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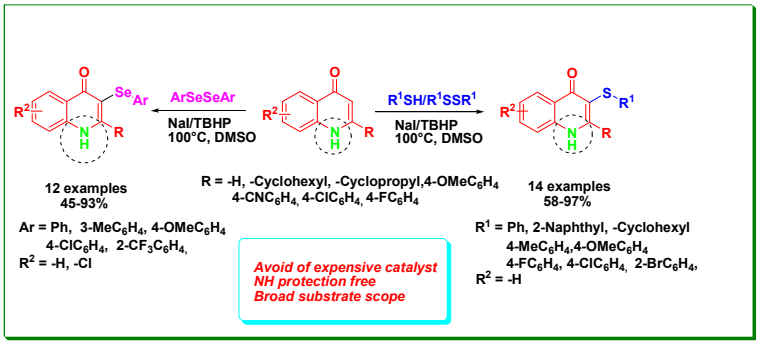
Generation of ArS and ArSe substituted 4-quinolone derivatives using sodium iodide as an inducer

Prasanjit Ghosh, Aritra Kumar Nandi, Gautam Chhetri and Sajal Das*

Department of Chemistry, University of North Bengal, Darjeeling 734 013, India.

E-mail: sajal.das@hotmail.com; Fax: +91-353-2699-001; Tel: +91-353-2776-381



Abstract: An operationally simple sodium iodide mediated C-S and C-Se bond formation protocol involving substituted 4-quinolone and thiols/diselenide to generate different ArS/ArSe substituted 4-quinolone derivatives in excellent yields was developed. The versatility of this methodology has been successfully demonstrated by extension of the suitable reaction conditions to the both substrates having different substituents. This regioselective C-H bond activation approach provides a direct access of structurally diverse 3-sulfenylated/selenylated 4-quinolone derivatives. Moreover, this new method proceeds without transition metal catalyst and pre-requisite NH-protection of 4-quinolone derivatives.

Introduction:

Transition metal catalysis brings a new horizon in organic synthesis by introducing a number of unique catalytic systems. It has huge contribution in almost all classes of organic transformations. For example, the C-hetero atom bond forming reaction is an important milestone in the field of transition metal catalysis.[1] Comparing with the other C-heteroatom, construction of C-S and C-Se bonds are relatively new. Formation of C-S bond is an important area of research because many natural products and biologically active molecules are generally comprised of this C-S linkage.[2] Diaryl sulfides and a variety of thioethers have incredible applications in treatment of various diseases like Alzheimer's,[3] Parkinson's,[4] Breast cancer,[5] HIV infections,[6] etc. The application of organoselenium compound as synthetic substrates and their useful biological activities have engrossed lots of interest to the synthetic chemists.[7] The toxicological and pharmacological properties of a compound can easily be tuned by introducing Se, as functional group. On account of hydrogen bond

acceptor and electron donor properties, organoselenium compounds can dramatically enhance the biological activity of the native substrate.[8] In 1980, Ebselen, an organoselenium compound was firstly discovered which act as promising neuroprotective and antioxidant agent.[9] Some of the diaryl sulfide and diaryl selenide containing biologically active moieties are shown in Fig. 1. Therefore, many researchers put their best efforts to develop highly efficient and environmentally benign protocol for the construction of C-S bond.[10] Recently, an alternative approach for the transition-metal-catalyzed C-S bonds formation *via* C-H bond functionalization has been developed which is known as sulfenylation reaction.[11]In these reactions arylsulfonyl chlorides,[12] aryl sulfonyl hydrazides,[13] sodium sulfinates,[14] sulfinic acids[15] and diaryldisulfides[16] are mostly used as the sulfenylating reagents in the presence of some transition metal catalyst. Even though these methods are advantageous but certain limitations comprising the use of toxic reagents and metal catalyst are still persist. Removal of trace amounts of transition-metal residues from desired bioactive products is quite challenging, costly and consumption of transition metal also hampers the sustainable development.[17] This inspired the researchers to develop some alternative efficient and practical method for transition metal free C-S/Se bond forming reactions. Metal free approach for the construction of C-S and C-Se are rare in literature. In this context, direct use of thiols/diselenide as the sulfenylation/selenation reagent to generate C–S/C-Se bond appears to be the attractive and synthetically desirable.

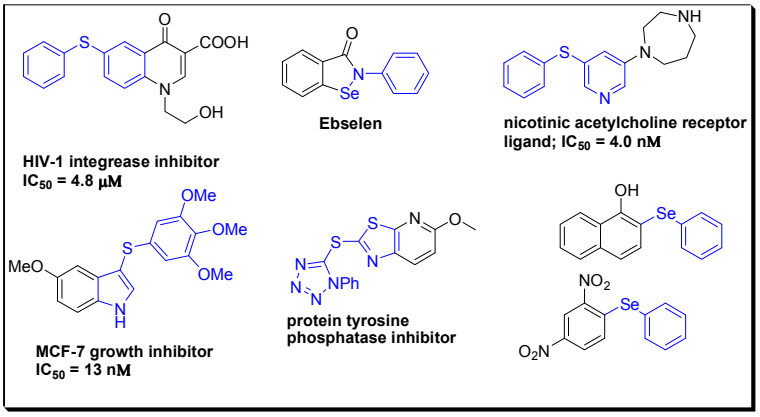


Fig 1: Representative examples of some important biologically active diaryl sulfide and diaryl selenide scaffolds

On the other hand, 4-quinolone represents an important class of potent privileged structures having huge application as anticancer,[18] anti-HIV,[19] antimalarial,[20] and antidiabetic agent.[21] Our research effort is to develop the simple protocol for the synthesis of this biologically active scaffold and its selective functionalization. In this arena, we have previously reported the Carbonylative Sonogashira annulations sequence for the synthesis of 4-quinolone,[22] construction of 6-aryl substituted-4-quinolones *via*

regioselective bromination followed by Suzuki cross-coupling reaction,[23] nitro derivatives of 4-quinolones *via* regio-controlled nitration at ambient condition,[24] ligand free approach for the Cu(II)-mediated C-NH_2 arylation of 4-quinolone derivatives[25] and 3-aroyl-quinolin-4(1*H*)-one from 3-iodo-quinolin-4(1*H*)-one using Carbonylative Suzuki coupling reaction.[26] There is a single report in the literature, where -SAr functionality inserted in the 4-quinolone moiety *via* Pd-catalyzed decarboxylation reaction.[27] Nevertheless, this protocol consisted of some drawbacks like harsh reaction condition, prolonged reaction time; essentially requires halogen substituted starting material and most importantly prerequisite protection of -NH functional group. Herein, we disclose a simple and efficient metal free route for the direct C-S and C-Se bond formation of 2-substituted/unsubstituted-4-quinolone scaffolds. It is worth noting that both thiols and organodiselenide are effectively coupled with 4-quinolone derivatives and furnished the desired product in good to excellent yields (Fig 2).

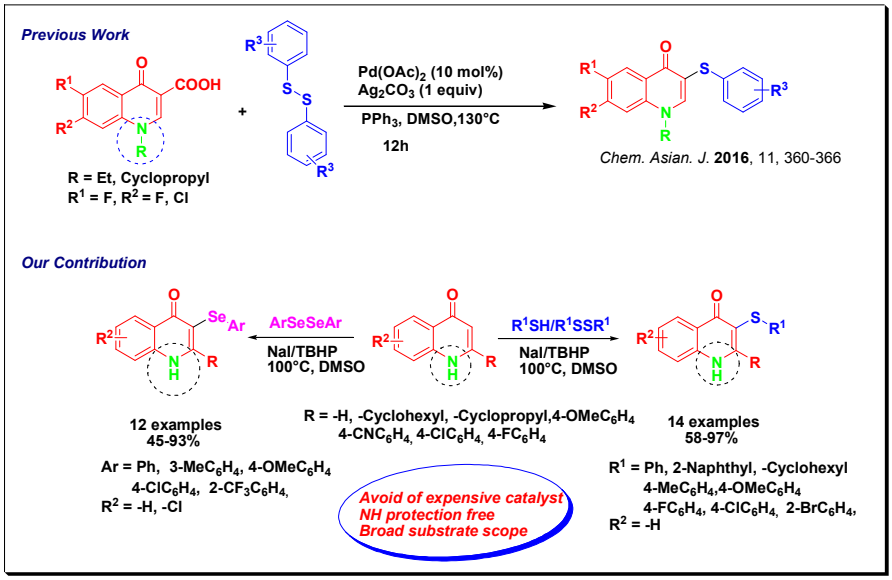


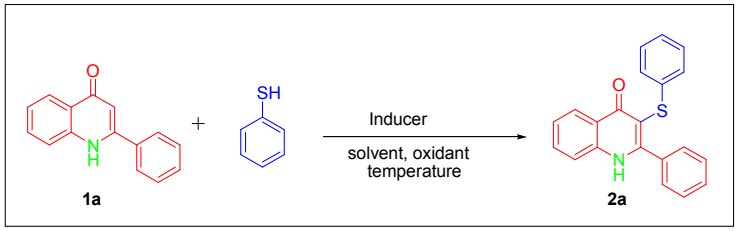
Fig 2: Previous protocol for the synthesis of thioether derivatives of 4-quinolone. Metal free approach for the synthesis of ArS/ArSe substituted product of 4-quinolone is reported herein.

Results and Discussion:

We began our studies with the optimization of C-S cross coupling reaction where 2-phenyl 4-quinolone (**1a**) and thiophenol were used as model coupling partner. The initial attempts to couple them in the presence of NaI as an inducer, TBHP as an oxidant in DCE at room temperature was unsuccessful. This was improved when we switched the solvent. A good yield of the coupled product **2a** was observed when DMF was used as solvent. The yield of the product **2a** was further increased to 97% upon performing the reaction in DMSO (Table 1, entry 5) under the same reaction conditions.

We next turned our attention to find the optimal reaction temperature by tuning it from rt to 135°C (Table 1, entries 6-8). Yield of the coupled product was shrunk upon reducing the reaction temperature, whereas a comparable yield (94%) was observed when the reaction was carried out at 135°C (Table 1, entry 8). By comparison, the identical reaction, in the presence of the other oxidant, H_2O_2 resulted in only 38% yield of the coupled product **2a** (Table 1, entry 9). Yield of the product **2a** was significantly reduced when the inducer, NaI was replaced by the other variety of iodide source (Table 1, entries 10-12). It is noteworthy that the presence of other inducers and oxidant appear to be redundant in this reaction. On the other hand, when the amount of inducer and oxidant was reduced in the same reaction under identical condition, resulted in poor yield of the coupled product **2a** (Table 1, entry 13). Additionally, a trace amount of product was observed in the absence of the oxidant, TBHP (Table 1, entry 14). So it is clear from the optimization table that a combination of NaI (3 equiv.) as inducer and TBHP (3 equiv.) as oxidant in DMSO at 100°C, was found to be optimal for the C-S coupling of 2-phenyl 4-quinolone and thiophenol, leading to excellent yield (97%) of the product **2a** after 15 h.

Table 1: Screening of the reaction conditions[a]



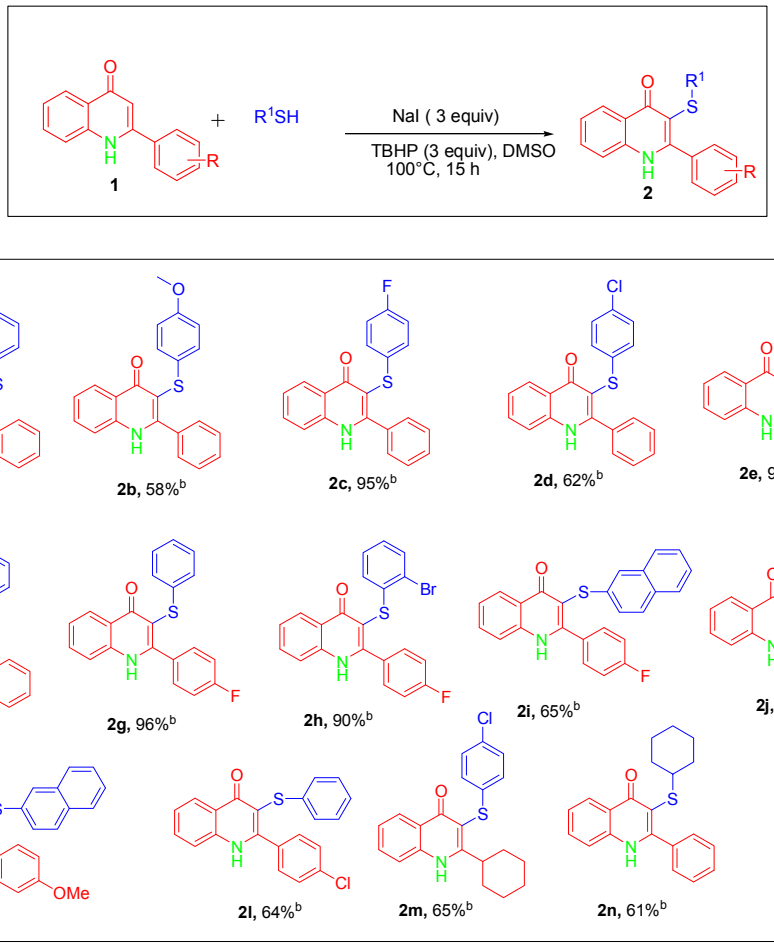
entry	inducer (equiv.)	oxidant (equiv.)	solvent (ml)	temp (°C)	time (h)	yield (%)
1.	NaI (3)	TBHP (3)	DCE	100	15	NR
2	NaI (3)	TBHP (3)	EtOH	100	15	NR
3	NaI (3)	TBHP (3)	Toluene	100	15	NR
4	NaI (3)	TBHP (3)	DMF	100	15	71
5	NaI (3)	TBHP (3)	DMSO	100	15	97
6	NaI (3)	TBHP(3)	DMSO	rt	15	Trace
7	NaI (3)	TBHP (3)	DMSO	80	15	61
8	NaI (3)	TBHP (3)	DMSO	135	15	94
9	NaI (3)	H_2O_2 (3)	DMSO	100	15	38
10	TBAI (3)	TBHP (3)	DMSO	100	15	35

11	KI (3)	TBHP (3)	DMSO	100	15	44
12	I_2 (3)	TBHP (3)	DMSO	100	15	28
13	NaI (1)	TBHP (1)	DMSO	100	15	29
14	NaI (3)	-	DMSO	100	15	trace

[a]**Reaction condition:** 4-quinolone (0.125 mmol, 1 equiv.), thiol (0.1875 mmol, 1.5 equiv.), inducer (1 or 3 equiv.), solvent (2 ml), oxidant (3 equiv.). [b]Isolated yields based on the reactants **1a**, the reaction was run for 15 h.

After establishing the optimal reaction conditions for the C-S coupling reaction between 2-phenyl 4-quinolone (**1a**) and thiophenol, the scope and generality of this protocol was investigated. A variety of 2-substituted 4-quinolones were treated with a broad range of benzene thiol and the corresponding results are presented in scheme 1. The coupling reaction proceeded smoothly and resulted in the desired 3-sulfenylated product (**2**) in good to excellent yield. A marked influence in the product yield was observed with the substituents present at the benzene thiol. An electron releasing group substituted benzene thiol resulted in low yield of the corresponding coupled product compare to electron withdrawing group this might be due the formation of more stable dimer (see fig. 3). Best yield of the product (**2c**) was obtained in case of –F substituted benzene thiol as fluorine is more electron withdrawing group than the other halogens. Bromo-substituted benzene thiol always resulted in higher yield of the corresponding products (**2e**, **2h**) than the corresponding chloro-derivative (**2d**, **2j**). This can be explained on the basis of the stability of the intermediate disulphide. Presence of bulky bromo group at the *ortho* position, destabilized the dimer and accordingly facilitated the reaction. Yield of the final products was found to vary with the electronic effects of the group present at C-2 position of 4-quinolone derivatives. Comparatively, a higher yield of the coupled product always obtained in the presence of electron releasing group at C-2 position of 4-quinolones (**2a**, **2l** and **2i**, **2k**). Aliphatic thiol smoothly participated in this sulfenylation reaction and furnished the desired product (**2n**) in good yield.

Scheme 1: Scope of different substituted 4-quinolone and thiol derivatives for NaI mediated sulfenylation[a]

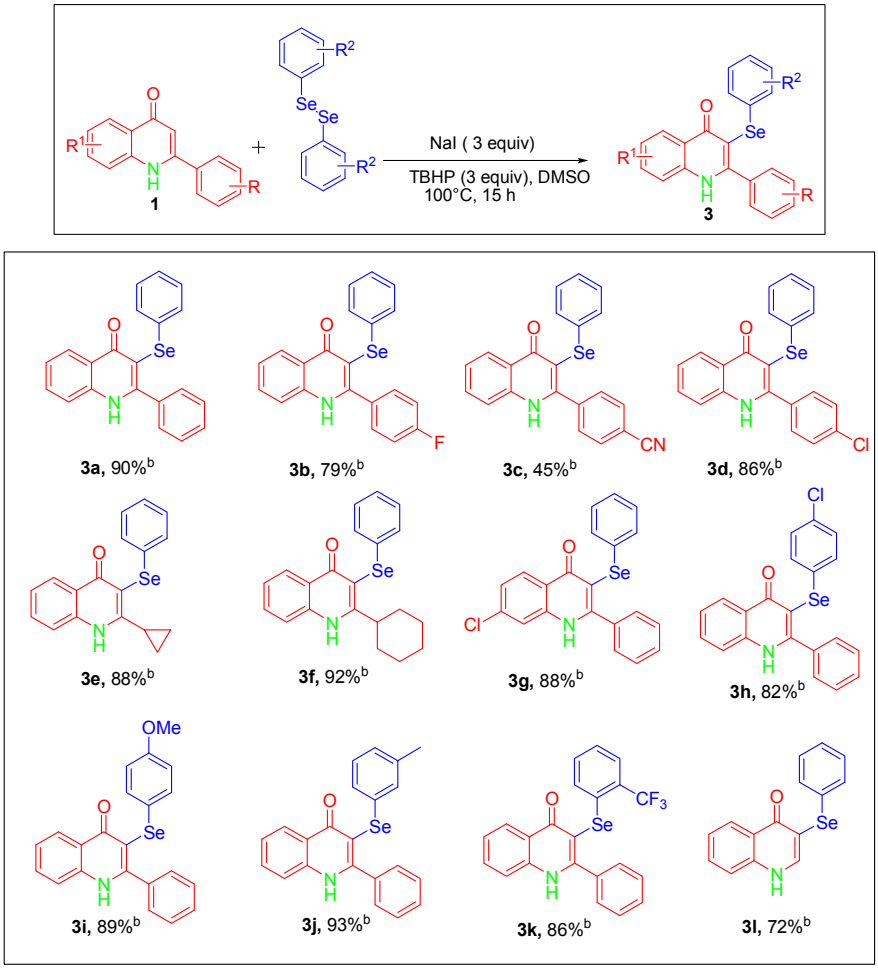


[a]**Reaction conditions:** 4-quinolone (0.125 mmol, 1 equiv.), thiol (0.1875 mmol, 1.5 equiv.), NaI (0.375 mmol, 3 equiv.), DMSO (2 ml), aqueous TBHP (70 wt% in water, 3 equiv.). [b]Isolated yields based on the reactants **1**, the reaction was run for 15 h.

With the successfully establishment of a facile and practical protocol for the sulfenylation reaction, it was employed to investigate the scope of C-Se cross-coupling reaction between 2-substituted 4-quinolones and diphenyl diselenide for the installation of -SePh group at C-3 position of 4-quinolone (scheme 2). Diphenyl diselenide was efficiently coupled with diverse functionalized 2-substituted 4-quinolones, resulting in excellent yield of the final coupled product **3**. Notably, the electronic effects of the substituents present at C-2 position of 4-quinolone have profound impact in the yield of final coupled products. Alkyl group substituted (cyclopropyl and cyclohexyl) 4-quinolone derivatives reacted efficiently with diphenyl diselenide and resulted in 88% and 92% yield of the corresponding products (entries **3e and 3f**) respectively. Whereas, in the presence of electron withdrawing group such as 4-chloro and 4-fluoro phenyl substituted 4-quinolone resulted in comparatively low yield of the coupled

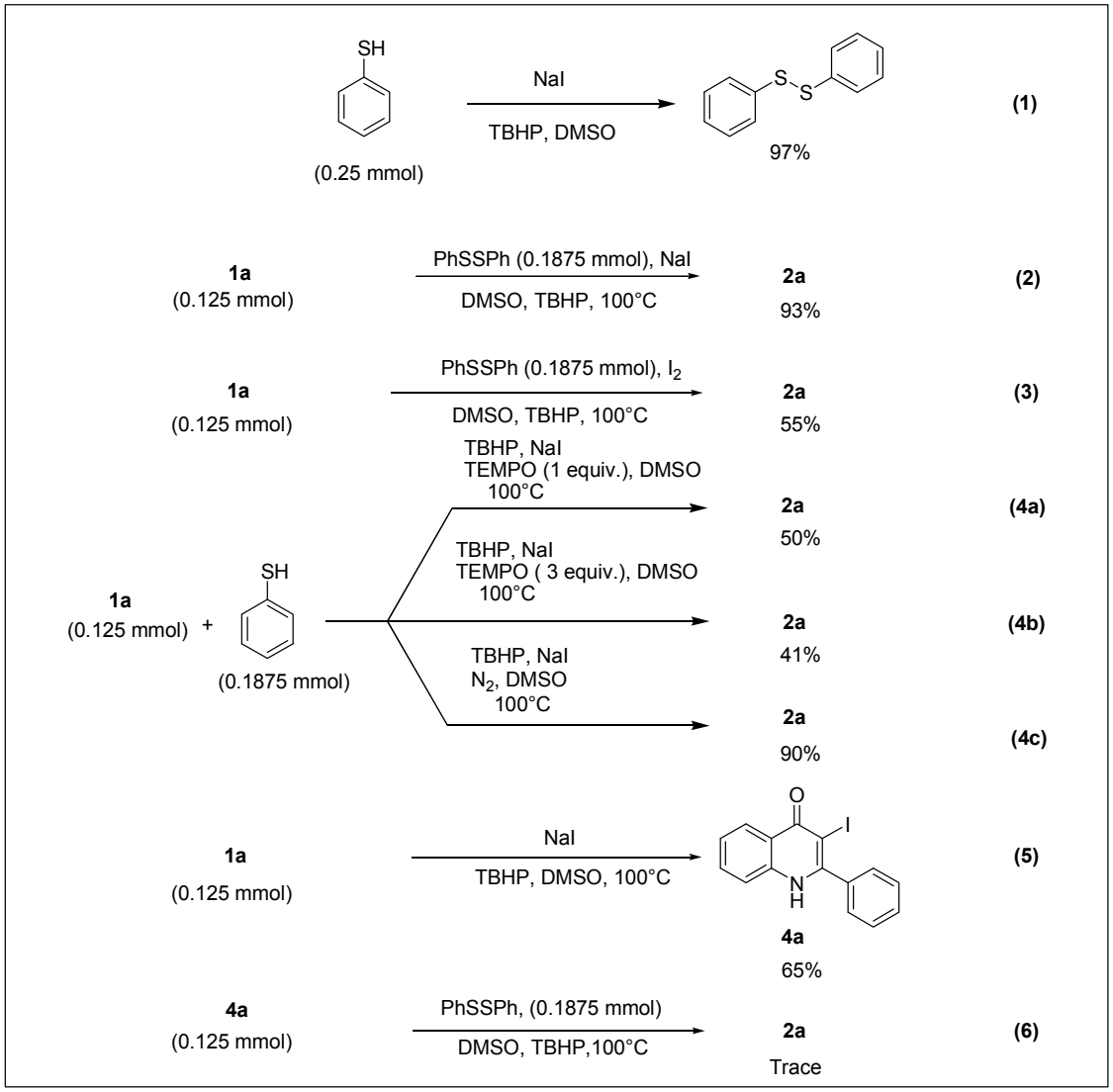
products (entries **3b** and **3d**). Lowest yield (45%) of the final product (**3c**) was observed in case of 4-cyano phenyl substituted 4-quinolone derivative. 1,2-bis(4-chlorophenyl)diselane were also employed as coupling partner, afforded the C-Se coupled product with good yield (entry **3h**). Most reactions of 2-phenyl substituted 4-quinolone with various electron releasing group (-OMe and –Me) containing organodiselenides proceeded well, giving excellent yields of quinolone selenide derivatives (entries **3i** and **3j**). Even, sterically crowded ortho-trifluoromethyl group bearing selenide provided the desired product in 86% yield (entry **3k**). Gratifyingly, C-2 unsubstituted 4-quinolone upon reaction with diphenyldiselenide furnished the corresponding selenide derivative in good yield (entry **3l**).

Scheme 2: Scope of different substituted 4-quinolone derivatives for NaI mediated selenylation[a]



[a]**Reaction conditions:** 4-quinolone (0.125 mmol, 1 equiv.), organodiselenide (0.1875 mmol, 1.5 equiv.), NaI (0.375 mmol, 3 equiv.), DMSO (2 ml), aqueous TBHP (70 wt% in water, 3 equiv.). [b]Isolated yields based on the reactants **1**, the reaction was run for 15 h.

Scheme 3: Studies of reaction mechanism



To gain further insight into the reaction mechanism, a series of control experiments were performed that are summarized in scheme 3. Under the optimised condition, the benzene thiols were successfully converted into 1,2-diphenyl sulfane in 97% yield (scheme 3, eq. **1**) which indicated that 1,2-diphenyl sulfane might be the important intermediate in the present transformation. Next, we performed the coupling reaction of 2-phenyl 4-quinolone (**1a)** with diphenyl disulphide instead of thiophenol under our established condition and the corresponding desired coupled product was isolated in 93% yield (scheme 3, eq. **2**). This observation, clearly indicated, 1,2-diphenyl sulfane may be an intermediate in this transformation. We have also screened the reactivity of iodine instead of NaI in reaction with PhSSPh and 2-phenyl substituted 4-quinolone and isolated lesser amount (55%) of the desired product **2a** (scheme 3, eq. **3**). From this observation, it is very much evident that *in situ* generation of iodine

from sodium iodide may effectively catalyses the reaction and delivered the excellent yield of the desired product **2a**.

To determine, whether this sulfenylation protocol is a radical process, a set of experiments was performed in the presence of free radical quencher, TEMPO (scheme 3, eq. **4a**, **4b**). Surprisingly, the yield of the final coupled product **2a** decreased to 50% in presence of 1 equiv. of TEMPO. The yield further decreased to 41% when 3 equiv. of TEMPO was used in the same reaction. Further, the reaction was performed in inert atmosphere (under N_2 atmosphere), the sulfenylated product **2a** was isolated in 90% yield, implying the arial oxygen was not the sole oxidant in the present reaction (scheme 3, eq. **4c**). Observations in equation **4**, ruling out the possibility of free radical pathway and confirming, 1,2-diphenyl sulfane is an essential intermediate in this reaction. Low yield of the product **2a** in presence of TEMPO could be due to incomplete conversion of thiophenol to 1,2-diphenyl sulfane, as scavenger may reduce the activity of the oxidant.

Reaction of 2-phenyl-4-quinolone and NaI in presence of TBHP, resulted in the corresponding 3-iodo derivative (**4a**) in excellent yield (scheme 3, eq. **5**). Unfortunately, this iodo product (**4a**) when subjected to the coupling reaction with diphenyl disulphide in absence of NaI, a trace amount of product (**2a**) was detected. This suggested that iodinated derivative of 4-quinolone was not formed in the catalytic cycle (scheme 3, eq. **6**).

Non radical Pathway

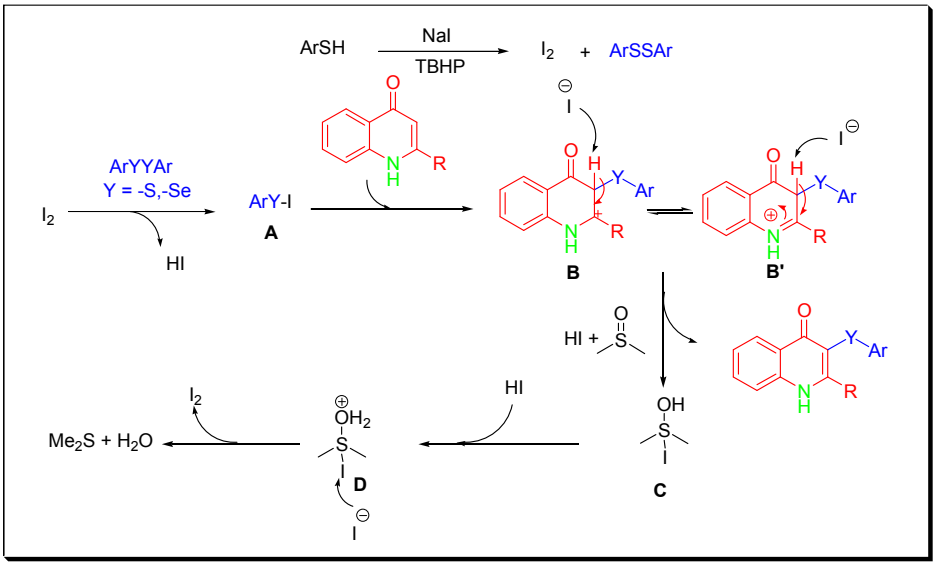


Fig 3: Proposed mechanism for the possible reaction

Based on the results of controlled experiments (scheme 3) together with the literature reports,[28] a proposed mechanism of the C-S/Se coupling reaction between 2-substituted 4-quinolone with thiophenol/diphenyl diselenide is shown in Fig 3. Initially, thiols were readily converted into disulfides under the present reaction conditions. Disulfides/diselenide in presence of I_2, generated an electrophilic intermediate ArY-I (**A**). The intermediate, ArY-I quickly reacted with 2-substituted-4-quinolone to form an ionic species **B/B'**, which could be stabilized by the adjacent nitrogen atom. With the loss of proton in the form of HI, the intermediate, **B** furnished the desired couple products. The HI immediately reacted with DMSO to generate the intermediate **C**, which reacted with HI to give intermediate **D**. Finally, nucleophilic attack of iodide ion on the iodide atom of **D** took place to regenerate I_2 releasing DMS and H_2O. Proper investigations on the more detailed mechanism are in progress in our laboratory.

Conclusion:

In summary, we have disclosed a method for NaI and TBHP initiated reaction of different 4-quinolone and thiols/diselenide, providing direct access to various C-S/C-Se linkage 4-quinolone moieties. Our protocol is operationally simple and avoids the use of any expensive metal catalyst. Moreover, this sulfenylation/selenylation methodology is excellent and corresponding products are obtained in good yields.

Experimental section:

General Considerations:

Unless stated otherwise, all reagents such as various thiols, phenyl diselenide, TBHP, NaI and solvents were used as received from commercial suppliers. NMR spectra were recorded on 300 MHz spectrometer at 298 K with calibration done on the basis of solvent residual peak. Products were purified using column chromatography on silica gel (60-120 mesh). Ethyl acetate and petroleum ether (60-80°C) were used as eluents. Progress of reaction was monitored using silica gel TLC.

Preparation of various thioether and Seleno ether substituted 4-quinolones (2a-2n/3a-3l):

Initially, various 2-(aryl/alkyl) substituted 4-quinolone (0.125 mmol), thiophenol/diselenide (0.1875 mmol), NaI (0.375 mmol, 56 mg) and TBHP (3 equiv.) were taken in DMSO (2 ml) in 25 ml round bottomed flask. Afterwards, the reaction mixture was heated at 100°C for 15 h. Then, it was cooled and diluted with water and the product was extracted with ethyl acetate (3 x 20 mL). Organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was then purified using column chromatography.

Physical characteristics and spectral data of compounds:

2-phenyl-3-(phenylthio)quinolin-4(1*H*)-one (2a): White solid, Yield = (97%, 39.9 mg), melting point: 191-193°C, ^{1}H NMR (300 MHz, DMSO-d_6) □ 6.97-7.05 (m, 3H), 7.14-7.20 (m, 2H), 7.41 (s, 1H), 7.48-7.54 (m, 5H), 7.71-7.73 (m, 2H), 8.11 (d, *J* = 7.8Hz, 1H), 12.29 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 108.5, 119.2, 124.5, 124.7, 124.8, 125.5, 125.9, 128.5, 129.0, 129.1, 130.2, 132.8, 135.5, 138.8, 139.9, 175.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{16}NOS$ calcd for 330.0952; found 330.0972

3-(4-methoxyphenylthio)-2-phenylquinolin-4(1*H*)-one (2b): White solid, Yield = (58%, 26.0 mg), melting point: 242-244°C, ^{1}H NMR (300 MHz, DMSO-d_6) □ 3.67 (s, 3H), 6.78 (dd, *J* = 6.9Hz, 1.8Hz, 2H), 6.98 (dd, *J* = 6.9Hz, 1.8Hz, 2H), 7.40-7.43 (m, 1H), 7.51-7.55 (m, 5H), 7.70-7.72 (m, 2H), 8.11 (d, *J* = 8.1Hz, 1H), 12.22 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 52.1, 107.0, 111.4, 115.7, 121.1, 121.1, 122.4, 124.9, 125.0, 125.7, 125.8, 126.7, 129.3, 132.1, 136.4, 153.0, 154.2, 172.2. HRMS (ESI-TOF) m/z: $[M]^+$ $C_{22}H_{17}NO_2S$ calcd 359.0980; found 359.0984.

3-(4-fluorophenylthio)-2-phenylquinolin-4(1*H*)-one (2c): White solid, Yield = (95%, 41.0 mg), melting point: 240-242°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 7.02-7.05 (m, 4H), 7.39-7.44 (m, 1H), 7.50-7.54 (m, 5H), 7.71-7.74 (m, 2H), 8.12 (d, *J* = 7.5Hz, 1H), 12.28 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 105.8, 105.9, 112.4, 112.7, 115.7, 121.2, 122.4, 124.4, 124.5, 124.7, 125.1, 125.6, 126.7, 129.3, 130.7, 132.0, 136.5, 153.4, 155.5, 158.7, 172.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{15}FNOS$ calcd 348.0853; found 348.0855.

(4-chlorophenylthio)-2-phenylquinolin-4(1*H*)-one (2d): White solid, Yield = (62%, 28.2 mg), melting point: 235-237°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 6.96 (d, *J* = 1.5Hz, 2H), 6.99 (d, *J* = 1.8Hz, 2H), 7.17-7.20 (m, 1H), 7.38-7.49 (m, 5H), 7.68-7.70 (m, 2H), 8.07 (d, *J* = 7.8Hz, 1H); ^{13}C NMR (75 MHz DMSO-d_6) □ 107.7, 118.7, 124.1, 124.3, 125.4, 126.8, 128.1, 128.5, 128.8, 129.7, 132.4, 134.9, 137.4, 139.4, 156.5, 174.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{15}ClNOS$ calcd 364.0563; found 364.0568.

3-(2-bromophenylthio)-2-phenylquinolin-4(1*H*)-one (2e): White solid, Yield = (97%, 49.0 mg), melting point:> 260°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 6.86 (dd, *J* = 8.1Hz, 1.5Hz, 1H), 6.99 (dt, *J* = 7.5Hz, 1.5Hz, 1H), 7.18 (dt, *J* = 7.8Hz, 1.2Hz, 1H), 7.41-7.54 (m, 7H), 7.74-7.76 (m, 2H), 8.13 (d, *J* = 7.8Hz, 1H), 12.38 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 107.8, 119.3, 119.5, 124.6, 124.8, 125.9, 126.2, 126.3, 128.3, 128.6, 128.9, 130.3, 132.8, 132.9, 135.3, 139.5, 140.0, 157.4, 175.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{15}BrNOS$ calcd 408.0052; found 408.0053.

3-(4-methylphenylthio)-2-phenylquinolin-4(1*H*)-one (2f): White solid, Yield = (69%, 29.6 mg), melting point:185-187°C,^{1}H NMR (300 MHz, DMSO-d_6) □ 2.20 (s, 3H), 6.95 (d, *J* = 8.4Hz, 2H), 6.99 (d, *J* = 8.4Hz, 2H), 7.38-7.73 (m, 8H), 8.10-8.16 (m, 1H), 12.25 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 20.9, 109.1, 119.2, 124.5, 124.6, 125.9, 128.5, 128.9, 129.1, 129.4, 129.8, 130.1, 130.3, 132.8, 134.1, 135.2, 135.6, 139.9, 156.8, 175.6. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{22}H_{18}NOS$ calcd 344.1109; found 344.1108.

2-(4-fluorophenyl)-3-(phenythio)quinolin-4(1*H*)-one (2g): White solid, Yield = (96%, 41.7 mg), melting point: 230-232°C,^{1}H NMR (300 MHz, DMSO-d_6) □ 6.99-7.07 (m, 3H), 7.15-7.20 (m, 2H), 7.30-7.44 (m, 3H), 7.57-7.62 (m, 2H), 7.69-7.77 (m, 2H), 8.12 (d, *J* = 7.5Hz, 1H), 12.30 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 108.8, 115.4, 115.6, 119.2, 124.5, 124.7, 124.9, 125.6, 125.9, 129.2, 131.5, 131.6, 131.8, 131.9, 132.9, 138.6, 139.9, 156.0, 161.6, 14.9, 175.5. HRMS (ESI-TOF) m/z: $[M]^+$ $C_{21}H_{14}FNOS$ calcd 347.0780; found 347.0782.

3-(2-bromophenylthio)-2-(4-fluorophenyl)quinolin-4(1*H*)-one (2h): White solid, Yield = (90%, 47.9 mg), melting point: 229-231°C, ^{1}H NMR (300 MHz, DMSO-d_6) □ 6.85 (dd, *J* = 7.8Hz, 1.5Hz, 1H), 7.00(dt, *J* = 7.5Hz, 1.5Hz, 1H), 7.15-7.20 (m, 1H), 7.31-7.37 (m, 2H), 7.41-7.61 (m, 4H), 7.73-7.76 (m, 2H), 8.13 (dd, *J* = 7.8Hz, 1.2Hz, 1H), 12.30 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 108.0, 115.5, 115.7, 119.3, 119.5, 124.6, 124.9, 125.9, 126.2, 126.3, 128.4, 131.4, 131.5, 131.6, 131.7, 132.8, 133.0, 139.4, 140.0, 156.5, 161.7, 162.8, 165.0, 175.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{14}BrFNOS$ calcd 425.9958; found 425.9960.

2-(4-fluorophenyl)-3-(naphthalene-2-ylthio)quinolin-4(1*H*)-one (2i): White solid, Yield = (65%, 32.3 mg), melting point: 170-172°C, ^{1}H NMR (300 MHz, DMSO-d_6) □ 7.21 (dd, *J* = 8.4Hz, 2.1Hz, 1H), 7.30-7.47 (m, 6H), 7.62-7.82 (m, 7H), 8.12 (d, *J* = 7.8Hz, 1H), 12.34 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 108.8, 115.4, 115.7, 119.2, 122.9, 124.7, 124.9, 125.4, 125.9, 126.9, 127.1, 127.9, 128.5, 131.2, 131.5, 131.6, 131.9, 132.8, 133.9, 136.4, 140.0, 156.1, 161.6, 164.9, 175.6. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{25}H_{17}FNOS$ calcd 398.1015; found 398.1010.

3-(4-chlorophenylthio)-2-(4-fluorophenyl)quinolin-4(1*H*)-one (2j): White solid, Yield = (55%, 26.6 mg), melting point : 158-160°C,^{1}H NMR (300 MHz, DMSO-d_6) □ 7.01-7.04 (m, 2H), 7.22-7.25 (m, 2H), 7.32-7.45 (m, 3H), 7.57-7.62 (m, 2H), 7.69-7.75 (m, 2H), 8.12 (d, *J* = 8.1Hz, 1H), 12.35 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 107.9, 114.9, 115.2, 118.8, 124.1, 124.3, 125.4, 126.8, 128.5, 128.9, 130.9, 131.1,

131.2, 131.3, 132.4, 137.3, 139.4, 156.6, 161.1, 164.4, 174.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{14}ClFNOS$ calcd 382.0469; found 382.0475.

2-(4-methoxyphenyl)-3-(naphthalene-2-ylthio)quinolin-4(1*H*)-one (2k): White solid, Yield = (75%, 38.4 mg), melting point:>260°C, ^{1}H NMR (300 MHz, DMSO-d_6) □ 3.78 (s, 3H), 7.03 (dd, *J* = 6.6Hz, 2.1Hz, 2H), 7.20 (dd, *J* = 8.7Hz, 1.8Hz, 1H), 7.37-7.46 (m, 4H), 7.53 (dd, *J* = 6.9Hz, 2.1Hz, 2H),), 7.70-7.82 (m, 5H), 8.11 (d, *J* = 7.8Hz, 1H), 12.23 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 55.8, 108.3, 113.9, 119.2, 122.5, 124.5, 124.6, 124.8, 125.4, 125.9, 126.9, 127.1, 127.7, 128.0, 128.5, 130.7, 131.2, 132.8, 133.9, 136.8, 140.0, 156.9, 160.9, 175.6. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{26}H_{20}NO_2S$ calcd 410.1215; found 410.1280.

2-(4-chlorophenyl)-3-(phenythio)quinolin-4(1*H*)-one (2l): White solid, Yield = (64%, 29.1 mg), melting point: 243-245°C, ^{1}H NMR (300 MHz, DMSO-d_6) □ 6.99-7.07 (m, 3H), 7.16-7.21 (m, 2H), 7.40-7.45 (m, 1H), 7.57 (s, 4H), 7.68-7.77 (m, 2H), 8.12 (d, *J* = 7.2Hz, 1H), 12.30 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 108.7, 119.2, 124.6, 124.7, 124.9, 125.6, 125.9, 128.6, 129.2, 131.0, 132.9, 134.2, 135.0, 138.5, 139.9, 155.8, 175.5. HRMS (ESI-TOF) m/z: $[M+H]^+$, $C_{21}H_{15}ClNOS$ calcd 364.0563; found 364.0569.

3-(4-chlorophenylthio)-2-cyclohexylquinolin-4(1*H*)-one (2m): White solid, Yield = (65%, 28.9 mg), melting point: 238-240°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 1.21-1.29 (m, 3H), 1.63-1.98 (m, 7H), 3.69 (t, *J* = 1.2Hz, 1H), 7.02-7.13 (m, 4H), 7.35 (t, *J* = 7.2Hz, 1H), 7.59 (dt, *J* = 7.2Hz, 1.5Hz, 1H), 7.80-7.83 (m, 1H), 8.05 (dd, *J* = 8.1Hz, 1.2Hz, 1H), 11.34 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 25.6, 26.3, 30.5, 42.5, 108.8, 116.1, 116.4, 118.9, 124.3, 124.4, 125.8, 128.3, 128.4, 132.6, 134.1, 134.2, 139.9, 162.5, 175.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{21}ClNOS$ calcd 370.1032; found 370.1037.

3-(cyclohexylthio)-2-phenylquinolin-4(1*H*)-one (2n): Brownish white solid, Yield = (61%, 25.5 mg), melting point: 236-238°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 0.98-1.23 (m, 6H), 1.45-1.51 (m, 3H), 1.66 (d, *J* = 11.4Hz, 2H), 7.35-7.40 (m, 1H), 7.49-7.58 (m, 5H), 7.62-7.67 (m, 2H), 8.13 (d, *J* = 7.8Hz, 1H), 12.01 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) □ 25.7, 25.9, 33.0, 43.4, 111.6, 118.9, 124.0, 124.1, 125.7, 128.4, 129.7, 129.8, 132.3, 136.1, 139.7, 154.7, 176.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{22}NOS$ calcd 336.1422; found 336.1418.

2-phenyl-3-(phenylselanyl)-quinolin-4(1*H*)-one (3a): Yellow solid, Yield = (90%, 42.4 mg), melting point:181-183°C, ^{1}H NMR (300 MHz, DMSO-d_6) □ 7.09-7.15 (m, 5H), 7.41-7.44 (m, 1H), 7.48-7.51 (m, 4H), 7.72 (dd, *J* = 6.0Hz, 1.5 Hz, 2H), 8.12 (d, *J* = 7.7Hz, 1H), 12.22 (s, 1H); ^{13}C NMR (75 MHz, DMSO-

d_6) □ 108.8, 119.1, 124.0, 124.6, 125.8, 126.1, 128.4, 128.8, 129.1, 129.3, 130.0, 132.7, 134.0, 136.8, 140.1, 156.7, 175.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{16}NOSe$ calcd 378.0397; found 378.0394.

2-(4-fluorophenyl)-3-(phenylselanyl)-quinolin-4(1*H*)-one (3b): Yellow solid, Yield = (79%, 39.0 mg), melting point: 230-232°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 7.08-7.14 (m, 5H), 7.32 (t, *J* = 9.0Hz, 2H), 7.38-7.43 (m, 1H), 7.54-7.59 (m, 2H), 7.67-7.72 (m, 2H), 8.12 (d, *J* = 7.8Hz, 1H), 12.24 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 109.0, 115.2, 115.5, 119.1, 124.0, 124.6, 125.8, 126.1, 128.7, 129.4, 131.6, 131.7, 132.8, 133.2, 133.2, 133.8, 140.0, 155.7, 161.5, 164.8, 175.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{15}FNOSe$ calcd 396.0303; found 396.0307.

4-(1,4-dihydro-4-oxo-(3-(phenylselanyl)-quinolin-2-yl)-benzonitrile (3c): Yellow solid, Yield = (45%, 22.6 mg), melting point: 171-173°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 7.13 (s, 5H), 7.42 (t, *J* = 6.9Hz, 1H), 7.65-7.76 (m, 4H), 7.96 (d, *J* = 8.1Hz, 2H), 8.13 (d, *J* = 7.8Hz, 1H), 12.36 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 108.8, 112.6, 118.9, 119.1, 124.1, 124.8, 126.0, 126.1, 128.9, 129.4, 130.3, 132.4, 132.9, 133.5, 140.1, 141.0, 155.0, 175.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{22}H_{15}N_2OSe$ calcd 403.0349; found 403.0340.

2-(4-chlorophenyl)-3-(phenylselanyl)-quinolin-4(1*H*)-one (3d): Light yellow solid, Yield = (86%, 44.1 mg), melting point: 162-164°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 7.08-7.13 (m, 5H), 7.41 (t, *J* = 8.1Hz, 1H), 7.54 (s, 4H), 7.65-7.73 (m, 2H), 8.12 (d, *J* = 8.1Hz, 1H), 12.26 (s, 1H), ^{13}C NMR (75 MHz, DMSO-d_6) □ 109.0, 119.1, 124.1, 124.7, 125.9, 126.1, 128.5, 128.9, 129.4, 131.1, 132.8, 133.7, 134.8, 135.5, 140.1, 155.5, 175.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{15}ClNOSe$ calcd 412.0007; found 411.9988.

2-cyclopropyl-3-(phenylselanyl)-quinolin-4(1*H*)-one (3e): White solid, Yield = (88%, 37.4 mg), melting point: 221-223°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 1.06-1.22 (m, 4H), 2.74-2.76 (m, 1H), 7.11-7.20 (m, 5H), 7.33 (t, *J* = 7.5Hz, 1H), 7.65 (t, *J* = 7.2Hz, 1H), 7.76-7.79 (m, 1H), 8.04 (d, *J* = 8.1Hz, 1H), 10.71 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 9.43, 17.3, 110.3, 118.8, 123.9, 124.2, 125.9, 126.0, 128.9, 129.4, 132.2, 133.7, 139.8, 155.8, 174.7. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{18}H_{16}NOSe$ calcd 342.0397; found 342.0396.

2-cyclohexyl-3-(phenylselanyl)-quinolin-4(1*H*)-one (3f): White solid, Yield = (92%, 43.9 mg), melting point: 238-240°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 1.24 (d, *J* = 8.4Hz, 3H), 1.63-1.80 (m, 7H), 3.70 (s, 1H), 7.13-7.20 (m, 5H), 7.35 (t, *J* = 7.8Hz, 1H), 7.68 (t, *J* = 8.4Hz, 1H), 7.81 (d, *J* = 8.1Hz, 1H), 8.05 (d,

J = 7.8Hz, 1H), 11.25 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 25.6, 26.3, 30.5, 44.9, 109.0, 118.7, 123.9, 124.2, 126.0, 129.2, 129.5, 132.4, 133.9, 140.1, 162.0, 175.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{22}NOSe$ calcd 384.0867; found 384.0868.

7-chloro-2-phenyl-3-(phenylselanyl)-quinolin-4(1*H*)-one (3g): Tan powder, Yield = (88%, 45.2 mg), melting point:>270°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 7.14 (s, 5H), 7.42-7.51 (m, 6H), 7.72 (s, 1H), 8.11 (d, *J* = 8.7Hz, 1H), 12.25 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 109.5, 118.2, 122.6, 124.9, 125.9, 128.5, 128.8, 129.1, 129.4, 130.2, 133.6, 136.6, 137.2, 140.9, 157.1, 174.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{15}ClNOSe$ calcd 412.0007; found 412.0008.

3-(4-chlorophenylselanyl)-2-phenylquinolin-4(1*H*)-one (3h): Yellow powder, Yield = (82%, 42.1 mg), melting point: 245-247°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 7.17 (q, *J* = 8.6Hz, 4H), 7.39-7.43 (m, 1H), 7.49 (s, 5H), 7.70-7.72 (m, 2H), 8.12 (d, *J* = 7.9Hz, 1H), 12.28 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) □ 108.6, 119.1, 124.1, 124.6, 126.1, 128.5, 129.1, 129.2, 130.1, 130.5, 130.6, 132.7, 132.8, 136.7, 140.1, 156.7, 175.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{21}H_{15}ClNOSe$ calcd 412.0007; found 412.0011.

3-(4-methoxyphenylselanyl)-2-phenylquinolin-4(1*H*)-one (3i): Yellow powder**,** Yield = (89%, 45.2 mg), melting point: 235-237°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 6.74(d, *J* = 8.7Hz, 2H), 7.10 (q, *J* = 4.8Hz, 2H), 7.38-7.41 (m, 1H), 7.48-7.50 (m, 5H), 7.67-7.70 (m, 2H), 8.11 (d, *J* = 8.1Hz, 1H), 12.14 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) □ 55.5, 110.2, 115.1, 119.0, 123.4, 124.0, 124.4, 126.0, 128.4, 129.3, 130.0, 131.8, 132.6, 136.9, 140.0, 156.1, 158.4, 175.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{22}H_{18}NO_2Se$ calcd 403.0503; found 403.0505.

3-(*m*-tolyl selanyl)-2-phenylquinolin-4(1*H*)-one (3j): White powder**,** Yield = (93%, 45.3 mg), melting point: 228-230°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 2.51 (s, 3H), 6.91 (s, 2H), 6.96 (s, 1H), 7.00-7.03 (m, 1H), 7.40-7.43 (m, 1H), 7.49 (s, 5H), 7.70 (s, 2H), 8.13 (d, *J* = 7.8Hz, 1H), 12.19 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) □ 21.3, 109.3, 119.0, 124.1, 124.4, 126.1,126.4, 126.7, 128.3, 129.0, 129.1, 129.9, 132.5, 133.7, 136.9, 138.4, 140.1, 156.4, 175.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{22}H_{18}NOSe$ calcd 392.0554; found 392.0560.

3-(2-(trifluoromethyl)phenylselanyl)-2-phenylquinolin-4(1*H*)-one (3k): White powder**,** Yield = (86%, 47.7 mg), melting point: 287-289°C; ^{1}H NMR (300 MHz, DMSO-d_6) □ 7.21 (d, *J* = 7.5Hz, 1H), 7.26-7.39 (m, 2H), 7.41-7.49 (m, 6H), 7.61 (d, *J* = 7.8Hz, 1H), 7.73-7.75 (m, 2H), 8.12 (d, *J* = 8.1Hz, 1H), 12.36 (s,

1H). ^{13}C NMR (75 MHz, DMSO-d_6) □ 109.0, 120.2, 125.3, 125.7, 126.9, 127.1, 127.9, 128.0, 128.1, 129.4, 130.0, 131.1, 131.5, 133.8, 133.9, 134.8, 137.5, 141.3, 158.4, 176.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{22}H_{15}F_3NOSe$ calcd 446.0271; found 446.0265.

3-(phenylselanyl)-quinolin-4(1*H*)-one (3l)[29]: Yellow powder, Yield = (72%, 27.0 mg); ^{1}H NMR (300 MHz, DMSO-d_6) □ 7.22-7.30 (m, 3H), 7.36-7.41 (m, 3H), 7.59 (d, *J* = 8.1Hz, 1H), 7.67-7.72 (m, 1H), 8.11-8.18 (m, 2H), 12.16 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) □ 109.9, 118.8, 124.3, 124.7, 125.8, 126.9, 129.6, 131.2, 131.8, 132.3, 140.1, 143.9, 174.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ $C_{15}H_{12}NOSe$ calcd 302.0084; found 302.0077.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of the ^{1}H and ^{13}C NMR spectra of the products (PDF) are available in the supporting information.

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