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Creation of 4-Quinolone Thioether and Selenoether Derivatives via Pd-NHC Catalysed Cross-Coupling Reaction

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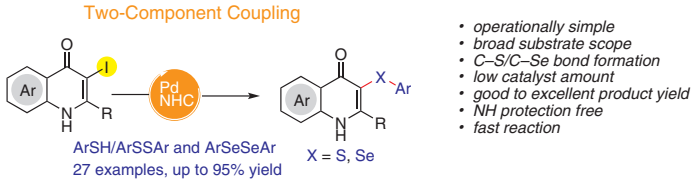

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Abstract Pd-NHC catalysed direct sulfenylation and selenylation of 3-iodo-4-quinolones has been developed. This protocol provides an alternative route for the construction of *ipso*-C–S and C–Se bond formation in 4-quinolones under aerobic conditions.

Key words 4-quinolone, Pd-NHC, sulfenylation, selenylation, cross-coupling

Thioether-functionalised heterocycles are an important class of compounds that are widely found in organic dyes, pharmaceuticals, functional materials, agrochemicals, bioactive products and drugs.[1] As a result, various methods are available for C–S cross-coupling reactions since its first report by Migita et al. in 1978.[2] A variety of thioethers have been found to have applications in the treatment of various diseases such as Parkinson's,[3] Alzheimer's,[4] HIV,[5] and breast cancer.[6] Similarly, organoselenium compounds have been shown to demonstrate anticancer, antiviral, antitumor, antimicrobial and antioxidant activities.[7] On account of their hydrogen-bond acceptor and electron-donor properties, organoselenium compounds can dramatically enhance the biological activity of the parent structure.[8] An example is Ebselen, an organoselenium compound introduced in 1980 as a neuroprotective and antioxidant agent.[9] Structures of representative biologically active moieties containing diaryl sulfide and selenide moieties are shown in Figure 1. In view of their importance in the field of biology, the development of highly efficient and simple protocols for construction of C–S and C–Se linkages continues to be of interest.[10]

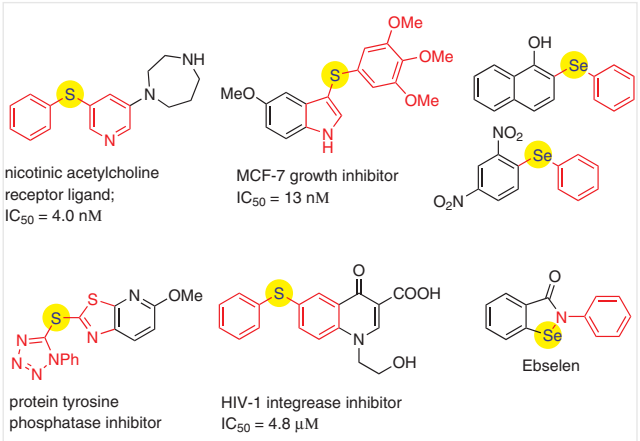
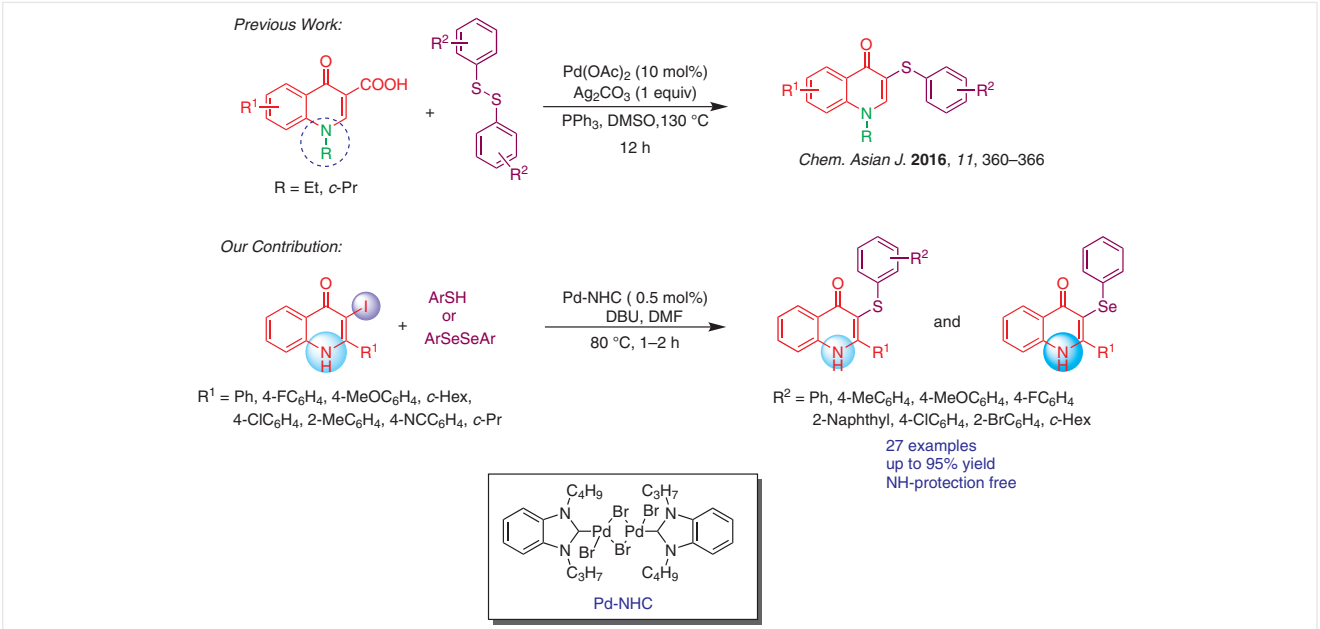


Figure 1 Representative examples of important biologically active scaffolds containing C–S and C–Se linkages

4-Quinolones frequently feature in pharmaceutical chemistry exhibiting properties such as antibacterial,[11] antimalarial,[12] and anticancer activities.[13] As a consequence, the synthesis of 4-quinolones and their derivatives has received considerable interest and various synthetic procedures are available in the literature.[14] 3-Aryl- or 3-heteroaryl-substituted quinolones have been widely explored because of their profound biological activities.[15] However, functionalisation at C-3 of quinolin-4-ones remains a challenging task due to the requirement for NH prefunctionalisation and protection. Recently, Zhang et al. introduced a technique for thioetherification at C-3 of 4-quinolones via Pd catalysed decarboxylation.[16] However, this protocol has



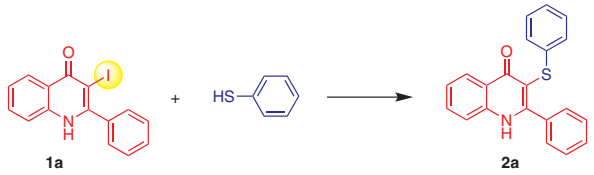
Scheme 1 Previous methodologies for the synthesis of thioether derivatives of 4-quinolone. An approach for the synthesis of C–S and C–Se cross-coupled product is reported herein.

some limitations including harsh reaction conditions, extended reaction times, requiring halogen-substituted 4-quinolone substrates and prerequisite NH protection.

In this area, we have previously reported the regiocontrolled nitration at C-5 and C-7 of 4-quinolones under ambient conditions,[17a] regioselective bromination at C-6 and subsequent arylation via Suzuki cross coupling,[17b] synthesis of 3-aroyl-quinolin-4(1*H*)-ones from 3-iodo-quinolin-4(1*H*)-ones using carbonylative Suzuki coupling,[17c] carbonylative Sonogashira annulation for the formation of 2-substituted 4-quinolone derivatives,[17d] synthesis of *N*-arylated derivatives under ligand free and ambient conditions,[17e] and NaI-mediated, metal-free synthesis of thioether and selenoether derivatives.[17f] More recently, we have disclosed a transition-metal free approach for the regioselective C-3 thiocyanation and selenocyanation of the 4-quinolone scaffold.[17g] Herein, we disclose a novel, simple and efficient route for Pd-NHC[18] catalysed thioetherification and selenylation of 3-iodo-4-quinolones in good yields under aerobic conditions (Scheme 1). To our knowledge, no such study has been documented before.

Our initial study began with the reaction between 3-iodo-2-phenyl-4-quinolone (**1a**) and thiophenol. After a reaction mixture containing 5 mol% $Pd(OAc)_2$ and 2 equiv of DBU in DMF was heated at 80 °C for 4 h, compound **2a** was isolated in 80% yield (Table 1, entry 1). Under identical conditions, when switching to an inorganic base (K_2CO_3) the yield of product **2a** decreased to 71%. In the presence of K_2CO_3, commercially available Pd salts such as $Pd(OAc)_2$, $PdCl_2$, and $Pd(acac)_2$ resulted in similar yields of the cross-coupled product (entries 2–4). Furthermore the yield of the

Table 1 Pd-NHC Catalysed C–S Cross Coupling: Effect of Reaction Parameters[a]

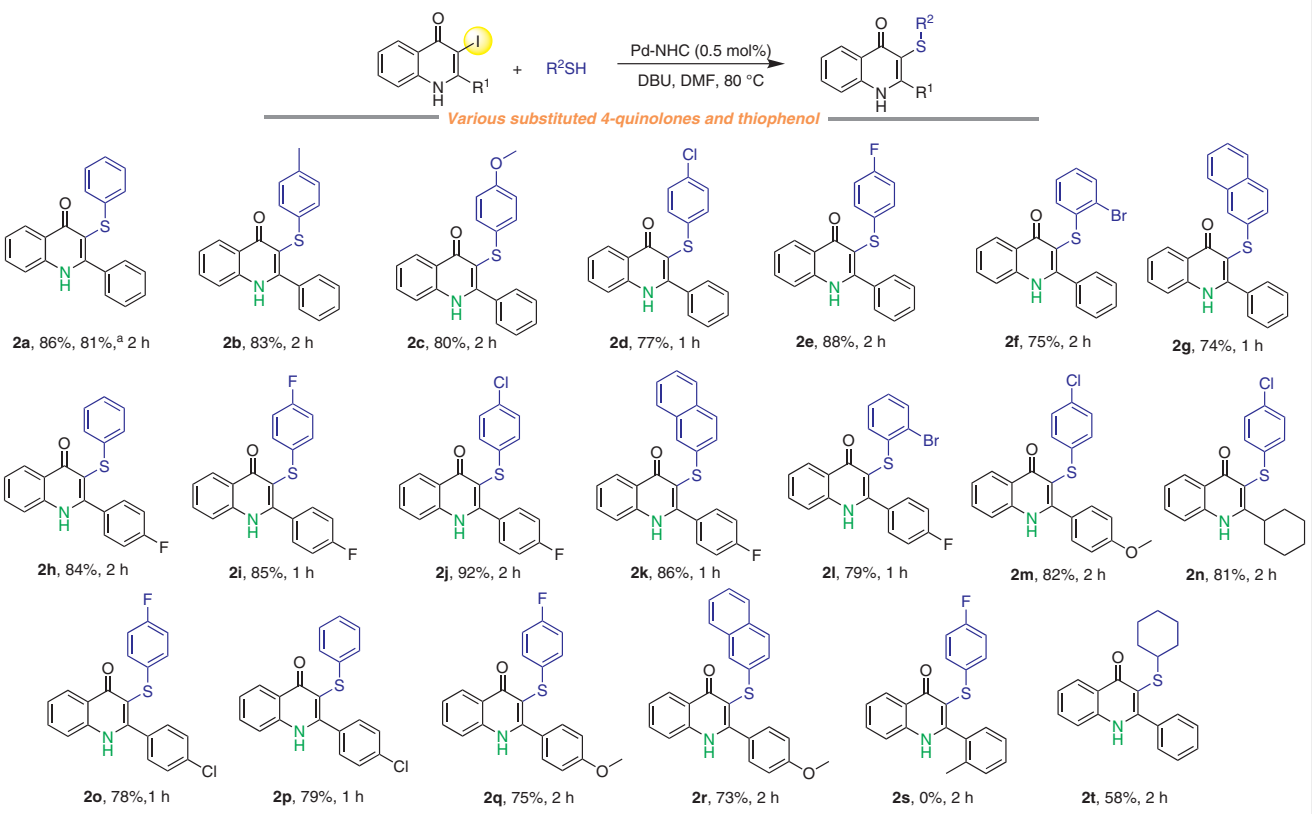


Entry	Catalyst (mol%)	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$ (5)	DBU	DMF	80	4	80
2	$Pd(OAc)_2$ (5)	K_2CO_3	DMF	80	4	71
3	$PdCl_2$ (5)	K_2CO_3	DMF	80	4	73
4	$Pd(acac)_2$ (5)	K_2CO_3	DMF	80	4	70
5	$Pd(PPh_3)_4$ (5)	K_2CO_3	DMF	80	4	53
6	Pd-NHC (2)	K_2CO_3	DMF	80	2	75
7	Pd-NHC (1)	DBU	DMF	80	2	83
8	Pd-NHC (1)	Et_3N	DMF	80	2	79
9	Pd-NHC (1)	Cs_2CO_3	DMF	80	2	52
10	Pd-NHC (1)	DBU	1,4-dioxane	80	2	70
11	Pd-NHC (1)	DBU	DMF	40	2	67
12	Pd-NHC (1)	DBU	DMF	rt	2	59
13	Pd-NHC (0.5)	K_2CO_3	DMF	80	2	72
14	Pd-NHC (0.5)	DBU	DMF	80	2	86

[a] Reaction conditions: 3-iodo-2-phenyl substituted 4-quinolone (0.25 mmol, 86 mg), thiophenol (1.5 equiv, 0.375 mmol, 41 mg), base (0.5 mmol).
[b] Isolated yield after purification by column chromatography.

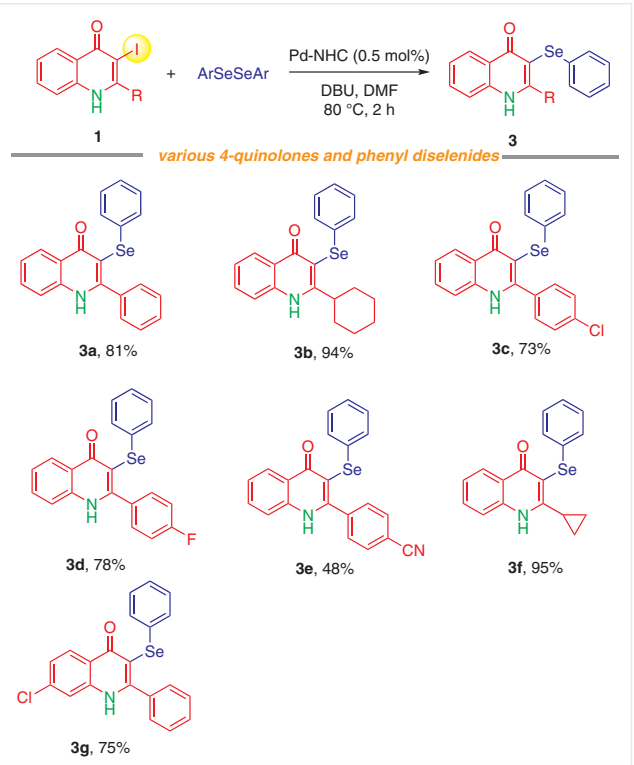
anticipated thioether derivative decreased when $Pd(PPh_3)_4$ was used as catalyst (entry 5). It was found that in the presence of just 2 mol% of Pd-NHC catalyst the reaction was complete within 2 h, resulting in the desired cross-coupled product in 75% yield (entry 6). From the optimization table, it is evident that organic bases are more effective. When the cross-coupling reaction was carried out in the presence of 1 mol% Pd-NHC catalyst, after 2 h, 83% of the cross-coupled product was isolated when DBU was used as base (entry 7). An similar yield of product was observed using Et_3N as base but upon using Cs_2CO_3 as base the yield dropped to 52% (entry 9). Furthermore, we found a direct relationship between yield of cross-coupled product and the reaction temperature. Carrying out the reaction at lower temperatures resulted in lower yields (entries 11, 12). After screening the different parameters, we found the combination of Pd-NHC as catalyst, DBU as base and DMF as solvent was optimal. Notably, 0.5 mol% of Pd-NHC as catalyst afforded **2a** in 86% yield within 2 h at 80 °C and served as optimal conditions for this protocol (entry 14).

With the optimised reaction conditions in hand, we explored the substrate scope of both 3-iodo-substituted 4-quinolones and variously substituted thiols (Scheme 2). A broad range of thiophenols were reacted with various 3-iodo-2-phenylquinolin-4-(1*H*)ones, affording the corresponding 3-aryl sulfide-4-quinolones in good to excellent yields. Both thiophenols possessing electron-donating and electron-withdrawing groups performed well in this transformation. 4-Fluorothiophenol coupled with 3-iodo-2-phenylquinolin-4-(1*H*)one, resulting in 88% yield of the desired product **2e**. Likewise, 2-thionaphthol furnished moderate to excellent yields (73–86%; **2g**, **2k**, **2r**). The greater steric bulk of the naphthyl might play a role in lowering the yield of **2g** and **2r**. Next, we examined the influence of various groups at C-2 of the 4-quinolone substrate. It was found that electron-withdrawing groups at C-2 afforded much higher yields in comparison to electron-donating substituents (**2h–l**, **2m**, **2n**, **2q**, **2r**). 2-Cyclohexyl-4-quinolone also proved to be a good coupling partner with 4-chlorothiophenol (**2n**). The highest yield was obtained when 2-(4-fluorophenyl)-3-iodo-4-quinolone was coupled with 4-fluorothiophenol to give **2j**. Surprisingly, 2-(2-methylphenyl)-3-iodo-4-quinolone did not afford the corresponding product **2s**. The reaction was complete in 1–2 h. Cyclohexanethiol smoothly participated in this sulfenylation reaction and furnished the desired product **2t** in 58% yield.



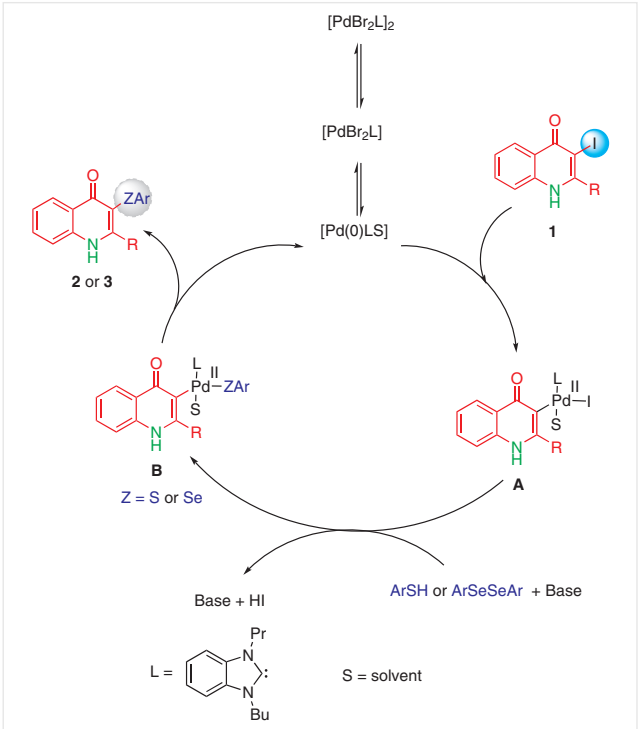
Scheme 2 Substrate scope for the Pd-NHC catalysed thioetherification. *Reagents and conditions*: 3-iodo-2 substituted-4-quinolone (0.25 mmol), thiophenol (0.375 mmol), DBU (0.5 mmol, 76 mg), DMF (2 mL) at 80 °C. Isolated yield after column chromatography. [a] Using PhSSPh (1.5 equiv).

Once the synthesis of various thioethers had been explored, we extend the protocol to the corresponding C–Se cross-coupling between various 3-iodo-2-phenyl-4-quinolones and diphenyl diselenide. Gratifyingly, the methodology proved to be general and we obtained the corresponding products **3a–g** in good to excellent yields (Scheme 3). It is important to note that electronic effects of the 2-substituents on the 4-quinolone have a profound impact on the yield of selenide derivatives. 4-Quinolones possessing 2-cyclohexyl and 2-cyclopropyl substituents gave the highest yields of the corresponding products **3b** and **3f**, whereas 2-aryl substituents possessing electron-withdrawing group such as 4-chloro and 4-fluoro resulted in comparatively low yields of the coupled products **3c** and **3d**. The lowest yield was observed for 2-(4-cyanophenyl)-4-quinolone, which furnished only 48% of the desired coupling product **3e**.



Scheme 3 Substrate scope of the Pd-NHC catalysed selenylation. *Reagents and conditions*: 3-iodo-2-substituted- 4-quinolone (0.25 mmol), diphenyl diselenide (0.375 mmol), DBU (0.5 mmol, 76 mg), DMF (2 mL) at 80 °C. Isolated yield after purification by column chromatography.

The catalytic cycle for the C–S and C–Se cross-coupling reactions of 4-quinolone derivatives initiated from in situ generation of Pd(0) species follows the standard pathway and is shown in Scheme 4. Oxidative addition to the 3-iodo-2-substituted-4-quinolone affords aryl palladium intermediate **A**. Next, transmetallation of the thiophenol or organodiselenide with aryl palladium complex **A** forms intermediate **B** and the desired 3-sulfenylated or 3-selenylated derivative is obtained after reductive elimination with concomitant regeneration of the Pd(0) species, which enters the next catalytic cycle.



Scheme 4 Plausible mechanism of the Pd-NHC catalysed C–S/C–Se cross-coupling of 4-quinolone

In summary, we have revealed an alternative method for the synthesis of *ipso*-C–S and C–Se substituted 4-quinolone derivatives through Pd-NHC catalysed cross-coupling reaction.[19] This method should be attractive to the synthetic and pharmaceutical chemistry community for the library synthesis of 4-quinolone derivatives. Biological screenings of all compounds synthesised herein are under investigation in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690897.

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(19) **2-Phenyl-3-(phenylthio)quinolin-4(1*H*)-one (2a); Typical Procedure**: 3-Iodo-2-phenyl-substituted 4-quinolone (0.25 mmol), thiophenol (0.375 mmol), DBU (0.5 mmol, 76 mg) and Pd-NHC (0.5 mol%, 1.2 mg) were dissolved in DMF (2 mL) in a 25 mL round-bottomed flask and the mixture was heated to 80 °C for 1–2 h. The mixture was then cooled, diluted with water, and the product was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by column chromatography, eluting with petroleum ether/ethyl acetate to give the product as a white solid (mp 191–193 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.29 (s, 1 H), 8.11 (d, *J* = 7.8 Hz, 1 H), 7.71–7.73 (m, 2 H), 7.48–7.54 (m, 5 H), 7.41 (s, 1 H), 7.14–7.20 (m, 2 H), 6.97–7.05 (m, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 175.5, 139.9, 138.8, 135.5, 132.8, 130.2, 129.1, 129.0, 128.5, 125.9, 125.5, 124.8, 124.7, 124.5, 119.2, 108.5. HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}NOS$: 330.0952; found: 330.0972.