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

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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 ailments[12] 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 stearoyl-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

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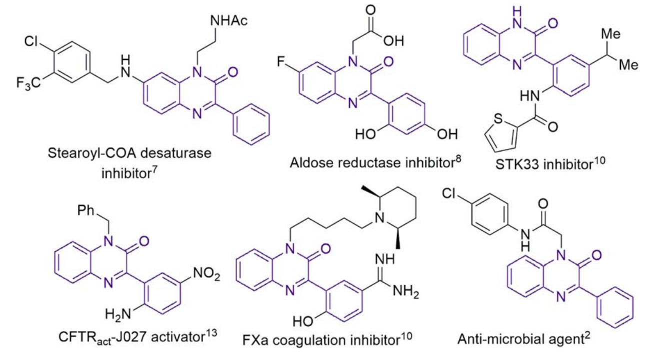

Fig. 1 Examples of bioactive molecules containing 3-phenylquinoxalin-2(1*H*)-one as a key motif.

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 as powerful tools for the direct functionalization of quinoxalin-2(1*H*)-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(1*H*)-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(1*H*)-ones, emphasizing the scope, mechanistic aspects, and synthetic utility of these transformations.

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2. Scope of review

There is a need to disseminate how wondrously *N*-alkyl-3-phenylquinoxalin-2(1*H*)-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 *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 acetoxylated 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]

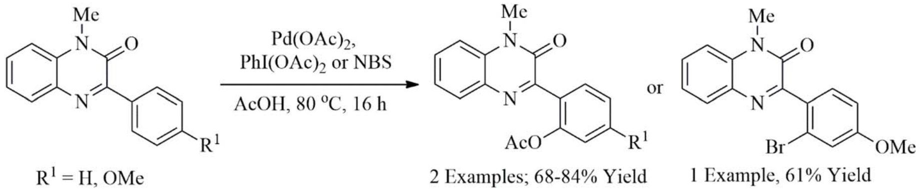
Carrer *et al.*, in 2013, reported the Pd-catalyzed oxidative C-3 arylation of quinoxalin-2(1*H*)-ones with arylboronic acids. To explore the versatility of the developed method, the authors carried out the regioselective C–H functionalization of the synthesized C-3 arylated products.[64] Delightfully,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

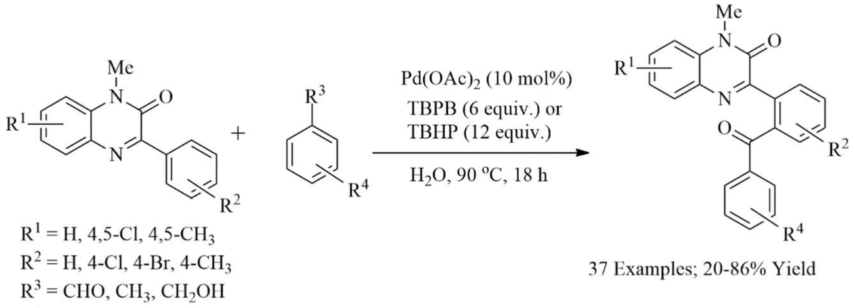
Ketones serve as fundamental building blocks in the synthesis of various bioactive molecules,[68] pharmaceuticals,[69–73] dyes,[74] and electronic materials.[75] Over the past decade, cross-coupling strategies have emerged as powerful tools for the direct synthesis of ketones *via* the selective acylation 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-phenylquinoxalim-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-

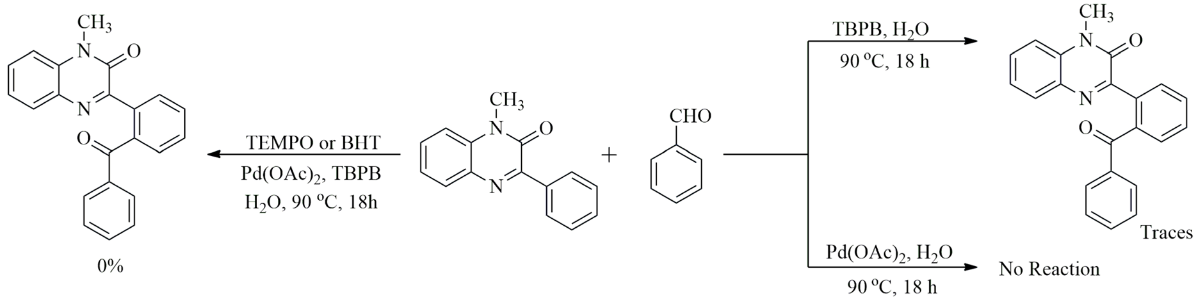


Scheme 1 Pd-catalyzed *N*-assisted C–H acetoxylation/bromination of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones.

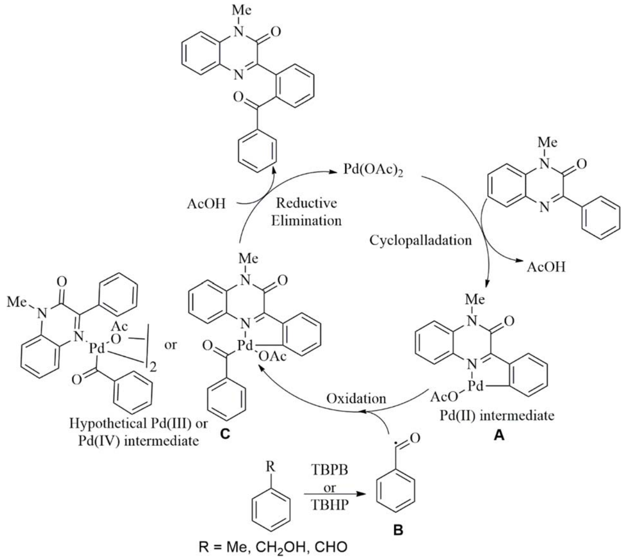


R^1 = H, 4,5-Cl, 4,5-CH_3
R^2 = H, 4-Cl, 4-Br, 4-CH_3
R^3 = CHO, CH_3, CH_2OH
R^4 = H, 2-OCH_3, 2-F, 2-Br, 3-OCH_3, 3-NO_2, 3-NO_2, 4-Br, 4-Cl,
4-NO_2, 4-CH_3, 4-OCH_3, 4-OH, 2-F & 4-Br, 4-F & 4-Cl,
3-Br & 4-F, 2,4-F, 3,4-CH_3, 3.4-OCH_3, 2,5-OCH_3,

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



Scheme 3 Control experiments.

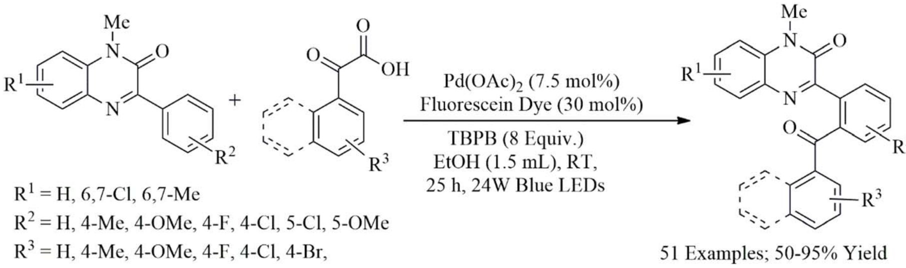


Scheme 4 Proposed reaction mechanism for the Pd-catalyzed regioselective acylation of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones.

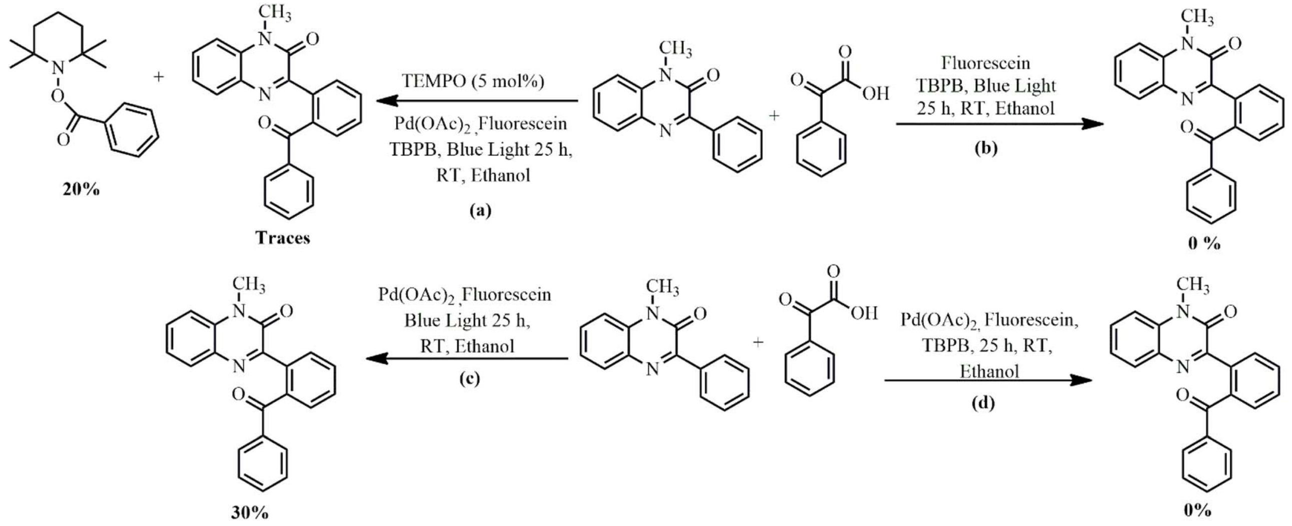
phenylquinoxalin-2(1*H*)-one to generate Pd(II) intermediate **A**. Simultaneously, an acyl radical (**B**) is generated by the action of TBPB on aldehyde/benzyl alcohol and TBHP on toluene. Then, intermediate **A** undergoes oxidation with the acyl radical (**B**) to generate Pd(IV) or dimeric Pd(III) 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).

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-phenyl-quinoxalin-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*-methyl-quinoxalin-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).

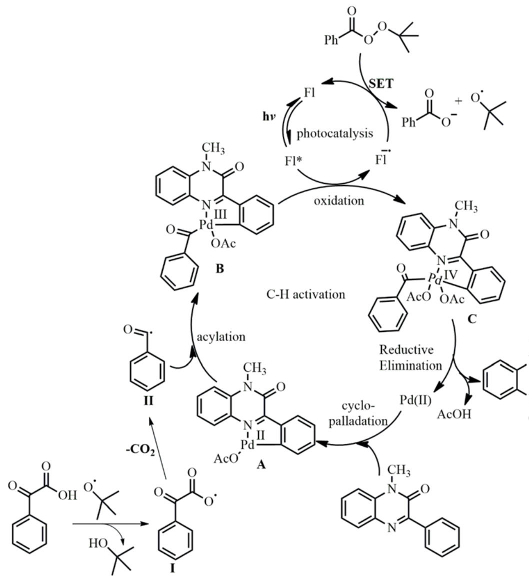
Based on the outcomes of these controlled experiments and other literature facts, a plausible mechanism was established by the authors (Scheme 7). The catalytic mechanism initiated by visible-light irradiation, which promotes fluorescein (FI) to its excited state (FI*). Concurrently, cyclopalladation 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 5 Pd-catalyzed regioselective decarboxylative C–H acylation of *N*-methyl 3-phenylquinoxalin-2(1*H*)-ones using α-oxo-2-phenylacetic acids.



Scheme 6 Control experiments.



Scheme 7 Plausible reaction mechanism.

complex **C**, accompanied by reductive quenching of FI* to the fluorescein radical anion ($\mathrm{FI}^{-\bullet}$). The $\mathrm{FI}^{-\bullet}$ 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 Pd(IV) complex **C** delivers the desired halogenated product and regenerates the Pd(II) catalyst.

3.3. Halogenation

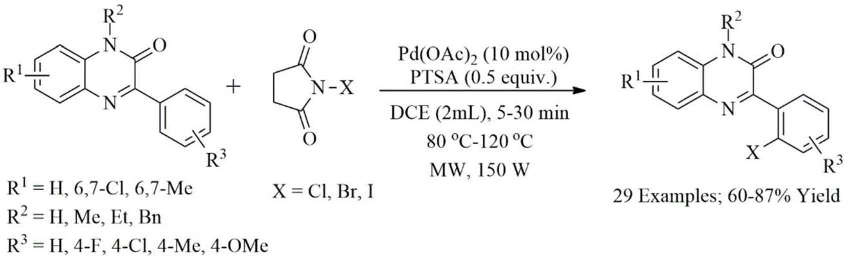
Halogenation of aromatic compounds is an essential transformation in modern synthetic chemistry, as aromatic halides represent one of the most fundamental classes of organic molecules and serve as highly versatile electrophilic partners in transition-metal-catalyzed cross-coupling reactions.[85–94] Therefore, 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 $Pd(OAc)_2$ (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).

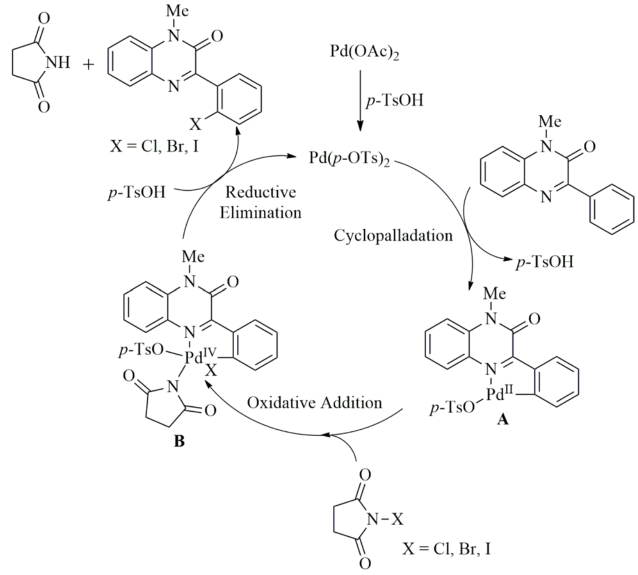
A plausible reaction mechanism for this transformation is outlined in Scheme 9. The catalytic cycle is initiated by the reaction of $Pd(OAc)_2$ and PTSA to generate active $Pd(OTs)_2$ species. Subsequent directed C–H activation of 1-alkyl- or 1-benzyl-3-phenyloxalin-2(1*H*)-one affords cyclopalladated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



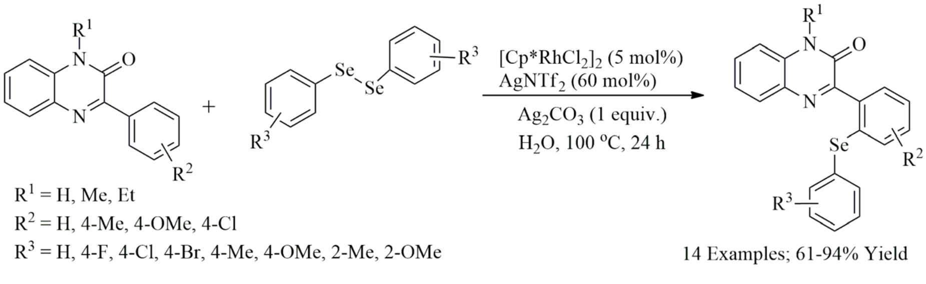
Scheme 9 Plausible reaction mechanism for *ortho*-monohalogenation of 3-phenylquinoxalin-2(1*H*)-one.

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]

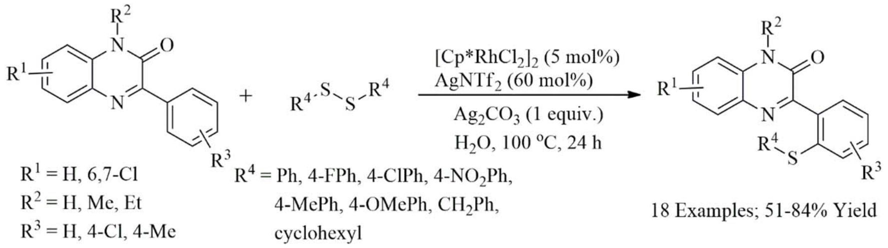
Lalji and co-workers developed a rhodium-catalyzed approach for the regioselective selenylation and sulfenylation of *N*-substituted-3-phenylquinoxalin-2(1*H*)-ones *via N*-directed C–H activation in aqueous medium.[137] The compatibility of the developed protocol towards C–Se bond formation was first 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.

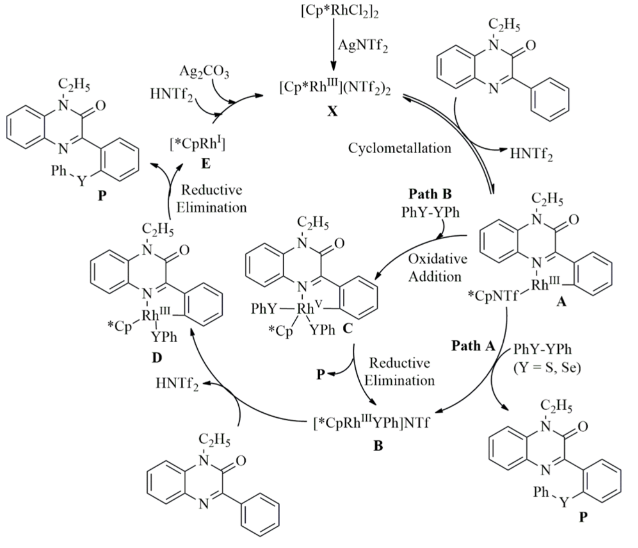
Two mechanistic pathways were proposed for these transformations (Scheme 12). The mechanism is initiated by the reaction of dimeric $[Cp^*RhCl_2]_2$ with silver triflimide, resulting in the *in situ* generation of active rhodium(III) species **X**. The newly generated catalyst **X** subsequently undergoes cyclometallation 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).

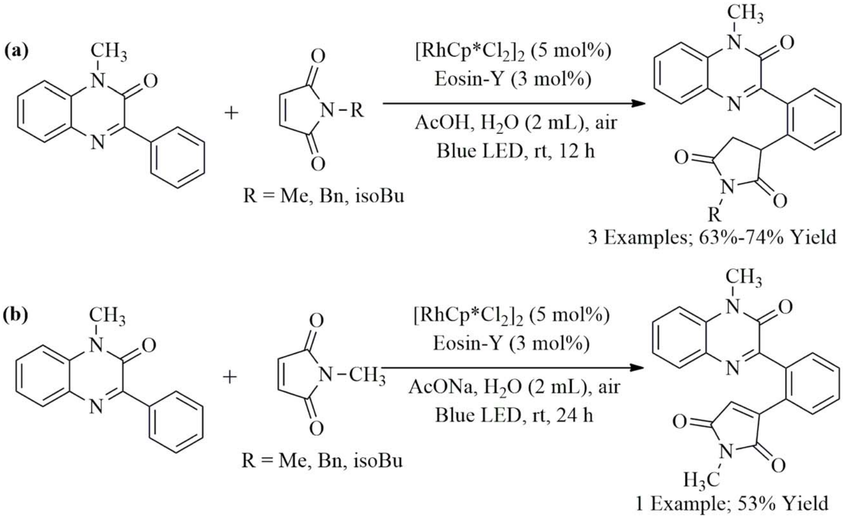
The authors also proposed an alternative mechanistic pathway (Scheme 12, path B), wherein cyclometalated intermediate **A** undergoes oxidative addition with diphenyl diselenide or diphenyl sulfide to generate high-valent rhodium(v) complex **C**. Subsequent, reductive elimination from **C** furnishes 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 cyclometallated intermediate **D**. Reductive elimination from **D** produces Rh(I) complex **E** and the desired product **P**.

3.5. Alkylation and alkenylation

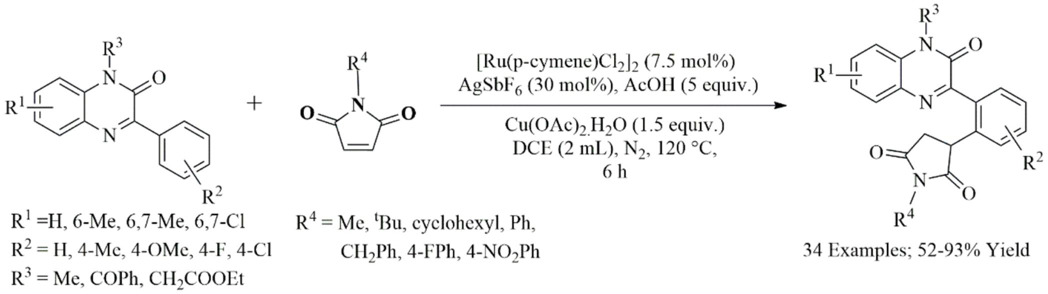
Transition-metal-catalyzed C–H alkylation and alkenylation reactions have emerged as powerful tools in contemporary synthetic chemistry, offering direct and atom-economical routes to functionalized organic molecules.[138–140] More recently, the merger of visible-light photoredox catalysis with transition-metal 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*Cl$_2$]$_2$ 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)Cl$_2$]$_2$/AgSbF$_6$/AcOH/Cu(OAc)$_2$·H$_2$O as an effective catalytic system. The reactions were carried out in 1,2-dichloroethane solvent at 120 °C under an N$_2$ 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.

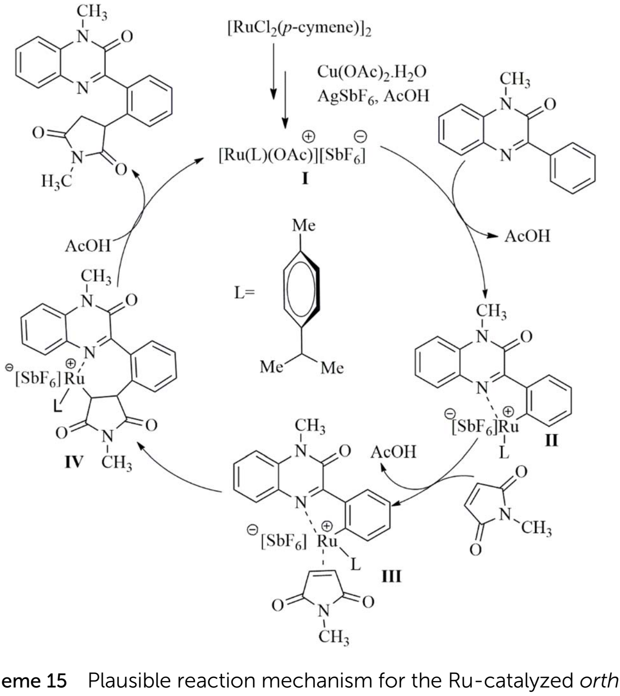


Scheme 14 Ru-catalyzed *ortho* C–H alkylation of 3-phenyl ring of *N*-methyl-3-phenylquinoxalin-2(1*H*)-ones with maleimides.

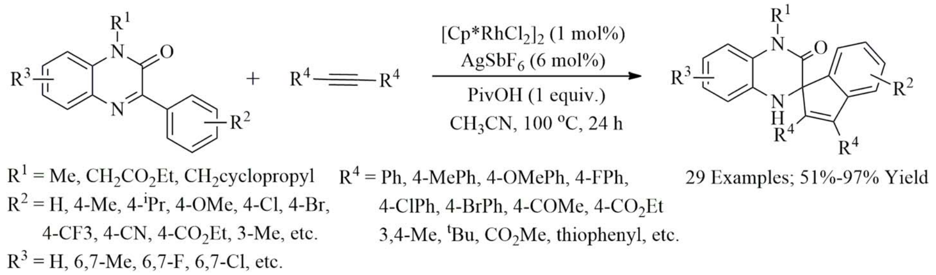
3-phenylquinoxalin-2(1*H*)-one could afford the products in 60–62% yield. The scope of various *N*-substituted maleimides was also examined for this transformation, and all the tested maleimides furnished the targeted alkylated products in good to excellent yields. The authors also proposed a plausible reaction mechanism, as shown in Scheme 15. Initially, a catalytically active cationic ruthenium species (**A**) is generated from [Ru(*p*-cymene)Cl$_2$]$_2$ in the presence of AgSbF$_6$, AcOH and Cu(OAc)$_2$·H$_2$O. 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.



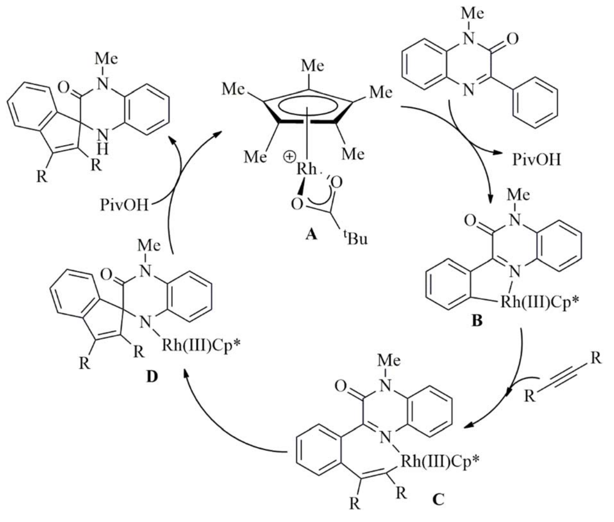
Scheme 16 Rh(III)-catalyzed synthesis of spiro-quinoxalinone derivatives of 3-arylquinoxalin-2(1*H*)-ones.

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 stereocontrol.[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(1*H*)-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% $[Cp^*RhCl_2]_2$ as the catalyst.

To begin with the development of this approach, *N*-methyl-3-phenylquinoxalin-2(1*H*)-one and 1,2-diphenylethyne were allowed to stir at 100 °C for 24 h in the presence of 1 mol% $[Cp^*RhCl_2]_2$ in combination with 4 mol% $AgSbF_6$ as the catalytic system. This delivered the spiro compound in 62% yield; however, the addition of 1 equiv. of PivOH additive accelerated the C–H activation process, resulting in 86% product yield. This protocol was compatible with various substituted 3-phenylquinoxalin-2(1*H*)-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, CF_3, CN, and CO_2Et) (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).



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

4. Conclusion and future perspectives

Recent years have witnessed the versatility of the transition-metal-catalyzed chelating-group-assisted selective functionalization of C(sp^2)-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(sp^2)-H bond of the 3-phenyl ring of *N*-alkyl-3-phenylquinoxalin-2(1*H*)-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 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.

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