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# Metal-free switchable *ortho*/*ipso*-cyclization of *N*-aryl alkynamides: divergent synthesis of 3-selenyl quinolin-2-ones and azaspiro[4,5] trienones†

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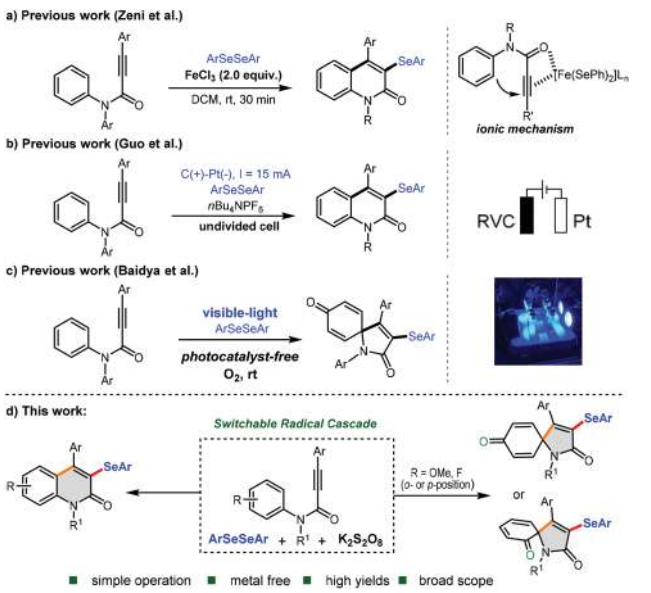
**A selenium radical triggered switchable *ortho*/*ipso*-cyclization cascade of *N*-aryl alkynamides has been devised under metal-free conditions to access 3-selenyl quinolin-2-ones and 3-selenospiro [4,5]trienones in high yields (up to 98%). The simple protocol is scalable and the mechanistic studies suggest that the radical cascade proceeds through a spirocyclic intermediate which is formed *via* an intramolecular *ipso*-cyclization route.**

Quinolinones and their derivatives represent the central skeleton of various biologically active heterocycles including natural products and have received increasing attention in pharmaceutical and medicinal chemistry.[1] Consequently, efficient synthetic strategies towards the diversification of the quinolinone scaffold are in high demand. Meanwhile the incorporation of a selenium atom into the framework of organic molecules often significantly enhances their activities and also changes their physical and pharmacological properties. In fact, hydrogen-bond acceptor or electron donor attributes of selenium atom could alter the chemical characteristics of enzyme active sites.[2] Therefore, we envisioned that selenium functionalized quinolinones might exert useful biological properties and pursued the development of a simple strategy for the production of selenylated quinolinones.

Recently, *N*-aryl alkynamide frameworks have judiciously been employed to furnish high-value nitrogen heterocycles.[3,4] In 2014, Zeni and coworkers reported the *ortho*-cyclization of *N*-aryl alkynamide with diaryl diselenides for the synthesis of 3-selenyl quinolin-2-ones. However, more than a stoichiometric amount of iron(III) chloride (2.0 equiv.) was necessary to promote this reaction and mechanistically this protocol proceeds *via* an electrophilic cyclization pathway (Scheme 1a).[5] Recently, Guo *et al.* established the electrochemical (constant current electrolysis in an undivided cell) oxidative *ortho*-cyclization of *N*-aryl alkynamides with diaryl diselenides to prepare 3-selenyl quinolin-2-ones (Scheme 1b).[6] We have also demonstrated that irradiation of *N*-aryl alkynamides with diaryl diselenide under blue LED effects *ipso*-cyclization at room temperature, delivering spiro-cycles embracing selenium functionality (Scheme 1c).[7] With our continuous interest in organoselenide chemistry,[8] herein, we disclosed a simple metal-free atom-transfer-radical addition reaction for the *ortho*-cyclization of *N*-arylpropynamides with diselenides *en route* to the production of 3-selenyl quinolin-2-ones in high yields (Scheme 1d). A switch in selectivity towards *ipso*-cyclization occurred when *N*-arylpropynamide substrates bearing *para*- and *ortho*-alkoxy and halogen substitutions in the *N*-aryl ring were employed, offering 3-selenospiro[4,5]trienones in good yields.




**Scheme 1** Switchable selenylative oxidative cyclization of *N*-aryl alkynamides.

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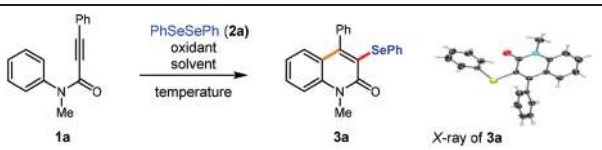
We commenced our studies on the annulation cascade reaction with *N*-aryl propiolamide **1a** and commercially available diphenyldiselenide **2a** (Table 1). To our delight, when the mixture of **1a** and **2a** in MeOH was exposed to $K_2S_2O_8$ oxidant at 80 °C under a nitrogen atmosphere, the selenium functionalized *ortho*-cyclization product **3a** was obtained in 17% isolated yield (entry 1). The structure of the product **3a** was unambiguously confirmed by single-crystal X-ray analysis.[9] Encouraged by this preliminary result, we intently evaluated various reaction parameters. A screening of solvents unveiled DCE as the best solvent, rendering the desired product **3a** in 94% yield (entries 2–7). Other persulfates were also effective; $Na_2S_2O_8$ and $(NH_4)_2S_2O_8$ gave **3a** in 86% and 79% yields, respectively (entries 8 and 9). Reaction yields decreased upon lowering or increasing the reaction temperature (entries 10 and 11). Notably, in the absence of $K_2S_2O_8$, the cyclization process was unfruitful with the recovery of both starting materials, suggesting the crucial role of the oxidant in this reaction (entry 12).

It is worth noting that, no products were obtained in the case of diphenyl disulfide (PhSSPh) and diphenyl diteluride (PhTeTePh) under optimal conditions and starting materials were recovered in both cases. Interestingly, outcomes of the selenium-based radical cascade reaction of *N*-aryl alkynamide and aryl alkynoate are completely different at elevated temperatures. In the latter case, 1,1-dichalcogenide olefin was formed *via* $CO_2$ extrusion (eqn (1)).[8f]

(1)

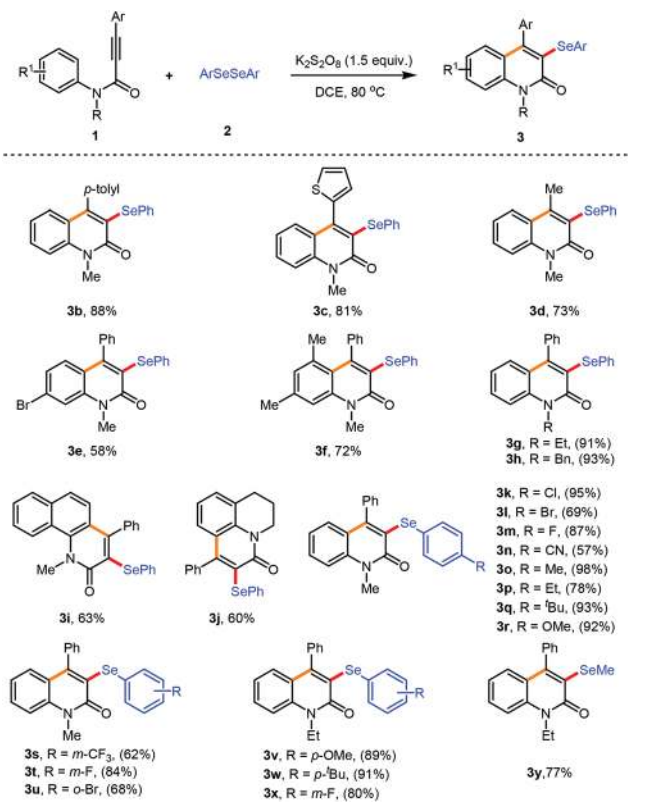
With the standard reaction conditions in hand, the scope of the selenium radical triggered cascade cyclization reaction of *N*-aryl alkynamides was explored (Scheme 2). The reaction is quite general. At first, substitutions at the C(sp)–aryl unit were investigated. Satisfyingly, amides having tolyl (**3b**), thienyl (**3c**), and alkyl such as methyl (**3d**) substitutions smoothly reacted to deliver the desired products in high yields (73–88%). *N*-Aryl alkynamides with different substitutions at the *N*-aryl ring (**3e, f**) also effectively participated in this reaction. Furthermore, amides with *N*-ethyl (**3g**) and easily removable *N*-benzyl (**3h**) substitutions gave the corresponding products in 91% and 93% yields, respectively. Substrates derived from 1-naphthylamine and cyclic tetrahydroquinoline were also suitable, offering tricyclic annulated products **3i** and **3j** in 63% and 60% yields, respectively. Also, various diaryldiselenides having halogen functionalities (**3k–m**) and electron-donating groups (**3o–r** and **3v–w**) at the *para*-position uniformly delivered the desired products in high yields. In the case of strongly electron-withdrawing cyano-substituted diaryldiselenide, product **3n** was isolated in moderate yield (57%). Using fluoro- and trifluoromethyl-substituted diaryl diselenides, useful fluorine containing 3-selenyl quinolin-2-ones **3m**, **3s–t** and **3x** were prepared in good to high yields. Gratifyingly, the reaction tolerates dialkyl diselenide as the selenium radical precursor, the desired product **3y** was isolated in 77% yield with dimethyldiselenide.

**Table 1** Optimization of the radical cyclization of *N*-aryl alkynamides[a]

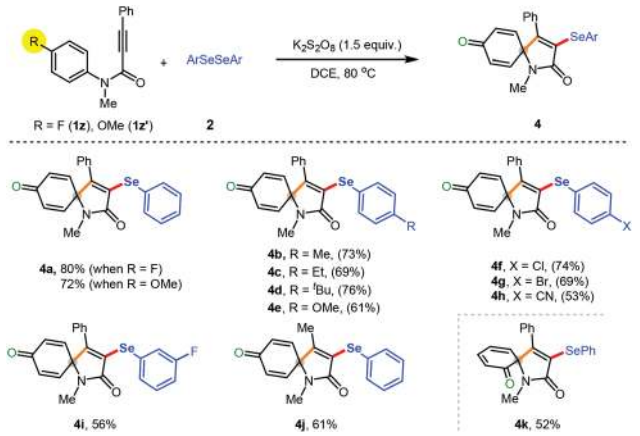



| Entry | Oxidant | Solvent | Temp (°C) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $K_2S_2O_8$ | MeOH | 80 | 17 |
| 2 | $K_2S_2O_8$ | DMC | 80 | 12 |
| 3 | $K_2S_2O_8$ | $H_2O$ | 80 | — |
| 4 | $K_2S_2O_8$ | DMSO | 80 | 0 |
| 5 | $K_2S_2O_8$ | Toluene | 80 | 32 |
| 6 | $K_2S_2O_8$ | MeCN | 80 | 62 |
| 7 | **$K_2S_2O_8$** | **DCE** | **80** | **94** |
| 8 | $Na_2S_2O_8$ | DCE | 80 | 86 |
| 9 | $(NH_4)_2S_2O_8$ | DCE | 80 | 79 |
| 10 | $K_2S_2O_8$ | DCE | 60 | 68 |
| 11 | $K_2S_2O_8$ | DCE | 100 | 73 |
| 12 | — | DCE | 80 | — |

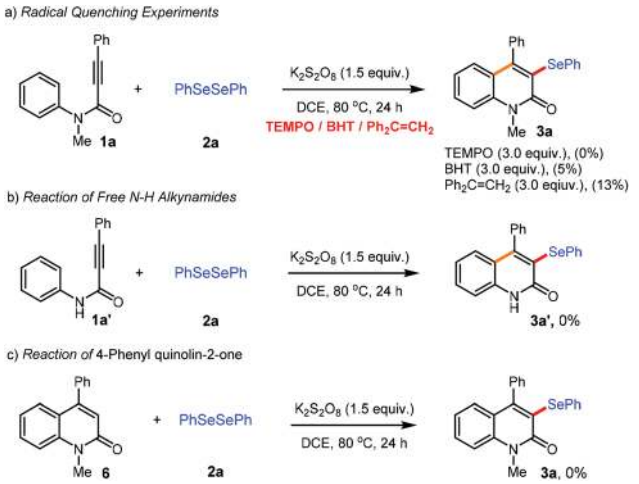
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), oxidant (0.3 mmol), solvent (1.5 mL), under a $N_2$ atmosphere, 24 h. [b] Isolated yields. DMC = Dimethyl carbonate.




**Scheme 2** Substrate scope for the radical cascade selenylation of *N*-aryl alkynamides. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $K_2S_2O_8$ (0.3 mmol), DCE (1.5 mL), 80 °C, $N_2$ atmosphere, 24 h. Yields of isolated products are given.




**Scheme 3** Substrate scope for the radical cascade selenylative spirocyclization of *N*-aryl alkynamides. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $K_2S_2O_8$ (0.3 mmol), DCE (1.5 mL), 80 °C, 24 h. Amide **1z′** was used for **4b–i** and yields of isolated products are given.




**Scheme 5** Control experiments.

Interestingly, when propiolamides bearing *para*-heteroatom substitutions such as *para*-fluoro (**1z**) and *para*-methoxy (**1z′**) in the *N*-aryl ring were tested under standard conditions, *ortho*-cyclization was not detected. Rather, we observed *ipso*-cyclization, forming a spiro-cyclic product 3-selenyl azaspiro [4,5]trienone (**4a**) in high yields for both amides (Scheme 3). The efficiency of *ipso*-cyclization was also evaluated with different diselenides having electron donating functionalities such as alkyl (**4b–d**) and methoxy (**4e**), halogens (**4f–g** and **4i**), and strongly electron-withdrawing cyano (**4h**) group and, for all cases, desired products were isolated in good to high yields (53–76%). *N*-Aryl alkynamides derived from butynoic acid also gave the desired product **4j** in 61% yield. Furthermore, when a substrate with the *ortho*-methoxy substitution in the *N*-aryl ring was employed, the challenging spiro-cyclized product **4k** with an *ortho*-quinoid framework was obtained in 52% isolated yield (Scheme 3). This spiro-cyclic product is very unique and, to the best of our knowledge, the effective synthesis to access such a scaffold is rare.

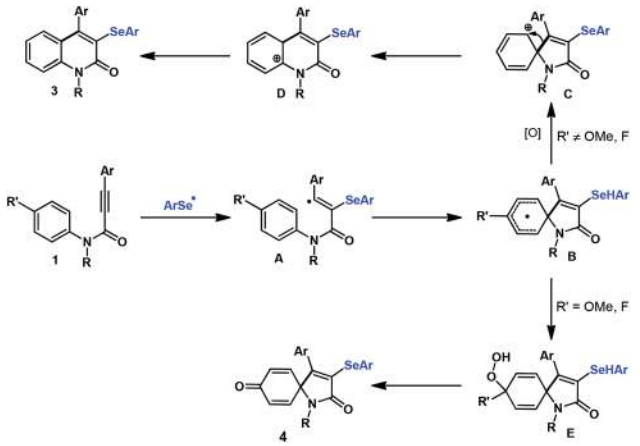
We have also executed the reaction on a gram scale with *N*-aryl alkynamides **1a** and **1h** (Scheme 4). The efficiency of the small-scale reaction was comparable upon scale-up, delivering **3a** and **3h** in 87% and 90% yields, respectively. Also, the exposure of product **3h** to *m*-CPBA gave the unsymmetrical selenoxide **5** in 58% yield.

To understand in more detail about the reaction mechanism, various controlled experiments were performed (Scheme 5). The reaction yields drastically decrease in the presence of various radical scavengers such as TEMPO, butylated hydroxytoluene (BHT), and 1,1-diphenylethylene with the recovery of *N*-aryl alkynamide **1a**, suggesting the participation of radical species in the cascade process (Scheme 5a). Despite careful investigations, characterization of any BHT or TEMPO adduct from the reaction mixture was unfruitful. No cyclization product **3a′** was formed when the free *N*-H alkynamides **1a′** were subjected to the standard conditions (Scheme 5b), albeit a mixture of inseparable products formed upon prolonging the reaction time. This finding signifies that the alkyl group at the *N*-centre is probably inducing the "*Thorpe–Ingold effect*" to bring the aryl group in close proximity for the intramolecular radical cyclization reaction. Also, when 4-phenyl quinolin-2-one **6** was treated with diphenyldiselenide **2a** under the standard reaction conditions, the formation of **3a** was not detected and most of the starting materials were recovered (Scheme 5c). Thus, the selenylation process did not occur after the ring closure step and 4-phenyl quinolin-2-one was not likely to be the intermediate of the *ortho*-cyclization. We believe a spiro-cyclic intermediate is most likely involved in the reaction mechanism.


**Scheme 4** Gram-scale reaction and post-functionalization.

Based on these observations and previous reports, a plausible reaction mechanism is depicted in Scheme 6. Upon treatment with $K_2S_2O_8$, the aryl selenium radical thus generated from ArSeSeAr reacts with *N*-aryl alkynamide **1** to give radical intermediate **A**. It undergoes intramolecular spirocyclization to forge the intermediate **B**, which further oxidised to give intermediate **C**. Intermediate **C** undergoes ring expansion to produce intermediate **D**, which on aromatization delivers the quinolone product **3**. In the case of *N*-aryl alkynamide bearing *para*-F/OMe substituents, the intermediate **B** further reacts with the solvated molecular oxygen to produce intermediate **E**. Then, intermediate **E** experiences O–O bond cleavage followed by defluorination/demethoxylation to deliver the desired product **4**.

In conclusion, we have revealed an efficient metal-free radical based switchable *ortho*/*ipso* oxidative cyclization



Scheme 6 Plausible mechanism.



cascade of *N*-aryl alkynamide using readily available diaryl diselenides as the selenium precursors and inexpensive $K_2S_2O_8$ as the oxidant. The reaction is operationally simple, scalable, and delivered a variety of 3-selenyl quinolin-2-ones and 3-selenospiro[4,5]trienones in good to excellent yields. Further implications of such a methodology in organic synthesis are currently underway in our laboratory.

## Conflicts of interest

There are no conflicts to declare.

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9 CCDC 1957705† contains the supplementary crystallographic data for compound **3a**.

 