepig.2016.10.034](https://doi.org/10.1016/j.dyepig.2016.10.034).
- 75 H. Zhang, T. Yuan, N. Zhumabay, Z. Ruan, H. Qian and M. Rueping, Ketone-functionalized conjugated organic polymers boost red-light-driven molecular oxygen-mediated oxygenation, *Chem. Sci.*, 2024, **15**, 17435, DOI: [10.1039/D4SC05816J](https://doi.org/10.1039/D4SC05816J).
- 76 P. Kumar, S. Dutta, S. Kumar, V. Bahadur, E. V. Van der Eycken, K. S. Vimalaswaran, V. S. Parmar and B. K. Singh, Aldehydes: magnificent acyl equivalents for direct acylation, *Org. Biomol. Chem.*, 2020, **18**, 7987, DOI: [10.1039/D0OB01458C](https://doi.org/10.1039/D0OB01458C).
- 77 D. M. Kitcatt, E. Pogacar, L. Mi, S. Nicolle and A. L. Lee, Light-Mediated Direct Decarboxylative Giese Arylations without a Photocatalyst, *J. Org. Chem.*, 2024, **89**, 16055, DOI: [10.1021/acs.joc.4c02163](https://doi.org/10.1021/acs.joc.4c02163).
- 78 M. Shahid, A. J. Punnya, S. S. Babu, S. Sarkar and P. Gopinath, Dual palladium-photoredox-mediated regioselective acylation of carbazoles and Indolines, *J. Org. Chem.*, 2023, **88**, 13686, DOI: [10.1021/acs.joc.3c01350](https://doi.org/10.1021/acs.joc.3c01350).
- 79 Y. He, G. Wang, W. Hu, D. Wei, J. Jia, H. Li and B. Yuan, Piezocatalyzed decarboxylative acylation of quinoxalin-2 (1H)-ones using ball milling, *ACS Sustain. Chem. Eng.*, 2023, **11**, 910, DOI: [10.1021/acssuschemeng.2c04720](https://doi.org/10.1021/acssuschemeng.2c04720).
- 80 V. Dinesh and R. Nagarajan, (NH₄)₂S₂O₈-mediated metal-free decarboxylative formylation/acylation of α -oxo/ketoacids and its application to the synthesis of indole alkaloids, *J. Org. Chem.*, 2022, **87**, 10359, DOI: [10.1021/acs.joc.2c00552](https://doi.org/10.1021/acs.joc.2c00552).
- 81 F. Penteado, E. F. Lopes, D. Alves, G. Perin, R. G. Jacob and E. J. Lenardão, α -Keto acids: acylating agents in organic synthesis, *Chem. Rev.*, 2019, **119**, 7113, DOI: [10.1021/acs.chemrev.8b0078](https://doi.org/10.1021/acs.chemrev.8b0078).
- 82 B. Yang and R. Y. Tang, Direct synthesis of dialkyl ketones from deoxygenative cross-coupling of carboxylic acids and alcohols, *Chem. Sci.*, 2024, **15**, 18405, DOI: [10.1039/D4SC05420B](https://doi.org/10.1039/D4SC05420B).
- 83 S. Kumar, R. S. K. Lalji, M. Gupta, P. Kumar, R. Kumar and B. K. Singh, Sustainable C-H activation approach for palladium-catalyzed, regioselective functionalization of 1-methyl-3-phenyl quinoxaline-2(1H)-ones in water, *Org. Biomol. Chem.*, 2022, **20**, 8944, DOI: [10.1039/D2OB01451C](https://doi.org/10.1039/D2OB01451C).
- 84 M. Prince, P. Kumar and B. K. Singh, Visible-light-driven regioselective decarboxylative acylation of *N*-methyl-3-phenylquinoxalin-2(1H)-one by dual palladium-photoredox catalysis through C-H activation, *ACS Omega*, 2023, **9**, 651, DOI: [10.1021/acsomega.3c06367](https://doi.org/10.1021/acsomega.3c06367).
- 85 A. de Meijere and F. Diederich, *Metal-catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, Germany, 2004.
- 86 K. C. Nicolaou, P. G. Bulger and D. Sarlah, Palladium-catalyzed cross-coupling reactions in total synthesis, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442, DOI: [10.1002/anie.200500368](https://doi.org/10.1002/anie.200500368).
- 87 J. Hassan, M. Sevignon, C. Gozzi, E. Schulz and M. Lemaire, Aryl-aryl bond formation one century after the discovery of the Ullmann reaction, *Chem. Rev.*, 2002, **102**, 1359, DOI: [10.1021/cr000664r](https://doi.org/10.1021/cr000664r).
- 88 A. F. Littke and G. C. Fu, Palladium-catalyzed coupling reactions of aryl chlorides, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176, DOI: [10.1002/1521-3773\(20021115\)41:22<4176::AID-ANIE4176>3.0.CO;2-U](https://doi.org/10.1002/1521-3773(20021115)41:22<4176::AID-ANIE4176>3.0.CO;2-U).
- 89 R. Stürmer, Take the Right Catalyst: Palladium-catalyzed C-C, C-N, and C-O bond formation on chloroarenes, *Angew. Chem., Int. Ed.*, 1999, **38**, 3307, DOI: [10.1002/\(SICI\)1521-3773\(19991115\)38:22<3307::AID-ANIE3307>3.0](https://doi.org/10.1002/(SICI)1521-3773(19991115)38:22<3307::AID-ANIE3307>3.0).
- 90 D. J. Spielvogel and S. L. Buchwald, Nickel-BINAP catalyzed enantioselective α -arylation of α -substituted γ -butyrolactones, *J. Am. Chem. Soc.*, 2002, **124**, 3500, DOI: [10.1021/ja017545t](https://doi.org/10.1021/ja017545t).
- 91 A. F. Littke and G. C. Fu, A Convenient and general method for pd-catalyzed suzuki cross-couplings of aryl chlorides and arylboronic acids, *Angew. Chem., Int. Ed.*, 1998, **37**, 3387, DOI: [10.1002/\(SICI\)1521-3773\(19981231\)37:24<3387::AID-ANIE3387>3.0](https://doi.org/10.1002/(SICI)1521-3773(19981231)37:24<3387::AID-ANIE3387>3.0).



- 92 B. M. Choudary, C. Sridhar, M. L. Kantam, G. T. Venkanna and B. Sreedhar, Design and evolution of copper apatite catalysts for n-arylation of heterocycles with chloro- and fluoroarenes, *J. Am. Chem. Soc.*, 2005, **127**, 9948, DOI: [10.1021/ja0436594](https://doi.org/10.1021/ja0436594).
- 93 M. Neetha, C. M. A. Afsina, T. Aneja and G. Anilkumar, Recent advances and prospects in the palladium-catalyzed cyanation of aryl halides, *RSC Adv.*, 2020, **10**, 33683, DOI: [10.1039/D0RA05960A](https://doi.org/10.1039/D0RA05960A).
- 94 K. Kolahdouzan, R. Khalaf, J. M. Grandner, Y. Chen, J. A. Terrett and M. P. Huestis, Dual Photoredox/nickel-catalyzed conversion of aryl halides to aryl aminooxetanes: computational evidence for a substrate-dependent switch in mechanism, *ACS Catal.*, 2020, **10**, 405, DOI: [10.1021/acscatal.9b03596](https://doi.org/10.1021/acscatal.9b03596).
- 95 P. B. D. De La Mare, *Electrophilic Halogenation*, Cambridge University Press, New York, 1976.
- 96 H. H. Hodgson, The Sandmeyer reaction, *Chem. Rev.*, 1947, **40**, 251, DOI: [10.1021/cr60126a003](https://doi.org/10.1021/cr60126a003).
- 97 T. Sandmeyer, Ueber die Ersetzung der Amidgruppe durch Chlor in den aromatischen Substanzen, *Ber. Dtsch. Chem. Ges.*, 1884, **17**, 1633, DOI: [10.1002/cber.18840170219](https://doi.org/10.1002/cber.18840170219).
- 98 S. Mukhopadhyay and S. Batra, Direct transformation of arylamines to aryl halides via sodium nitrite and n-halosuccinimide, *Chem. Eur. J.*, 2018, **24**, 14622, DOI: [10.1002/chem.201803347](https://doi.org/10.1002/chem.201803347).
- 99 R. Akhtar, A. F. Zahoor, N. Rasool, M. Ahmad and K. G. Ali, Recent trends in the chemistry of Sandmeyer reaction: a review, *Mol. Diversity*, 2022, **26**, 1837, DOI: [10.1007/s11030-021-10295-3](https://doi.org/10.1007/s11030-021-10295-3).
- 100 Z. Ma, H. Lu, K. Liao and Z. Chen, Tungstate-catalyzed biomimetic oxidative halogenation of (hetero)arene under mild condition, *iScience*, 2020, **23**, 101072, DOI: [10.1016/j.isci.2020.101072](https://doi.org/10.1016/j.isci.2020.101072).
- 101 V. Snieckus, Directed *ortho* metalation. tertiary amide and *O*-carbamate directors in synthetic strategies for polysubstituted aromatics, *Chem. Rev.*, 1990, **90**, 879, DOI: [10.1021/cr00104a001](https://doi.org/10.1021/cr00104a001).
- 102 P. Beak and V. Snieckus, Directed lithiation of aromatic tertiary amides: an evolving synthetic methodology for polysubstituted aromatics, *Acc. Chem. Res.*, 1982, **15**, 306, DOI: [10.1021/ar00082a002](https://doi.org/10.1021/ar00082a002).
- 103 K. Tanemura, Recent advances in the electrophilic halogenation of aromatic compounds using *N*-halosuccinimides (NXS), *Tetrahedron Lett.*, 2024, **155**, 155419, DOI: [10.1016/j.tetlet.2024.155419](https://doi.org/10.1016/j.tetlet.2024.155419).
- 104 P. Sharma, V. Luxami and K. Paul, C-H bond halogenation: unlocking regiodivergence and enhancing selectivity through directing group strategies, *Org. Chem. Front.*, 2025, **12**, 4066, DOI: [10.1039/D5QO00372E](https://doi.org/10.1039/D5QO00372E).
- 105 S. Kumar, P. Prince, M. Monika, P. Kumar, C. Len and B. K. Singh, A unified, microwave-assisted, palladium-catalyzed regioselective *ortho*-monohalogenation of 1-alkyl/benzyl-3-phenylquinoxalin-2(1*H*)-ones, *ChemistrySelect*, 2023, **8**, e202204821, DOI: [10.1002/slct.202204821](https://doi.org/10.1002/slct.202204821).
- 106 C. B. Mishra, S. Kumari and M. Tiwari, Thiazole: A promising heterocycle for the development of potent CNS active agents, *Eur. J. Med. Chem.*, 2015, **92**, 1, DOI: [10.1016/j.ejmech.2014.12.031](https://doi.org/10.1016/j.ejmech.2014.12.031).
- 107 S. E. Ayati, A. Asadipour, A. Shafiee and A. Foroumadi, Recent applications of 1,3-thiazole core structure in the identification of new lead compounds and drug discovery, *Eur. J. Med. Chem.*, 2015, **97**, 699, DOI: [10.1016/j.ejmech.2015.04.015](https://doi.org/10.1016/j.ejmech.2015.04.015).
- 108 P. Sun, D. Yang, W. Wei, L. Jiang, Y. Wang, T. Dai and H. Wang, DMSO-promoted regioselective synthesis of sulfenylated pyrazoles via a radical pathway, *Org. Chem. Front.*, 2017, **4**, 1367, DOI: [10.1039/C7QO00218A](https://doi.org/10.1039/C7QO00218A).
- 109 M. Klečka, R. Pohl, J. Čejka and M. Hocek, Direct C-H sulfenylation of purines and deazapurines, *Org. Biomol. Chem.*, 2013, **11**, 5189, DOI: [10.1039/C3OB40881G](https://doi.org/10.1039/C3OB40881G).
- 110 S. Patai, *The Chemistry of the Thiol Group*, Wiley, 1974.
- 111 L. A. Damani, *Sulfur Containing Drugs and Related Organic Compounds: Chemistry, Biochemistry, and Toxicology, Part B: Metabolism of Sulfur Functional Groups*, Ellis Horwood Ltd, Chichester, UK, 1989, vol. 1.
- 112 R. J. Cremllyn, *An Introduction to Organosulfur Chemistry*, Wiley & Sons, New York, 1996.
- 113 M. D. McReynolds, J. M. Dougherty and P. R. Hanson, Synthesis of phosphorus and sulfur heterocycles via ring-closing olefin metathesis, *Chem. Rev.*, 2004, **104**, 2239, DOI: [10.1021/cr020109k](https://doi.org/10.1021/cr020109k).
- 114 J. Zhao and X. Jiang, The application of sulfur-containing peptides in drug discovery, *Chin. Chem. Lett.*, 2018, **29**, 1079, DOI: [10.1016/j.cclet.2018.05.026](https://doi.org/10.1016/j.cclet.2018.05.026).
- 115 P. Chauhan, S. Mahajan and D. Enders, Organocatalytic carbon-sulfur bond-forming reactions, *Chem. Rev.*, 2014, **114**, 8807, DOI: [10.1021/cr500235v](https://doi.org/10.1021/cr500235v).
- 116 F. Bernardi, I. G. Csizmadia and A. Mangini, *Organic Sulfur Chemistry: theoretical and Experimental Advances*, Elsevier, 1985.
- 117 K. C. Nicolaou, C. R. H. Hale, C. Nilewski and H. A. Ioannidou, Constructing molecular complexity and diversity: total synthesis of natural products of biological and medicinal importance, *Chem. Soc. Rev.*, 2012, **41**, 5185, DOI: [10.1039/C2CS35116A](https://doi.org/10.1039/C2CS35116A).
- 118 M. Feng, B. Tang, S. H. Liang and X. Jiang, Sulfur containing scaffolds in drugs: synthesis and application in medicinal chemistry, *Curr. Top. Med. Chem.*, 2016, **16**, 1200, DOI: [10.2174/1568026615666150915111741](https://doi.org/10.2174/1568026615666150915111741).
- 119 E. A. Ilardi, E. Vitaku and J. T. Njardarson, Data-mining for sulfur and fluorine: an evaluation of pharmaceuticals to reveal opportunities for drug design and discovery, *J. Med. Chem.*, 2014, **57**, 2832, DOI: [10.1021/jm401375q](https://doi.org/10.1021/jm401375q).
- 120 L. Engman, I. Cotgreave, M. Angulo, C. W. Taylor, G. D. P. Murrieta and G. Powis, Diaryl chalcogenides as selective inhibitors of thioredoxin reductase and potential antitumor agents, *Anticancer Res.*, 1997, **17**, 4599.
- 121 J. A. Woods, J. A. Hadfield, A. T. McGown and B. W. Fox, Bioactivity and molecular modelling of diphenylsulfides and diphenylselenides, *Bioorg. Med. Chem.*, 1993, **5**, 333, DOI: [10.1016/S0968-0896\(00\)82139-2](https://doi.org/10.1016/S0968-0896(00)82139-2).



- 122 P. Diaz, F. Gendre and J. M. Bernardon, New selenium-containing acetylenic retinoids by direct coupling of alkynyl silanes with selenyl halides, *Tetrahedron Lett.*, 1998, **39**, 9003, DOI: [10.1016/S0040-4039\(98\)02038-3](https://doi.org/10.1016/S0040-4039(98)02038-3).
- 123 C. Sanchez, K. E. Asin and F. Artigas, Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data, *Pharmacol. Ther.*, 2015, **145**, 43, DOI: [10.1016/j.pharmthera.2014.07.001](https://doi.org/10.1016/j.pharmthera.2014.07.001).
- 124 S. F. Nielsen, E. O. Nielsen, G. M. Olsen, T. Liljefors and D. Peters, novel potent ligands for the central nicotinic acetylcholine receptor: synthesis, receptor binding, and 3D-QSAR analysis, *J. Med. Chem.*, 2000, **43**, 2217, DOI: [10.1021/jm990973d](https://doi.org/10.1021/jm990973d).
- 125 L. F. B. Duarte, R. L. Oliveira, K. C. Rodrigues, G. T. Voss, B. Godoi, R. C. Schumacher, G. Perin, E. A. Wilhelm, C. Luchese and D. Alves, Organoselenium compounds from purines: Synthesis of 6-arylselanylpurines with antioxidant and anticholinesterase activities and memory improvement effect, *Bioorg. Med. Chem.*, 2017, **25**, 6718, DOI: [10.1016/j.bmc.2017.11.019](https://doi.org/10.1016/j.bmc.2017.11.019).
- 126 R. J. Horton, Albendazole in treatment of human cystic echinococcosis: 12 years of experience, *Acta Trop.*, 1997, **64**, 79, DOI: [10.1016/S0001-706X\(96\)00640-7](https://doi.org/10.1016/S0001-706X(96)00640-7).
- 127 A. Gangjee, Y. Zeng, T. Talreja, J. J. McGuire, R. L. Kisliuk and S. F. Queener, Design and synthesis of classical and nonclassical 6-arylthio-2,4-diamino-5-ethylpyrrolo[2,3-d]pyrimidines as antifolates, *J. Med. Chem.*, 2007, **50**, 3046, DOI: [10.1021/jm070165j](https://doi.org/10.1021/jm070165j).
- 128 E. J. Lenardão, C. Santi and L. Sancineto, *New Frontiers in Organoselenium Compounds*, Cham, Switzerland: Springer, Vol. 6330, 2018, DOI: [10.1007/978-3-319-92405-2](https://doi.org/10.1007/978-3-319-92405-2).
- 129 E. Regis, L. D. O. Aguiar, P. Tuzimoto, E. Girott, T. E. Frizon, A. G. D. Bo, E. Zapp, R. Marra, H. Gallardo and A. A. Vieira, Effect of heteroatom exchange (S/Se) in the mesomorphism and physical properties of benzochalcogenodiazole-based liquid crystals, *Dyes Pigm.*, 2018, **157**, 109, DOI: [10.1016/j.dyepig.2018.04.049](https://doi.org/10.1016/j.dyepig.2018.04.049).
- 130 G. C. Hoover and D. S. Seferos, Photoactivity and optical applications of organic materials containing selenium and tellurium, *Chem. Sci.*, 2019, **10**, 9182, DOI: [10.1039/C9SC04279B](https://doi.org/10.1039/C9SC04279B).
- 131 A. E. Baumann, D. A. Burns, B. Liu and V. S. Thoi, Metal-organic framework functionalization and design strategies for advanced electrochemical energy storage devices, *Commun. Chem.*, 2019, **2**, 86, DOI: [10.1038/s42004-019-0184-6](https://doi.org/10.1038/s42004-019-0184-6).
- 132 D. A. Boyd, Sulfur and its role in modern materials science, *Angew. Chem., Int. Ed.*, 2016, **55**, 15486, DOI: [10.1002/anie.201604615](https://doi.org/10.1002/anie.201604615).
- 133 D. K. Dang, C. Sundaram, Y. L. T. Ngo, W. M. Choi, J. S. Chung, E. J. Kim and S. H. Hur, Pyromellitic acid-derived highly fluorescent N-doped carbon dots for the sensitive and selective determination of 4-nitrophenol, *Dyes Pigm.*, 2019, **165**, 327, DOI: [10.1016/j.dyepig.2019.02.029](https://doi.org/10.1016/j.dyepig.2019.02.029).
- 134 P. Gaur, A. Kumar, G. Dey, R. Kumar, S. Bhattacharyya and S. Ghosh, Selenium incorporated cationic organochalcogen: live cell compatible and highly photostable molecular stain for imaging and localization of intracellular DNA, *ACS Appl. Mater. Interfaces*, 2016, **8**, 10690, DOI: [10.1021/acsami.6b00675](https://doi.org/10.1021/acsami.6b00675).
- 135 G. Wang, Q. Guo, D. Chen, Z. Liu, X. Zheng, A. Xu, S. Yang and G. Ding, Facile and highly effective synthesis of controllable lattice sulfur-doped graphene quantum dots via hydrothermal treatment of durian, *ACS Appl. Mater. Interfaces*, 2018, **10**, 5750, DOI: [10.1021/acsami.7b16002](https://doi.org/10.1021/acsami.7b16002).
- 136 S. Yang, J. Sun, P. He, X. Deng, Z. Wang, C. Hu, G. Ding and X. Xie, Selenium doped graphene quantum dots as an ultrasensitive redox fluorescent switch, *Chem. Mater.*, 2015, **27**, 2004, DOI: [10.1021/acs.chemmater.5b00112](https://doi.org/10.1021/acs.chemmater.5b00112).
- 137 R. S. K. Lalji, M. Gupta, S. Kumar, A. Kumar and B. K. Singh, Rhodium-catalyzed selenylation and sulfenylation of quinoxalinones 'on water', *RSC Adv.*, 2023, **13**, 6191, DOI: [10.1039/D2RA07400A](https://doi.org/10.1039/D2RA07400A).
- 138 Z. Dong, Z. Ren, S. J. Thompson, Y. Xu and G. Dong, Transition-metal-catalyzed C-H alkylation using alkenes, *Chem. Rev.*, 2017, **117**, 9333, DOI: [10.1021/acs.chemrev.6b00574](https://doi.org/10.1021/acs.chemrev.6b00574).
- 139 D. Mandal, S. Roychowdhury, J. P. Biswas, S. Maiti and D. Maiti, Transition-metal-catalyzed C-H bond alkylation using olefins: recent advances and mechanistic aspects, *Chem. Soc. Rev.*, 2022, **51**, 7358, DOI: [10.1039/D1CS00923K](https://doi.org/10.1039/D1CS00923K).
- 140 S. L. Liu, C. Ye and X. Wang, Recent advances in transition-metal-catalyzed directed C-H alkenylation with maleimides, *Org. Biomol. Chem.*, 2022, **20**, 4837, DOI: [10.1039/D2OB00604A](https://doi.org/10.1039/D2OB00604A).
- 141 Q. Qin, H. Jiang, Z. Hu, D. Ren and S. Yu, Functionalization of C-H bonds by photoredox catalysis, *Chem. Rec.*, 2017, **17**, 754, DOI: [10.1002/tcr.201600125](https://doi.org/10.1002/tcr.201600125).
- 142 L. Guillemard and J. Wencel-Delord, When metal-catalyzed C-H functionalization meets visible-light photocatalysis, *Beilstein J. Org. Chem.*, 2020, **16**, 1754, DOI: [10.3762/bjoc.16.147](https://doi.org/10.3762/bjoc.16.147).
- 143 S. Tang, H. H. Zhang and S. Yu, Enantioselective reductive allylic alkylation enabled by dual photoredox/palladium catalysis, *Chem. Commun.*, 2023, **59**, 1153, DOI: [10.1039/D2CC06705F](https://doi.org/10.1039/D2CC06705F).
- 144 N. A. Stini, P. L. Gkizis, I. Triandafillidi and C. G. Kokotos, Photocatalytic CeCl₃-promoted C-H alkenylation and alkynylation of alkanes, *Chem. Eur J.*, 2025, **31**, e202404063, DOI: [10.1002/chem.202404063](https://doi.org/10.1002/chem.202404063).
- 145 S. Basak, T. Paul, S. Mandal, M. Barman, M. V. Nanjagowda and T. Punniyamurthy, Transition-metal-catalyzed auxiliary-assisted C-H functionalization using vinylcyclopropanes and cyclopropanols, *Chem. Commun.*, 2025, **61**, 6055, DOI: [10.1039/D5CC00599J](https://doi.org/10.1039/D5CC00599J).
- 146 L. Guillemard, L. Ackermann and M. J. Johansson, Late-stage meta-C-H alkylation of pharmaceuticals to modulate biological properties and expedite molecular optimisation in a single step, *Nat. Commun.*, 2024, **15**, 3349, DOI: [10.1038/s41467-024-46697-8](https://doi.org/10.1038/s41467-024-46697-8).
- 147 R. T. Bhawale, A. S. Chillal and U. A. Kshirsagar, Visible-light-enabled regioselective C-H alkylation and alkenylation of 2-aryl heterocycles using dual catalysis,



- Adv. Synth. Catal.*, 2025, **367**, e202401294, DOI: [10.1002/adsc.202401294](https://doi.org/10.1002/adsc.202401294).
- 148 P. Kumar, Monika and B. K. Singh, Ru(II)-catalyzed site-selective *N*-directed C(sp²)-H alkylation of quinoxalinones with maleimide, *Org. Biomol. Chem.*, 2025, **23**, 10743, DOI: [10.1039/D5OB01524C](https://doi.org/10.1039/D5OB01524C).
- 149 L. L. Romero-Hernández, A. I. Ahuja-Casarín, P. Merino-Montiel, S. Montiel-Smith, J. L. Vega-Báez and J. Sandoval-Ramírez, Syntheses and medicinal chemistry of spiro heterocyclic steroids, *Beilstein J. Org. Chem.*, 2024, **20**, 1713, DOI: [10.3762/bjoc.20.152](https://doi.org/10.3762/bjoc.20.152).
- 150 N. Moshnenko, A. Kazantsev, E. Chupakhin, O. Bakulina and D. Dar'in, Synthetic routes to approved drugs containing a spirocycle, *Molecules*, 2023, **28**, 4209, DOI: [10.3390/molecules28104209](https://doi.org/10.3390/molecules28104209).
- 151 J. Phukon, A. J. Borah and S. Gogoi, Transition-metal-catalyzed synthesis of spiro compounds through activation and cleavage of C-H bonds, *Asian J. Org. Chem.*, 2022, **11**, e202200581, DOI: [10.1002/ajoc.202200581](https://doi.org/10.1002/ajoc.202200581).
- 152 Y. Zhang, T. Huang, X. Li, M. Zhang, Y. Song, K. Huang and W. Su, Rh (III)-catalyzed spiroannulation of 3-arylquinoxalin-2(1*H*)-ones with alkynes: practical access to spiroquinoxalinones, *RSC Adv.*, 2020, **10**, 22216, DOI: [10.1039/D0RA03348K](https://doi.org/10.1039/D0RA03348K).

