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Cite this: *RSC Adv.*, 2023, **13**, 6191

Rhodium-catalyzed selenylation and sulfenylation of quinoxalinones 'on water'†

Ram Sunil Kumar Lalji,[ab] Prince,[a] Mohit Gupta,[ad] Sandeep Kumar,[a] Amit Kumar[c] and Brajendra Kumar Singh*[a]

Received 21st November 2022
Accepted 8th February 2023

DOI: 10.1039/d2ra07400a

rsc.li/rsc-advances

A rhodium-catalysed, regioselective synthetic methodology for selenylation and sulfenylation of 3-phenyl quinoxolinones has been developed through N-directed C–H activation in the presence of silver triflimide, and silver carbonate using dichalcogenides 'on water'. The methodology has been proven to be efficient, regioselective and green. Using this method, a range of selenylations and sulfenylations of the substrates has been carried out in good to excellent yields. Further, late-stage functionalisation produced potential anti-tumour, anti-fungal and anti-bacterial agents making these compounds potential drug candidates.

Introduction

Green chemistry, also known as sustainable chemistry, is composed of twelve principles that provide a scientific blueprint for researchers and scientists to reduce the negative impact of chemicals and chemical processes on the environment and to advance new technologies to improve economic, environmental and societal outcomes.[1] These twelve principles emphasize avoiding or eliminating the consumption and the production of hazardous chemicals in a chemical process. In the quest of developing a sustainable synthetic protocol, the choice of solvent is a constant source of worry as it is wasted in bulk quantities after the completion of a reaction and causes significant impact on health and the environment, if disposed of untreated.[2] From the perspective of green chemistry, water proved to be a sustainable solvent due to its benign nature, high availability, cost-effective, non-toxic and non-flammable properties.[3] Moreover, water exhibits exceptional reactivity and selectivity by stabilizing the transition state through hydrogen bonding and by exhibiting a hydrophobic effect.[4] Depending upon the solubility of reactants and products in water, the water-mediated reactions are categorized as "in water" and "on water" reactions. "In water" conditions refer to a system that utilizes additives to enhance the solubility of less soluble catalysts, adducts and other components to make the system homogeneous. On the other hand, the "on water" is a comparatively new approach and was developed by Sharpless and his group in 2005 to demonstrate the enhancement of reaction rate in an aqueous medium despite the insolubility of reactants and other components.[5] Moreover, heterogeneity of the "on water" system reduces tedious workups and introduces further sustainability to the protocol, unlike the "in water" system. The high dielectric constant of water, high heat capacity, high redox stability and ease of workup make the "on water" system highly desirable for the development of green and sustainable protocols for chemical synthesis.[6]

Organosulphur and organoselenium compounds have gained a prominent place in modern organic synthesis owing to their widespread applications in the field of pharmaceuticals,[7] agrochemicals[8] and polymer materials.[9] The pharmaceutical evaluation of FDA-approved drugs revealed that 25% of the USA's top two hundred prescribed drugs contain organosulphur compounds.[10] Some of the important biological activities of organosulphur and organoselenium compounds include human breast cancer cell growth inhibitors,[11] antitumor agents,[12] RAR agonists,[13] vortioxetine,[14] nicotine acetylcholine receptor ligands,[15] antioxidants,[16] albendazole,[17] antifolates,[18] *etc.* (Fig. 1).

Moreover, the introduction of selenium or sulphur into organic molecules framework dramatically affects compound's photo-physical and electronic properties.[19] Consequently, these organochalcogenides have significant applications as effective organic materials and as fluorescent probes.[20] Considering the immense importance of organosulphur and organoselenium compounds, the development of new synthetic protocols for the formation of C–Se and C–S linkages has attracted considerable attention in recent years.[21]

Over the past few decades, transition metal-catalysed cross-coupling reactions have emerged as a powerful synthetic tool for the construction of carbon–carbon and carbon–heteroatom bonds.[22] Several metal-mediated coupling reactions have been recently developed with selenium and sulphur nucleophiles for the preparation of biologically active compounds.[23] However, these cross-coupling reactions required several steps to prepare

[a]*Bio-Organic Research Laboratory, Department of Chemistry, University of Delhi, Delhi 110007, India. E-mail: singhbk@chemistry.du.ac.in*
[b]*Department of Chemistry, Kirori Mal College, University of Delhi, Delhi 110007, India*
[c]*Department of Chemistry, IIT Patna, Bihar 801106, India*
[d]*Department of Chemistry, L. N. M. S. College, Supaul, Birpur, Bihar 8543340, India*

† Electronic supplementary information (ESI) available. CCDC 2214690 and 2215006. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d2ra07400a

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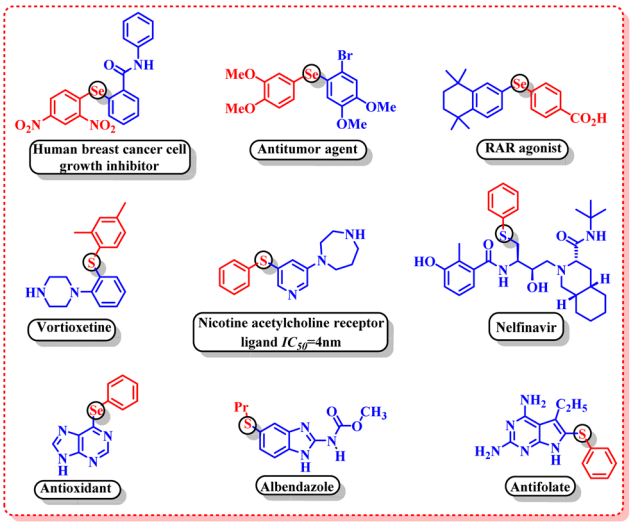

Fig. 1 Biologically active organosulphur and organoselenium compounds.

pre-functionalized substrates, limiting the reaction's atom economy and making the methodology expensive and laborious.[24] Conversely, direct C–H selenylation and sulfenylation provide a straightforward method for the installation of sulphur and selenium groups into the organic framework as it offers shorter routes with higher atom economy, requires less time and utilizes the readily available starting materials.[25] In this direction, palladium, nickel and copper complexes have been extensively explored for the direct sp^2 C–H chalcogenylation and have served the purpose well. Despite the vast progress, these catalytic systems suffer from less functional group tolerance, narrow substrate scope and high catalytic loading. Moreover, metal additives and stabilizing ligands are also required to prevent the decomposition of metal complexes which further restricts the practicality of these reactions on a large or industrial scale.[26]

In the field of C–H bond functionalization, rhodium-based catalysts outperform the catalytic ability of Pd, Ni and Cu by offering exceptional functional group tolerance, high efficiency, low catalytic loading, and broad synthetic applications. Rhodium(III), especially in the form of $[Cp^*RhCl_2]_2$ performs exceptionally well due to the more polarised Rh(III)–C(aryl) bond and the bulkier Cp* ligand promotes enough steric hindrance during the C–H activation process and make the catalyst thermally stable.[27] Owing to the inherent advantages of rhodium catalysis, remarkable progress has been witnessed in the area of rhodium(III) catalyzed direct C–H chalcogenylation, over the past few years. In 2014, Li and his co-workers carried out directed sulfenylation of arene C–H bonds using $[Cp^*RhCl_2]_2$.[28] Subsequently, rhodium-catalyzed direct C–H selenylation was reported by Xingwei Li and coworkers.[29]

Afterwards, many groups have explored the rhodium catalyst for direct C–H selenylation and sulfenylation[30] and have utilized a wide variety of organic solvents such as DMF, DMSO, 1,4-dioxane, *etc.* However, till date, direct selenylation and sulfenylation of heterocyclic compounds have not been reported 'on water'. Thus, in continuation of our efforts to develop the sustainable and greener protocols for the C–H functionalization of various biologically active heterocycles,[31] we herein are reporting the regioselective selenisation and sulfenylation of pharmaceutically important 3-phenyl quinoxalinones (Fig. 2) using rhodium(III) catalyst 'on water'.

Results and discussion

For our preliminary examination, 1-ethyl-3-phenylquinoxalin-2(1*H*)-one **1a** and commercially available 1,2-diphenyl diselenide **2a** were chosen as model substrates to carry out regioselective selenylation. The reaction was allowed to run at a ceiling temperature of 110 °C with 5 mol% of $[Cp^*RhCl_2]_2$ as a catalyst, 60 mol% of silver triflimide as an additive, 1.0 equivalent of silver carbonate as an oxidant and 1,4-dioxane as a solvent. The reaction completed in 24 hours and the regioselective, mono-selenylated product **3a** was obtained in 35% yield (Table 1, entry 1). In order to improve the product yield, a series of solvents were screened (Table 1, entries 2–6). Solvents such as DMSO and DMA were found completely ineffective for the reaction (Table 1, entries 3 and 4). However, in DMF, product **3a** was obtained in 25% yield (Table 1, entry 2). A dramatic increase in the product yield was observed when the reaction was performed in water (Table 1, entry 6). In water, 94% of desired product **3a** was isolated. Further, the effect of catalysts on the performance of the reaction was evaluated using water as a solvent. Inferior product yield was obtained with $Rh(COD)Cl_2$ and $[RuCl_2(p\text{-cymene})]_2$ catalysts (Table 1, entries 7 and 8). To improve the product yield further, we next screened different additives (Table 1, entries 9 and 10). No improvement in product yield was observed on changing the additive from silver triflimide to silver triflate and silver hexafluoroantimonate. Similarly, inferior product yield was obtained on replacing Ag_2CO_3 with Ag_2O and $AgNO_3$ (Table 1, entries 11 and 12). After a brief examination of the reaction temperature, 110 °C was found as the optimum temperature for this reaction. Incomplete conversion of the reactant was observed when the reaction was carried out at lower

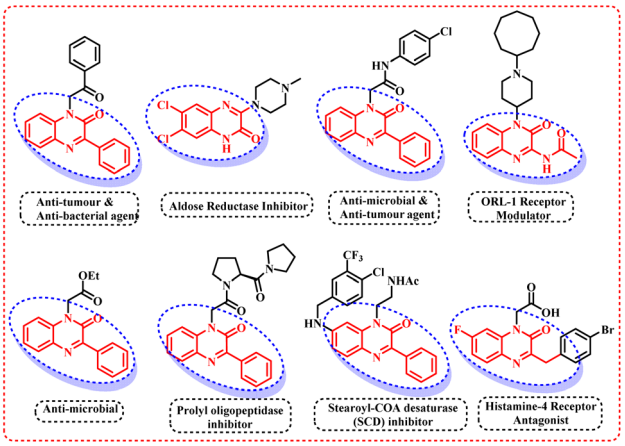

Fig. 2 Pharmaceutically active quinoxalinones.

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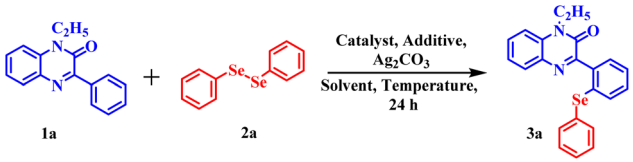
Table 1 Optimization of reaction conditions[a]



Sr. no.	Catalyst (5 mol%)	Additive (0.6 equiv.)	Solvent (1.5 mL)	Temp °C	Yield[b] (%)
1	$[Cp^*RhCl_2]_2$	$AgNTf_2$	Dioxane	110	35
2	$[Cp^*RhCl_2]_2$	$AgNTf_2$	DMF	110	25
3	$[Cp^*RhCl_2]_2$	$AgNTf_2$	DMSO	110	Traces
4	$[Cp^*RhCl_2]_2$	$AgNTf_2$	DMA	110	NR
5	$[Cp^*RhCl_2]_2$	$AgNTf_2$	Dioxane water	110	57[c]
6	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	110	94[d]
7	$[Rh(COD)Cl]_2$	$AgNTf_2$	H_2O	110	32
8	$[RuCl_2(p\text{-cymene})]_2$	$AgNTf_2$	H_2O	110	58
9	$[Cp^*RhCl_2]_2$	AgOTf	H_2O	110	48
10	$[Cp^*RhCl_2]_2$	$AgSbF_6$	H_2O	110	23
11	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	110	80[e]
12	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	110	61[f]
13	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	100	83
14	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	90	65
15	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	120	92
16	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	130	90
17	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	110	83[g]
18	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	110	94[h]
19	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	110	81[i]
20	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	110	92[j]
21	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	110	90[k]
22	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	110	94[l]
23	$[Cp^*RhCl_2]_2$	$AgNTf_2$	H_2O	110	46[m]

[a] Reagents and conditions: 1-ethyl-3-phenylquinoxalin-2(1*H*)-one (**1a**, 0.2 mmol), diphenyl diselenide (**2a**, 0.4 mmol) catalyst (5 mol%), additive (0.6 equiv.), and oxidant (1 equiv.) were stirred under indicated solvent at indicated temperature for 24 h. [b] Isolated yields. [c] 1 : 1 ratio of dioxane and water was used as the solvent. [d] Catalysts such as $Pd(OAc)_2$, $Pd(TFA)_2$, $NiCl_2$ and $Cu(OAc)_2$ instead of $[Cp^*RhCl_2]_2$ failed to facilitate the desired transformation. [e] Ag_2O was used as oxidant. [f] $AgNO_3$ was used as oxidant. [g] 0.3 equiv. of $AgNTf_2$ was used. [h] 0.9 equiv. of $AgNTf_2$ was used. [i] 1.5 equiv. of diphenyl diselenide was used. [j] 2.5 equiv. of diphenyl diselenide was used. [k] 3 mol% of catalyst was used. [l] 7 mol% of catalyst was used. [m] $Cu(OAc)_2$ instead of Ag_2CO_3 as oxidant gave 46% yield.

temperatures (Table 1, entries 13 and 14). Nevertheless, a slight decrease in product yield was observed when the reaction was carried out at higher temperatures (Table 1, entries 15 and 16). Further, neither the change in additive concentration nor the change in substrate concentration provided any improvement in the product yield (Table 1, entries 17–20). However, slightly inferior product yield was noted with 3 mol% and approximately the same yield was observed with 7 mol% of the catalyst respectively (Table 1, entries 21 and 22). Change of oxidant from silver carbonate to $Cu(OAc)_2$ did not have any fruitful outcome (Table 1, entry 23). Finally, we established the optimised condition as 1-ethyl-3-phenylquinoxalin-2(1*H*)-one (**1a**), 2 equiv. of commercially available 1,2-diphenyl diselenide (**2a**), 5 mol% of $[Cp^*RhCl_2]_2$ catalyst, 60 mol% of silver triflimide, 1 equiv. of silver carbonate and 1.5 mL of water.

Substrate scope

With this optimized protocol, we examined the scope and generality by employing a variety of 3-phenylquinoxalin-2(1*H*)-ones bearing both electron-donating and electron-withdrawing groups (Scheme 1). All the 3-phenylquinoxalin-2(1*H*)-one derivatives afforded the desired products in good to excellent yields. Electron-withdrawing group such as –Cl exhibited a significant adverse effect on product yield in comparison to the electron-donating group such as $-CH_3$ (Scheme 1, **3k**, **3m**). A similar trend was observed with *N*-substituted 3-phenylquinoxalin-2(1*H*)-ones. Stronger electron-donating groups such as $-C_2H_5$ provided better product yield as compared to milder electron-donating groups such as $-CH_3$ and –H (Scheme 1, **3a**, **3l** and **3n**). Electron-withdrawing groups present on the *para*-position of the benzene ring exhibited a disadvantageous effect on product yields as compared to electron donating group –H (Scheme 1, **3a** and **3j**). Subsequently, the electronic effect of substituent present on diphenyl diselenide was studied. Among the halogens substituted at the *para*-position of the diselenide, fluoro-diselenide afforded a better product yield than bromo and chloro counterparts (Scheme 1, **3b**, **3c** and **3d**). We also carried out the reaction with diselenides with methyl group at

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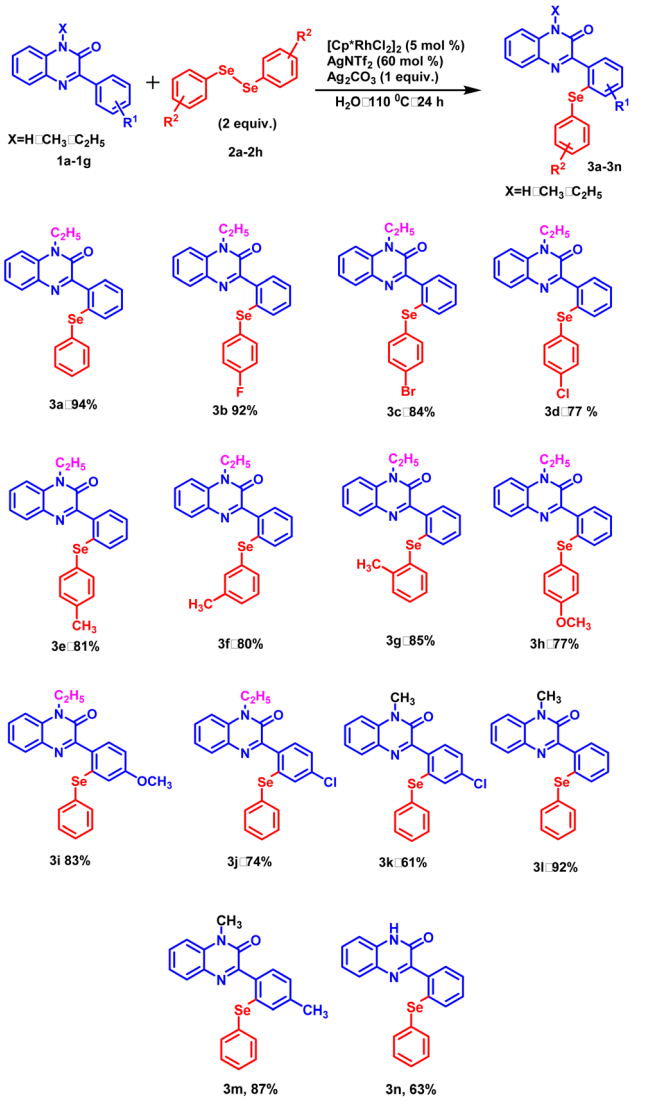
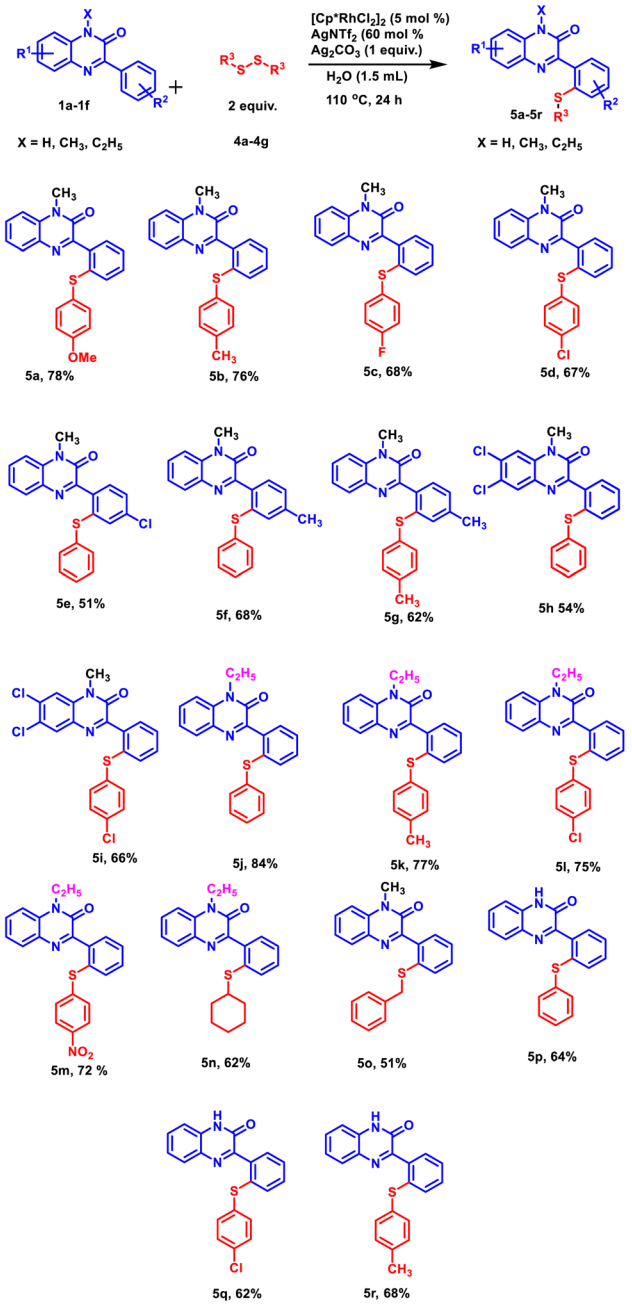


Scheme 1 Substrate scope of 3-phenylquinoxalin-2(1*H*)-ones and diphenyl diselenides.



Scheme 2 Substrate scope of 3-phenylquinoxalin-2(1*H*)-ones and diphenyl(dialkyl) disulfides.

ortho, *meta* and *para* positions and interestingly all of them produced the excellent yields (Scheme 1, **3e**, **3f** and **3g**).

Further, to explore the substrate scope, a range of differently substituted diphenyl disulphides were allowed to react with 3-phenylquinoxalin-2(1*H*)-ones under the optimized reaction condition (Scheme 2, **5a–5d**, **5m**, **5n**, and **5o**). The results demonstrated that all the diphenyl disulphide derivatives afforded the corresponding products in good to moderate yields. It was observed that diphenyl disulphide having electron-donating groups (–OCH_3 and –CH_3) (Scheme 2, **5a** and **5b**) furnished the desired products in higher yields as compared to electron-withdrawing groups such as (–F and –Cl) (Scheme 2, **5c** and **5d**). After studying the electronic effect of diphenyl disulphide, the electronic effect of substituents present on 3-phenylquinoxalin-2(1*H*)-one was examined. For this purpose, –CH_3 and –Cl groups were taken into the consideration at the *para*-position of the phenyl ring. It was observed that the methyl group afforded better product yield than the chloro group (Scheme 2, **5e** and **5f**). We were pleased to find that *N*-substituted as well as *N*-unsubstituted 3-phenylquinoxalin-2(1*H*)-ones delivered the corresponding products in good to moderate yields. However, stronger electron-donating groups afforded higher product yields as compared to less electron-donating groups (Scheme 2, **5j** and **5p**). Additionally, the established protocol was also found compatible with dialkyl disulfides (Scheme 2, **5n** and **5o**), suggesting a wide substrate scope of the established protocol.

A substantial improvement in the product yields was recorded with diphenyl diselenides as a coupling partner as

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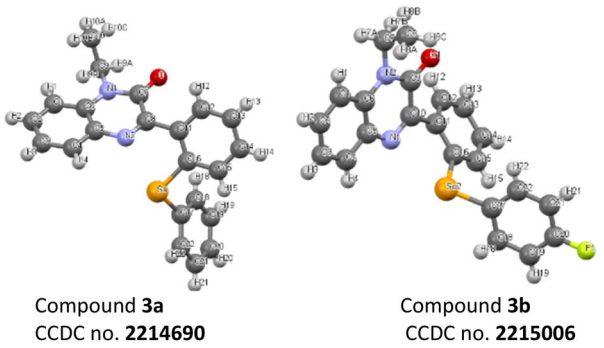
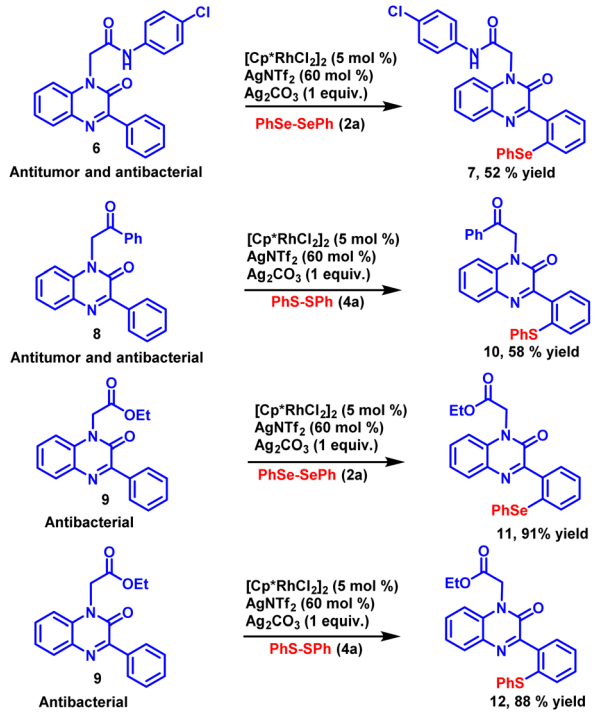


Fig. 3 Single crystal X-ray structure of the compounds **3a** and **3b**.

compared to diphenyl disulphides (Schemes 1 and 2). The higher reactivity of diphenyl diselenide is attributed to the higher nucleophilicity of the Se atom and the low bond dissociation energy of the Se–Se bond.[32] Although diphenyl disulphides smoothly delivered the targeted products in good to moderate yields, the chemical reactivity of diphenyl disulphide is lower due to its strong coordinating and absorptive affinity towards the catalysts.[33] The structure of compounds **3a** and **3b** are also confirmed by crystallography (Fig. 3).

Synthetic application

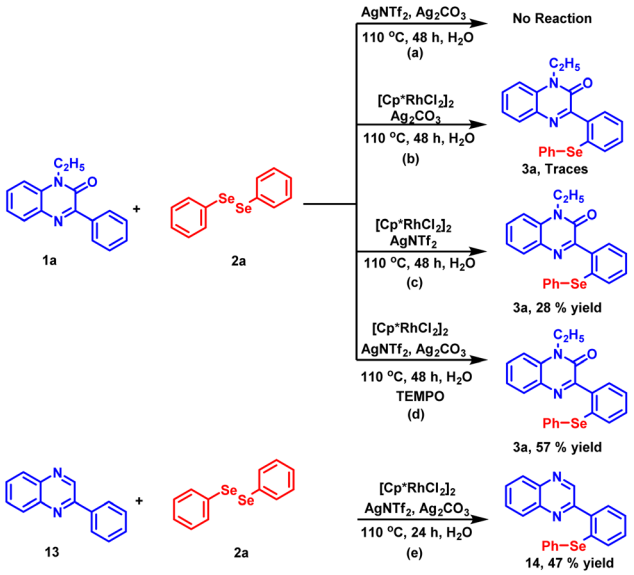
Modern drug discovery relies heavily on the identification of lead compounds and the synthesis of their related analogues. The late-stage functionalization of drug candidates offers a practical and viable alternative to access a large number of related analogous for structure–activity relationship (SAR) studies. To investigate the synthetic potential of the established methodology, late-stage functionalization of potential antimicrobial and antitumor compounds[34] was carried out (Scheme 3). *N*-(4-Chlorophenyl)-2-(2-oxo-3-phenylquinoxalin-1(2*H*)-yl)acetamide (**6**) was allowed to react with diphenyl diselenide **2a** under the standard reaction conditions. The reaction proceeded smoothly and selenylated product **7** was obtained with good yield. Late-stage functionalization of another potential antimicrobial and antitumor compound 1-(2-oxo-2-phenylethyl)-3-phenylquinoxalin-2(1*H*)-one (**8**) was also carried out with diphenyl disulfide **4a** as coupling partner with the newly developed reaction condition, the sulfenylated product **10** was obtained in 58% yield. Similarly, 1-(2-oxobutyl)-3-phenylquinoxalin-2(1*H*)-one (**9**), a synthon having anti-bacterial activity was subjected to sulfenylation and selenylation under the standard reaction condition, the respective selenylated and sulfenylated products **11** and **12** were obtained in excellent yields. The successful implementation of C–H chalcogenation on pharmacologically active compounds paves a rapid way to access drug-related analogues that finds a huge application in the process of drug discovery.



Scheme 3 Late-stage functionalization of potential anti-tumour and anti-microbial agents.

Control experiments

To gain an insight into the reaction mechanism, several control experiments were carried out (Scheme 4). In the first experiment, the coupling reaction between **1a** and **2a** was performed in the absence of the catalyst (Scheme 4a). As anticipated, no reaction took place and the starting material was recovered even after 48 hours. Next, the reaction was conducted by excluding silver triflimide from the standard reaction conditions (Scheme 4b) and the product was detected in traces. The absence of product formation indicates that the catalyst $[Cp^*RhCl_2]_2$ alone is unable to drive the reaction. In the next experiment, the reaction was performed in the absence of silver carbonate



Scheme 4 Preliminary mechanistic experiments.

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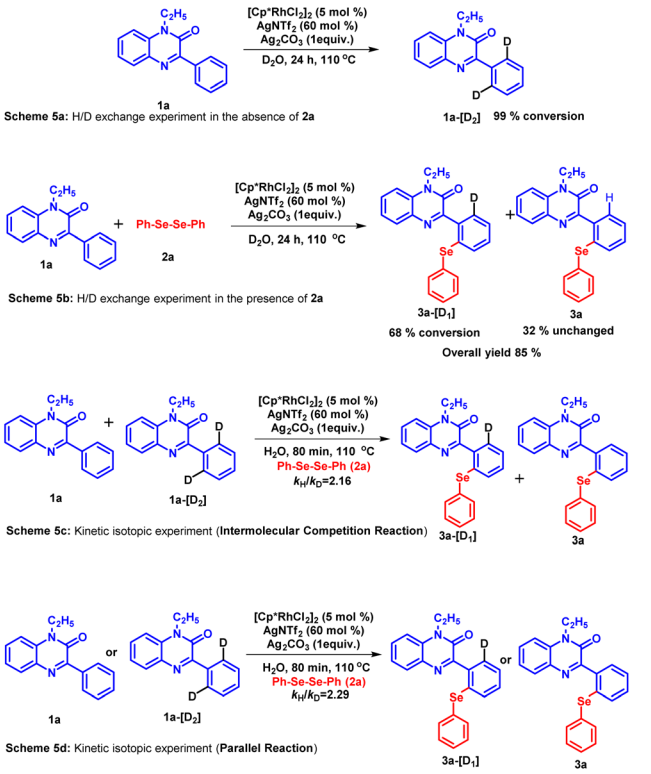
(Scheme 4c). The reaction did not proceed to completion and 28% of the desired product **3a** was isolated after 48 hours. The observation demonstrates the important role of silver carbonate as a co-oxidant. Further, when the radical scavenger experiment was carried out using TEMPO (Scheme 4d), product **3a** was obtained in 57% yield, which suggests that the radical process may not be involved in this reaction. To check whether the carbonyl group present at the C-2 position of the substrate has any directing influence on the reaction instead of nitrogen, we found that the reaction proceeds in the absence of the carbonyl group and compound **13** provided the synthesized product **14** in 47% yield.

H/D exchange and kinetic studies

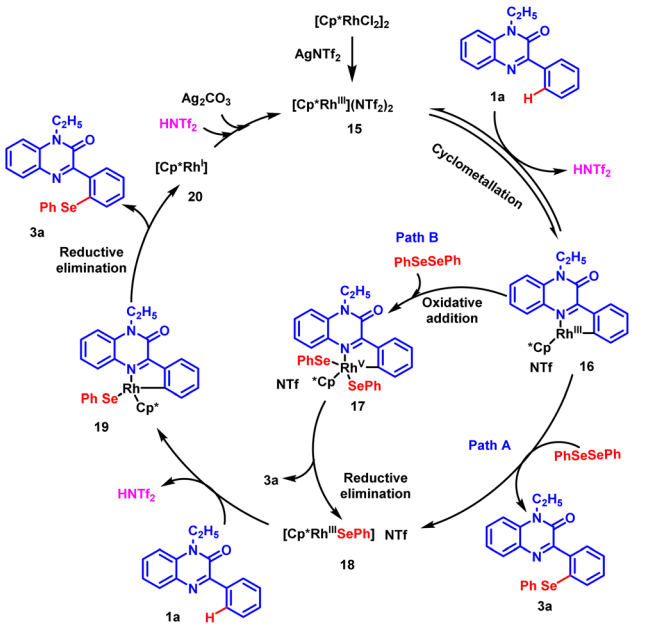
To assess the reversibility of the C–H activation step, a hydrogen–deuterium (H/D) exchange experiment was carried out using D_2O as a solvent (Scheme 5a and b).[35] These experiments were performed in the absence as well as in the presence of coupling partner **2a** under the standard condition. The ^{1}H NMR analysis of the recovered compound revealed a 99% conversion of substrate **1a** into **1a-[D$_2$]** (Scheme 5a). In the presence of coupling partner **2a**, the mixture of the product obtained contains 68% of **3a-[D$_1$]** and 32% of product **3a** (Scheme 5b). A significant amount of deuterium incorporation in both these experiments infers the reversibility of the C–H activation step. Furthermore, the kinetic isotopic experiment (KIE) was performed to investigate whether the C–H activation step is involved in the rate-determining step or not (Scheme 5c). The parallel experiment using **1a** and **1a-[D$_2$]** was subjected to react with diphenyl diselenide **2a** under the standard reaction conditions for 80 minutes. The ^{1}H NMR studies of the isolated product mixture revealed the kinetic isotopic effect value (k_H/k_D) as 2.29. While the intermolecular competition KIE experiment between the same coupling partners for 80 minutes yielded the k_H/k_D value as 2.16. The kinetic isotopic effect suggests the possible involvement of the C–H activations step in the rate-limiting step.[36]



Scheme 5 H/D exchange and deuterium kinetic isotope studies.

Mechanism

Based on the experimental results and the literature reports, a rational catalytic mechanism for Rh-catalyzed, regioselective chalcogenation of 1-ethyl-3-phenylquinoxalin-2(1*H*)-one is depicted in Scheme 6. It is believed that $[Cp^*RhCl_2]_2$ precursor reacts with silver triflimide ($AgNTf_2$) *in situ* to generate an active rhodium catalyst (**15**). The catalyst reacts with substrate **1a** and a cyclo-metallated rhodium complex **16** is generated possibly through a C–H activation step. Intermediate **16** further reacts with diphenyl diselenide **2a** through a nucleophilic substitution reaction and delivers the desired product **3a** and intermediate **18**. Alternatively, intermediate **16** may prefer path **B**, where oxidative addition with diphenyl diselenide produces a rhodium(v) complex **17**. Following this, the reductive elimination of complex **17** affords the desired product **3a** and Rh(III) intermediate **18** back.[37,38] Subsequently, another molecule of substrate **1a** participates in C–H activation with intermediate **18** to generate cyclo-metalled rhodium intermediate **19**. Afterwards, the reductive elimination of intermediate **19** results in the formation of Rh(I) complex **20** and the desired product **3a**. The oxidation of Rh(I) species by the action of silver carbonate and triflimide regenerates the active rhodium(III) catalyst **15** to complete the catalytic cycle.



Scheme 6 Plausible reaction mechanism for the regioselective chalcogenation of phenylquinoxalinones.

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Conclusion

In conclusion, we have successfully developed a green and sustainable method in an aqueous medium for the regioselective direct C–H chalcogenation of phenylquinoxalinones using $[Cp^*RhCl_2]_2$ as a catalyst, 'on water'. The metal-directing property of the nitrogen atom is utilized to afford the chalcogenated products in good to excellent yields. A wide variety of diphenyl disulphides, diphenyl diselenides and phenylquinoxalinones were found to be compatible with the established protocol thus offering remarkable substrate scope and excellent functional group tolerance. The tedious work-up step has been avoided. With this 'on water' method, the straightforward synthesis of the four bioactive compounds has been afforded *via* the late-stage functionalization of the potential antitumor, antifungal and the antimicrobial candidates and this has further widened the scope of the established protocol in the field of organic synthesis and drug discovery.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work has been supported financially by Institution of Eminence (IoE), University of Delhi. We also thank University Science Instrumentation Centre (USIC), University of Delhi for instrumental facilities. Prince acknowledges CSIR, New Delhi, India for providing Senior Research Fellowship and SK acknowledges University Grant Commission for Senior Research Fellowship.

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