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Electricity-driven, oxidative C–H selenylative and tellurylative annulation of *N*-(2-alkynyl)anilines: sustainable synthesis of 3-selanyl/tellanylquinolines†

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A metal- and oxidant-free, radical C–H selenylative and tellurylative annulation of *N*-(2-alkynyl)anilines with diorganyl dichalcogenides is developed under electrochemical conditions for the sustainable synthesis of valuable 3-selanyl/tellanylquinolines up to 92% yield at room temperature. The developed protocol required only electricity as the green reagent and offers high atom economy, broad substrate scope, and efficient scalability.
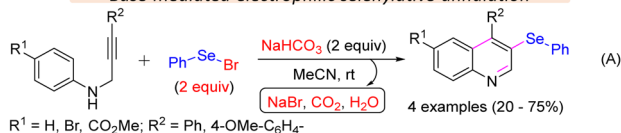
Quinoline is commonly found in many natural products, such as alkaloids,[1] and bioactive compounds with potential anticancer, antiviral, antiprotozoal, antimalarial, antibacterial, and antifungal properties.[2] Therefore, developing new synthetic techniques for efficient synthesis and modification of quinolines is a subject of great importance in synthetic organic and medicinal chemistry.[3]

Organoselenides have recently gained significant attention from the scientific community due to the unique chemical and biological properties of selenium.[4] These compounds have shown promise as synthetic intermediates and precursors to therapeutic compounds and as biologically active agents for treating various ailments, from cancer to cardiovascular disease.[5] Additionally, the distinctive redox properties of selenium have sparked interest in the field of materials and nanochemistry.[6] On the other hand, organotellurides are also found to have therapeutic applications in autoimmune diseases, enzymatic inhibition, and other biological activities.[7] However, the synthesis of organotellurides is underdeveloped.[7] Until now, limited methods have been documented for synthesizing selanylquinolines from acyclic starting materials. Larock and colleagues' seminal work showcased the use of relatively hazardous and unstable PhSeBr in over stoichiometric (2 equiv.) amounts to enable the electrophilic cyclization of *N*-(2-alkynyl)anilines, resulting in the formation of
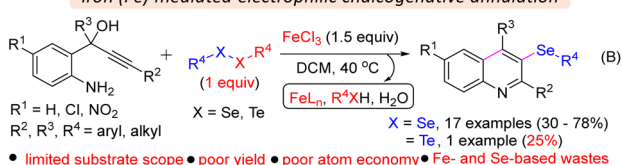
3-selanylquinolines (Scheme 1A).[8] Subsequently, the Zeni group introduced an alternative method utilizing 1.5 equiv. iron(III) chloride and diorganyl diselenides to produce 3-selanylquinolines through electrophilic selenylative annulation of 2-aminoaryl-2-ynols (Scheme 1B).[9] Recently, Lukesh and co-workers reported a radical selenylative annulation of *N*-(2-alkynyl)anilines with diorganyl diselenides using a hazardous metal-salt, CuCl₂ in stoichiometric (1 equiv.) amounts and hazardous chlorinated solvent, DCM (Scheme 1C).[10] Despite notable advancement, the developed
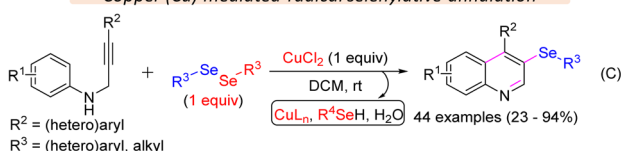

Scheme 1 Synthetic strategies to 3-chalcogenylquinolines.

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† Electronic supplementary information (ESI) available: Optimization table, experimental procedures, mass spectrum of **10**, cyclic voltammograms, calculation of faradaic efficiency, and copies of NMR spectra. See DOI: https://doi.org/10.1039/d4cc01780c

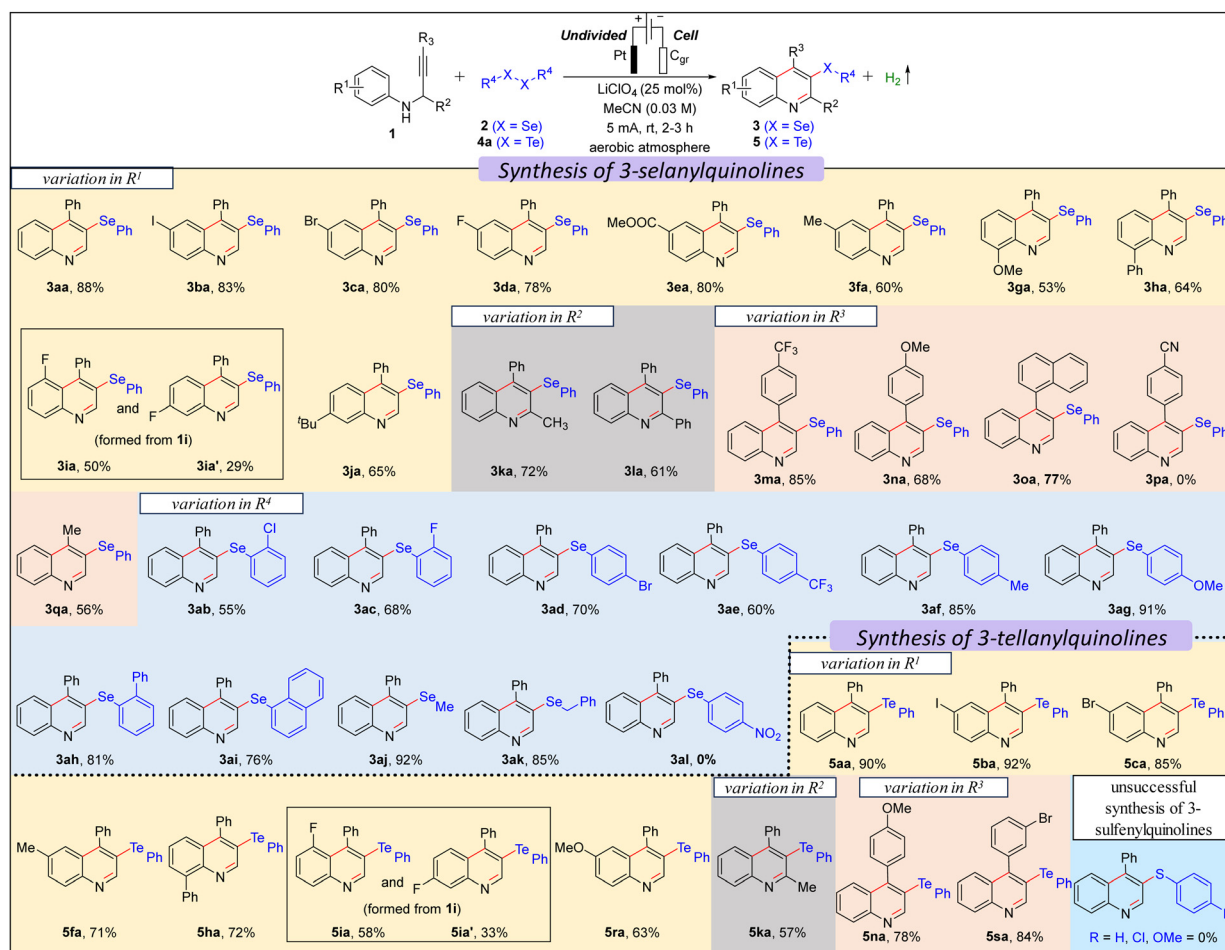‡ These authors contributed equally to the manuscript.

methods suffered from several serious limitations, such as (a) the requirement of hazardous PhSeBr or metallic reagents in over stoichiometric amounts, (b) limited substrate scope, (c) poor yield of products, (d) poor atom economy, (e) generation of Se- and/or Fe- and Cu-based stoichiometric waste. Moreover, these protocols were hardly employed for the tellurylative annulations and were only limited to synthesizing 3-selanylquinolines.

Only one example of the synthesis of 2,4-diphenyl-3-(phenyltellanyl)quinoline was reported by the Zeni group; however, the yield was poor (25%).[9] Hence, developing a metal- and stoichiometric reagent-free, sustainable synthetic strategy for synthesizing both 3-selanyl- and 3-tellanylquinolines is highly desirable, and we became interested in developing the same as a part of our continued interest in developing sustainable chalcogenative C–H annulation and functionalization reactions.[11] Recently, electro-organic synthesis has received tremendous attention from synthetic organic chemists.[12] Consequently, several electrochemical seleno-functionalization reactions have been developed so far for the synthesis of organoselenides.[13] Herein, we report a metal- and oxidant-free, highly atom-economic, scalable, and sustainable synthetic strategy for the oxidative C–H

annulation of N-(2-alkynyl)anilines with diorganyl diselenides and diorganyl ditellurides under electrochemical conditions to access 3-selanyl- and 3-tellanylquinolines, which eventually has overcome the limitations of the previously developed protocols.

We commenced our investigation with N-(3-phenylprop-2-yn-1-yl)aniline **1a** using 0.5 equiv. diphenyl diselenide **2a** in an undivided cell under constant current electrolysis (Table S1 in ESI†). When the reaction mixture was electrolyzed using 5 mA constant current in the presence of a Pt-anode, graphite (C_{gr}) cathode, and LiClO₄ (0.25 equiv.) in MeCN (0.03 M) for 3 h, gratifyingly, the desired product, 4-phenyl-3-(phenylselanyl)quinoline **3aa** was formed in 92% yield (entry 1, Table S1, ESI†) with 49.32% faradaic efficiency and no other byproduct was formed except H₂ as confirmed by the crude NMR (ESI†). While changing the cathode material from C_{gr} to Pt did not significantly affect the reaction outcome, switching the anode material from Pt to C_{gr} or Ni-foam had an adverse impact on the yield (entries 2–5 *vs.* 1, Table S1, ESI†). Altering the electrolyte from LiClO₄ to ⁿBu₄NBr, Et₄NBr, ⁿBu₄NClO₄, ⁿBu₄NPF₆, and KI, as well as changing the solvent from MeCN to EtOH, ⁱPrOH, DMF, and water, resulted in a decrease in the reaction yield (entries 6–14 *vs.* 1, Table S1, ESI†). Furthermore, the optimal loading of 0.5 equiv. of **2a** and

Table 1 Substrate scope for the electrochemical synthesis of 3-selanylquinolines and 3-tellanylquinolines[ab]

[a] Reaction conditions: **1** (0.5 mmol), **2** or **4a** (0.275 mmol, 0.5 equiv.), LiClO₄ (0.0125 mmol), MeCN (10 mL), Pt-anode (1 × 1 cm²), graphite sheet (1 × 1.5 cm²) cathode, constant current, I = 5 mA, r.t., aerobic atmosphere. [b] Isolated yield.
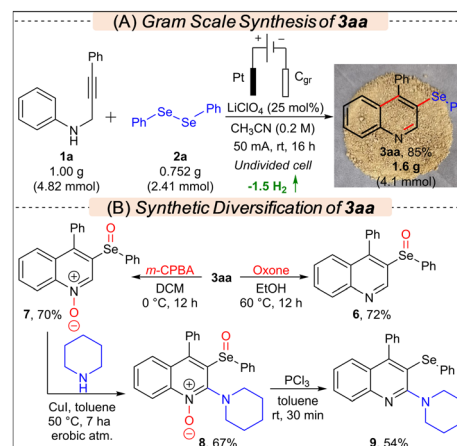
0.25 equiv. of $LiClO_4$ was determined to be the most effective (entries 15–18 *vs.* 1, Table S1, ESI†). The optimal reaction time and constant current were identified as 3 hours and 5 mA, respectively (entries 19–21 *vs.* 1, Table S1, ESI†). Control experiments emphasized the essential roles of electrolyte and electricity in the reaction (entries 22 and 23, Table S1, ESI†). Next, we explored the scope of the selenylative C–H annulation reaction of *N*-(2-alkynyl)anilines **1** with diorganyl diselenides **2** under the optimized conditions (Table 1). The model reaction between **1a** and **2a** furnished **3aa** in an 88% isolated yield. *Ortho-* and *para*-halogen (I, Br, Cl, and F), electron-withdrawing (Ph and CO_2Et), and electron donating (Me and OMe) group substituted *N*-(2-alkynyl)anilines underwent the reaction with **2a** smoothly to furnish the desired products (**3aa–3ha**) in moderate to good yield (53–88%). When *meta*-fluoro-substituted *N*-(2-alkynyl)aniline (**1i**) reacted with **2a**, a mixture of regioisomers, *i.e.*, **3ia** and **3ia′**, was formed in 52% and 30% yield, respectively. However, *meta-tert*-butyl-substituted *N*-(2-alkynyl)aniline (**1j**) furnished only **3ja** regioselectively, as controlled by the bulk of the ^tBu-group. Highly substituted quinolines, *i.e.*, **3ka** and **3la**, were formed from *N*-(1-substituted-2-alkynyl)anilines under standard conditions. Next, we explored the substrate scope with the variation in the alkyne part, and both electron-withdrawing (CF_3) and electron-donating (OMe) group substituted *N*-(2-alkynyl-3-aryl)anilines furnished the desired products (**3ma–3oa**) in good yield. However, 4-(3-(phenylamino)prop-1-yn-1-yl)benzonitrile did not furnish **3pa**. Moreover, 4-methyl-3-(phenylselanyl)quinoline **3qa** was formed in 60% yield from *N*-(but-2-yn-1-yl)aniline. The scope of the diorganyl diselenides was found to be good as both the diaryl diselenide, bearing either a halogen (Br, Cl, F), or a strong electron-withdrawing (CF_3) or electron-donating (OMe) group, and also dialkyl diselenides smoothly reacted with **1a** to furnish the desired products (**3ab–3ai** and **3aj–3ak**) in moderate to good yields, except for 1,2-bis(4-nitrophenyl)diselane (**3al**). Subsequently, we investigated the scope of the tellurylative C–H annulation of **1a** with diphenyl ditelluride **4a**, and, to our delight, the desired product, 4-phenyl-3-(phenyltellanyl)-quinoline **5aa** was formed in an excellent yield (90%) under standard conditions (Table 1). The versatility of the electrochemical tellurylative C–H annulation was notable as various substituted *N*-(2-alkynyl)anilines reacted with **4a** to afford the desired 3-tellanyl-quinolines (**5ba–5sa**) in satisfactory to excellent yields (60–92%), regardless of the type and position of the substituents. As predicted, **1i** yielded a mixture of regioisomers **5ia** and **5ia′** in 58% and 33%, respectively. Unfortunately, the C–H sulfenylative annulation of **1a** with various diaryl disulfides (R = H, Cl, OMe) under standard conditions did not furnish the desired 3-sulfenylquinolines.

To showcase the practicality of the protocol, a gram-scale synthesis involving compounds **1a** (1 g, 4.82 mmol) and **2a** was conducted using the standard conditions, resulting in the formation of 1.6 g (4.1 mmol) **3aa** in an 85% yield (Scheme 2A). To demonstrate the application of the developed protocol, **3aa** was synthetically diversified to various new classes of molecules *via* controlled oxidation, C–H amination, and deoxygenation reactions, as presented in Scheme 2B.[11d,14] When **3aa** was treated with Oxone, only chemoselective oxidation of selenium occurred leading to the selective synthesis of **6** in 72% yield; however, in the presence of *m*-CPBA, **7** was formed selectively in 70% yield. Subsequently, **7** was further modified

through a Cu-catalyzed C–H amination reaction with piperidine to access **8** in 67% yield, which after deoxygenation by PCl_3 furnished **9** in 54% yield. Synthesis of 2-aminoquinolines is important as they are prevalent in various alkaloids and bioactive molecules.[15]
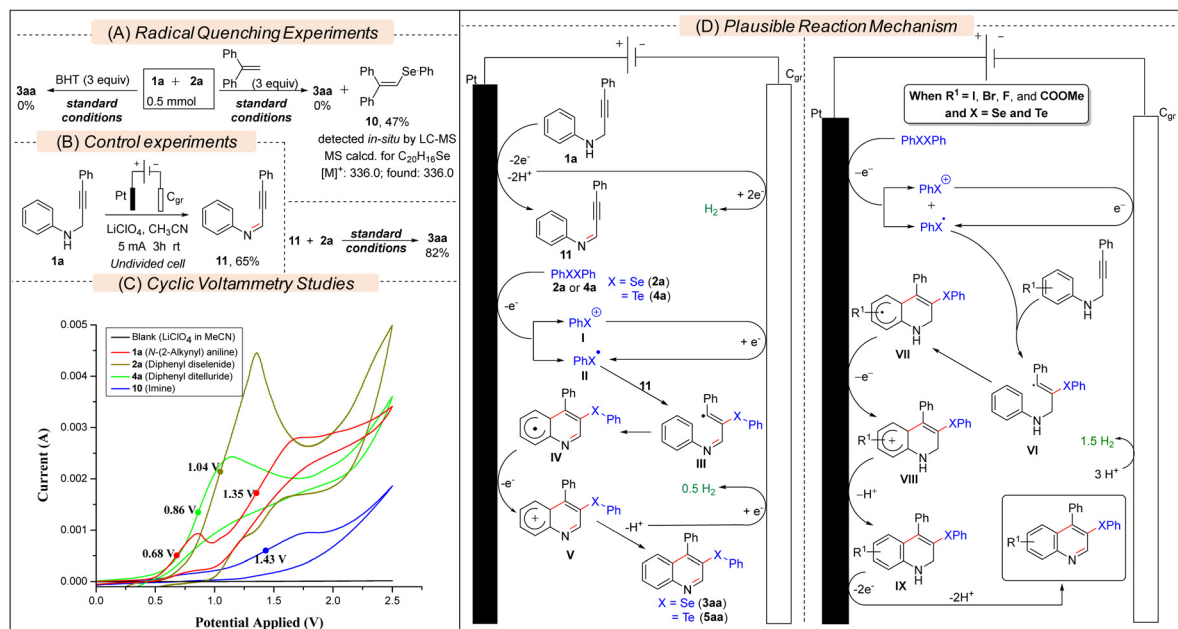
Several experiments have been conducted to get insights into the reaction mechanism. In the presence of a radical quencher, *i.e.*, BHT or 1,1-diphenylethene (DPE), the model reaction furnished no **3aa**, which suggested that the reaction proceeded *via* a free-radical pathway (Scheme 3A). Moreover, the detection and isolation of the radical adduct **10** revealed the involvement of a PhSe. radical as the key intermediate (Fig. S1, ESI†). In the absence of **2a**, **1a** was oxidized to (*Z*)-*N*,3-diphenylprop-2-yn-1-imine **11** (Scheme 3B). Then, **11** was subjected to reaction with **2a** under electrochemical conditions, and **3aa** was formed in 82% yield, revealing **11** as an intermediate of the reaction. The cyclic voltammetry (CV) experiments (Scheme 3C) revealed that the half-wave oxidation potentials ($E_{p/2}$) of diphenyl diselenide **2a** ($E_{p/2}$ = 1.04 V) and diphenyl ditelluride **4a** ($E_{p/2}$ = 0.86 V) are lower than that of the imine **11** ($E_{p/2}$ = 1.43 V). However, the half-wave first oxidation potential of **1a** ($E_{p/2}$ = 0.68 V) is quite a bit lower than that of **2a** and **4a**. Based on these experimental results and previous reports,[13b] we proposed that **1a** first oxidized to **11** *in situ* and then **2a** or **4a** underwent preferential one-electron oxidation at the anode to furnish the key PhSe. radical **II** (Scheme 3D). Then **II** was added to **11** to form the vinyl radical **III**, which, after cyclization followed by anodic oxidation and deprotonation, furnished the desired product (**3aa** or **5aa**). However, according to CV analysis of electron-withdrawing group (I, Br, F, and CO_2Me) substituted *N*-(2-alkynyl)anilines (Fig S2, ESI†), it is more likely that **2a** or **4a**, having lower $E_{p/2}$ than that of these substrates, first underwent preferential oxidation at the anode to form the chalcogenyl radical (PhX.) which after radical addition and annulation formed **IX**. Finally, **IX** underwent electrochemical oxidation to form the desired product. The half-wave oxidation potential of diphenyl disulfide, $(PhS)_2$ ($E_{p/2}$ = 1.53 V), is found to be much higher than that of **11** and **1a** (Fig. S2, ESI†), which could be the cause of the failure of the reaction.

In conclusion, we developed a highly atom-economic, cost-effective, scalable, and sustainable synthetic strategy for the selenylative and tellurylative C–H annulation of readily available

Scheme 2 Gram-scale synthesis of **3aa** and synthetic diversification.

Scheme 3 Mechanistic studies and plausible reaction mechanisms.

N-(2-alkynyl)anilines with diorganyl dichalcogenides to access a wide variety of valuable 3-selanyl/tellanylquinolines under electrochemical conditions. Electricity was used as the only green reagent, and hydrogen was formed as the only innocuous byproduct. Mechanistic studies revealed a radical pathway, and **3aa** was synthetically diversified to other quinoline derivatives. This protocol also serves as a unique strategy to access 3-tellanylquinolines, which has been underdeveloped to date.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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