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Copper-catalyzed decarboxylative Se insertion coupling of indoles and propiolic acids

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ABSTRACT

A novel and efficient copper-catalyzed decarboxylative alkynylselenation of indoles with Se powder and propiolic acids has been developed. The outstanding advantages of this protocol not only nicely avoid the use of prefabricated arylselenation reagent and address the facile over-selention issues, but also enrich the chemistry of selenium powder. Importantly, this reaction could be extended to pyrrole, and the practical utility of this transformation has been demonstrated in gram-scale synthesis and late-stage indolylselenation of Clofibrate-derived propiolic acid.

The incorporation of Se atom into organic small molecules could substantially unfold their important biological functions in antioxidant defense, regulation of inflammatory responses and metabolism of thyroid hormones [1,2]. In discovery chemistry, it has been realized that aryl alkynyl selenides are useful precursors for the preparation of multifunctional vinyl selenides by well-developed hydrofunctionalizations [3–6], and are valuable handles in cyclization [7] and cross-coupling reactions [8]. In this case, it has been of great interest to disclose concise and efficient protocols for preparing these privileged compounds. Although numerous attractive avenues for the construction of new C_{sp}-Se bonds have been developed, including the cross-coupling of alkynyl bromides with ArSeSeAr [9,10], terminal alkynes with ArSeBr [11–13], ArSeSeAr [14–19] or ArSeCN [20], and alkynylboronic acid [21,22] with ArSeSeAr through various mechanistic processes. The existing preparation of electrophilic arylselenation reagent, 1 equivalent ArSe-waste of ArSeSeAr and harsh reaction conditions would dramatically inhibit the research and development of new selenium-containing pharmaceutical molecules.

Alkynyl carboxylic acids have been employed as terminal alkyne surrogates in transition-metal catalyzed decarboxylative C-X bonds coupling reactions [23–26]. Recently, Pan reported copper-catalyzed decarboxylative arylselenation of aryl propiolic acids with electrophilic diaryl diselenides (Scheme 1A) [27]. However, the chemo-selectivity of these reactions was not well controlled. The unsaturated bonds in the product are liable to electrophilic addition with the excess electrophilic arylselenation reagent, thus, over-selenation pitfalls are facile to occur [28–32]. In addition, some heteroaryl selenating reagents are difficult to access mainly because of the lack of synthetic routes. On the other hand, the use of Se powder as imput linkage is attractive and fantastic, since it is bench-stable, inexpensive, and easy-to-handle. We assumed that the decarboxylative arylalkynylation of Se powder could be employed to avoid the above-mentioned limitations and insurmountable issues of over-arylselenation. As a rational design of this strategy (Scheme 1B), copper-catalyzed decarboxylative selenation of alkynyl carboxylic acids with Se powder to generate the nucleophilic alknylselenocopper intermediates, which was then coupled with nucleophilic heterocyclic compounds *via* analogous Chan-Lam coupling. As a continuous study on the difunctionalization of Se powder [33,34], herein, we describe a new protocol for the preparation of arylalknyl selenides through copper-catalyzed decarboxylative alkynylselenation of indole with Se powder and propiolic acids with the formation of double C-Se bonds. Compared with traditional alkynyl sources [35], the prominent reactivity of propiolic acids shows a higher exploitability and flexible propensity for selective decarboxylative selenation. This transformation not only enriched the chemical properties of selenium powder, but also broadened the new application value of alkynyl carboxylic acids.

At the beginning of our study, we chose indole (**1a**), selenium powder and phenylpropiolic acid (**2a**) as model substrates to explore the optimal reaction conditions. As illustrated in Table 1, the

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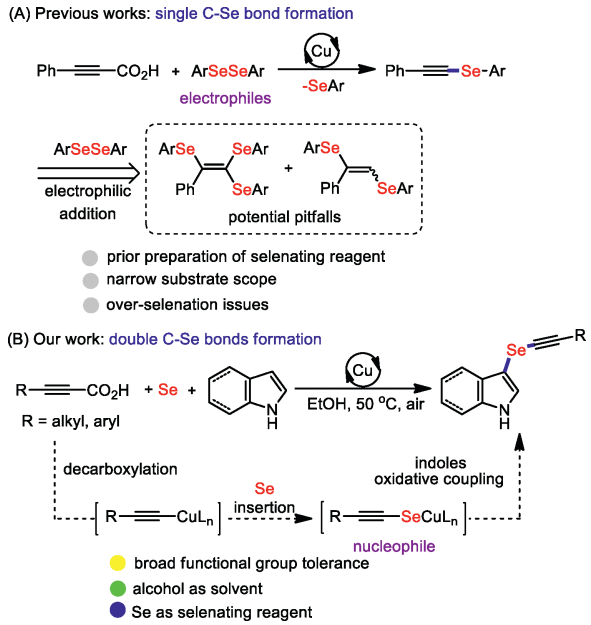
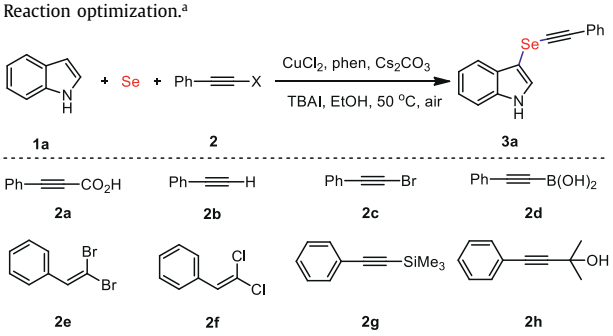


Scheme 1. Decarboxylative arylselenations.

reasonable choice of copper salt, solvent and base was found to be a critical success for the transformation. Among numerous copper catalysts, $CuCl_2$ displayed the highest catalytic activity, while $CuBr_2$ and $Cu(OAc)_2$ have relatively low performance (entries 1–3). It was found that using other alcohols solvent other than ethyl alcohol affected the transformation outcome (entries 4–6). In fact, common organic solvents such as DMSO and toluene could not realize the smooth conversion of the reaction (entries 7–11), and the target product was not detected. If the reaction does not add a phase transfer catalyst, the conversion efficiency decreases sharply (entry 12). When other carbonates were used instead of Cs_2CO_3, **3a** was not generated or the yield was significantly diminished (entries 13–15). We speculated that the suitable base plays an important role in the deprotonation of acetylenic acid and the activation of Se powder under these reaction conditions. The expected decarboxylative arylselenation reaction hardly occurred in the absence of copper catalyst and base (entries 16 and 17). In particular, the lack of 1,10-phen significantly reduced the yield of **3a** (entry 18). Importantly, when the reaction is conducted under N_2 atmosphere or elevating the reaction temperature all decrease the conversion of substrates (entries 19 and 21). In addition, when the reaction is carried out under O_2 atmosphere, the reaction efficiency is also very good, but it is slightly lower than that under air (entry 20).

It is worth noting that a small amount of 1,2-bis(phenylethynyl)diselane derived from the reaction of Se powder with propiolic acids and decarboxylative homocoupling of propiolic acids have always been observed [36], while over-selenation, decarboxylative addition or hydroamination of indole with propiolic acids byproducts did not detect during the optimization of reaction conditions [37]. Finally, the alkynylselenation of indole with other typical arylacetylene sources, such as phenylacetylene (**2b**), 1–bromo-2-phenylacetylene (**2c**), 2-phenyl-1-ethynylboronic acid (**2d**), 2,2-dibromostyrene (**2e**), (2,2-dichlorovinyl)benzene (**2f**), 1-Phenyl-2-(trimethylsilyl)acetylene (**2g**) and 2-methyl-4-phenyl-3-butyn-2-ol (**2h**) were proved to be completely invalid under otherwise identical reaction conditions. These results suggested that CO_2H group of propiolic acids plays a critical role in promoting the multi-component selenation reactions [38]. It is presumable that the coordination of CO_2H group with the copper center is beneficial to better substrate solubility and facilitates the insertion of selenium powder with the triple bonds.

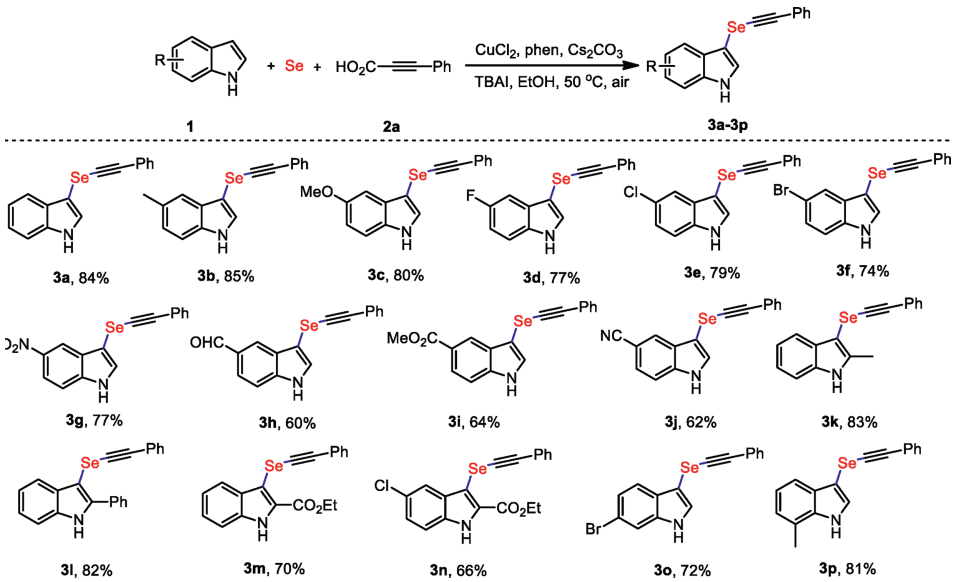
Table 1
Reaction optimization.[a]



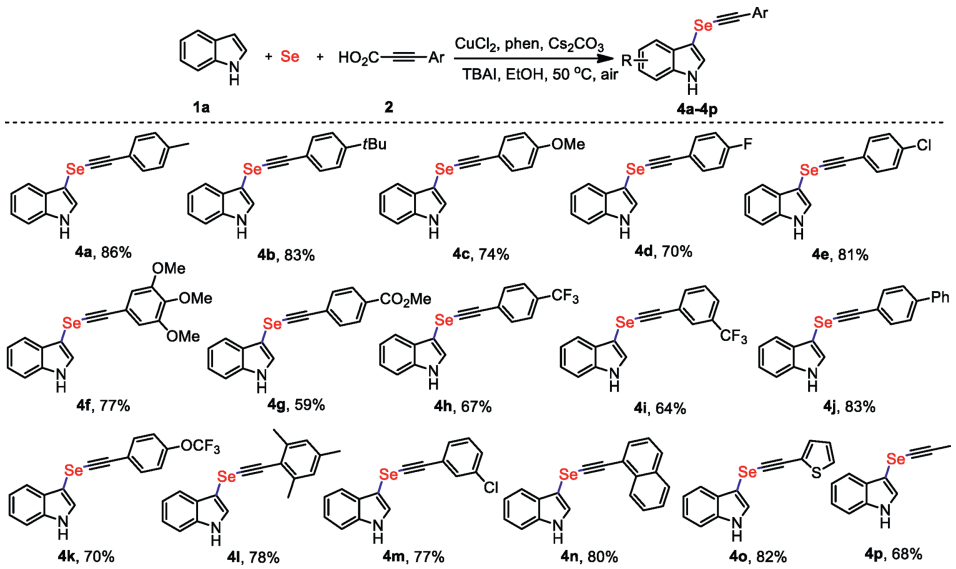
Entry	Alkyne	[Cu]	Solvent	Base	Yield (%)[b]
1	**2a**	$CuCl_2$	EtOH	Cs_2CO_3	84
2	**2a**	$CuBr_2$	EtOH	Cs_2CO_3	33
3	**2a**	$Cu(OAc)_2$	EtOH	Cs_2CO_3	56
4	**2a**	$CuCl_2$	1-Propanol	Cs_2CO_3	40
5	**2a**	$CuCl_2$	Isopropyl alcohol	Cs_2CO_3	27
6	**2a**	$CuCl_2$	Hexafluoroisopropanol	Cs_2CO_3	trace
7	**2a**	$CuCl_2$	DMSO	Cs_2CO_3	0
8	**2a**	$CuCl_2$	DMF	Cs_2CO_3	0
9	**2a**	$CuCl_2$	DCE	Cs_2CO_3	0
10	**2a**	$CuCl_2$	Toluene	Cs_2CO_3	0
11	**2a**	$CuCl_2$	THF	Cs_2CO_3	0
12[c]	**2a**	$CuCl_2$	EtOH	Cs_2CO_3	4
13	**2a**	$CuCl_2$	EtOH	Li_2CO_3	trace
14	**2a**	$CuCl_2$	EtOH	Na_2CO_3	7
15	**2a**	$CuCl_2$	EtOH	K_2CO_3	20
16	**2a**	–	EtOH	Cs_2CO_3	0
17	**2a**	$CuCl_2$	EtOH	–	0
18[d]	**2a**	$CuCl_2$	EtOH	Cs_2CO_3	11
19[e]	**2a**	$CuCl_2$	EtOH	Cs_2CO_3	trace
20[f]	**2a**	$CuCl_2$	EtOH	Cs_2CO_3	81
21[g]	**2a**	$CuCl_2$	EtOH	Cs_2CO_3	39
22	**2b**	$CuCl_2$	EtOH	Cs_2CO_3	0
23	**2c**	$CuCl_2$	EtOH	Cs_2CO_3	0
24	**2d**	$CuCl_2$	EtOH	Cs_2CO_3	0
25	**2e**	$CuCl_2$	EtOH	Cs_2CO_3	0
26	**2f**	$CuCl_2$	EtOH	Cs_2CO_3	0
27	**2g**	$CuCl_2$	EtOH	Cs_2CO_3	0
28	**2h**	$CuCl_2$	EtOH	Cs_2CO_3	0

[a] Reaction conditions unless specified otherwise: **1a** (0.2 mmol), Se (0.6 mmol), **2** (0.6 mmol), [Cu] (0.02 mmol), 1,10-phen (0.02 mmol), Cs_2CO_3 (0.6 mmol), TBAI (0.4 mmol), solvent (2.0 mL), under air, 50 °C, 24 h.
[b] Isolated yield.
[c] In the absence of TBAI.
[d] In the absence of 1,10-phen.
[e] Under N_2 atomosphere.
[f] Under O_2 atomosphere.
[g] At 60 °C.

Upon the optimization of feasible reaction conditions, a variety of functionalized indoles were used for the current three-component decarboxylative selenation (Scheme 2). Generally, various substituted indoles reacted smoothly. The substituting position and electronic nature of different substituents on the benzene ring of indoles showed little difference toward the transformation efficiency. It is worth noting that the nitro group is susceptible to reduction with Se powder, and can be tolerated on the indole ring to give **3g** in 77% yield [39]. The reaction efficiency was not affected by the different substituents (methyl and ester) at the 2-position of indole, and **3k**, **3m** and **3n** are generated with excellent yields. In addition, a substrate containing planar phenyl functional group (**3l**) can also be compatible and smoothly alkynylselenated as well. It was found that the free N–H bond of indole plays a critical role, and *N*-methylindole, *N*-acetylindole did not furnish the desired carboxylative alkynylselenation under our optimized reaction conditions. According to these experimental results, indoles bearing unprotected N–H bond for their generation the relatively stable carbanion for cross-coupling [40].



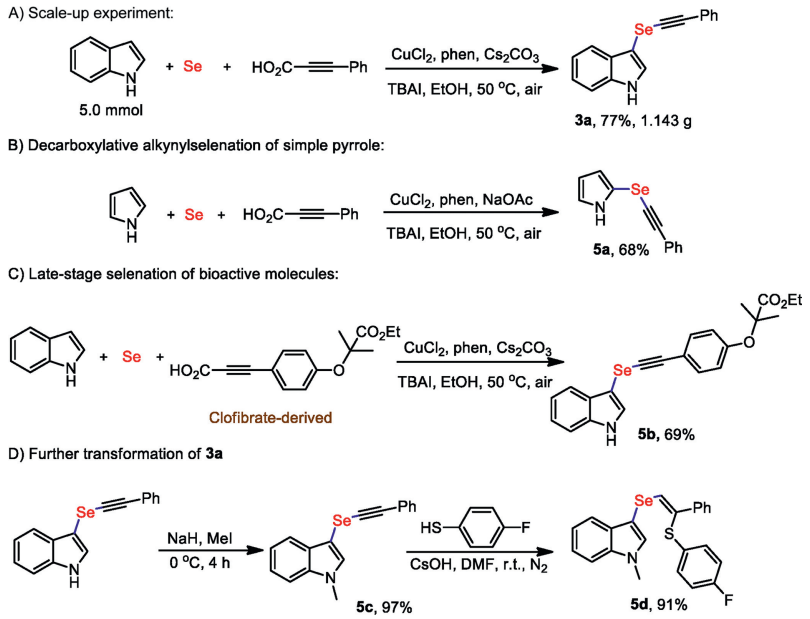
Scheme 2. Scope of indoles. Reaction conditions are the same as entry 1 in Table 1. Isolated yields after column chromatography are given.



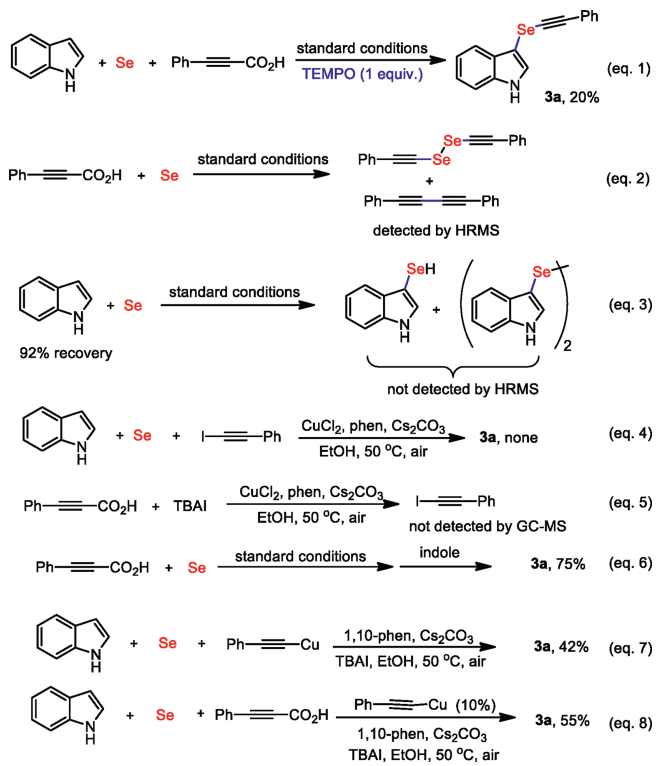
Scheme 3. Scope of propiolic acids. Reaction conditions are the same as entry 1 in Table 1. Isolated yields after column chromatography are given.

Next, a wide range of representative aryl-substituted propiolic acids were resoundingly converted into the expected indolyl alkynyl selenides in moderate to excellent yields (Scheme 3). Current mild reaction condition showed remarkable functional group compatibility, such as alkyl (**4a**, **4b**, **4l**), methoxyl (**4c**), halogen (**4d**, **4e**, **4m**), ester (**4g**), trifluoromethyl (**4h**, **4i**) and trifluoromethoxy (**4k**) had little effect on the reaction efficiency. Importantly, 3,4,5-trimethoxyl, an important pharmacophore in biologically active molecules, proceeded the transformation smoothly (**4f**). Remarkably, the sterically hindered substrate was a competent substrate and afforded **4l** with good efficiency. In addition to aryl ring substituents, naphthalene-substituted propiolic acid (**4n**) is also suitable for decarboxylative indolylselenation, and shows the broad substrate scope of this method. Moreover, thiophene-substituted propiolic acid worked as a viable substrate for decarboxylative arylselenation, providing the corresponding product **4o** in a step-economic manner. The preparation of selenides bearing heteroaromatic compounds is of great significance to the discovery and development of new drugs. Intriguingly, alkyl-substituted propiolic acid is feasible, which commonly displays low reactivity in previous copper-catalyzed cross-coupling reactions [41], and provided **4p** in good yield, which highlights the versatility of this protocol.

The practical utility of the copper-catalyzed decarboxylative Se insertion coupling reactions was directly demonstrated in an efficient gram-scale synthesis (Scheme 4A), and the target product **3a** was isolated in a 77% yield. Pyrrole derivatives, as nitrogen-containing heterocyclic compounds, widely exist in a series of bioactive molecules and solar materials [42]. Simple pyrrole could be successfully alkynylselenated under the slightly adjusted reaction conditions (Scheme 4B). More importantly, Clofibrate-derived propiolic acid, a hypolipidemic agent clinically used for atherosclerosis (Scheme 4C), was examined under the standard reaction condition and provided the desired product **5b** in useful yield. To examine the synthetic elaboration of alkynyl selenide a product (Scheme 4D), **3a** compound was selected to evaluate the known *N*-methylation obtained the **5c**. Upon treatment of **5c** with thiophenol in the presence of CsOH [43], the hydrothiolated product **5d** was isolated in 91%.



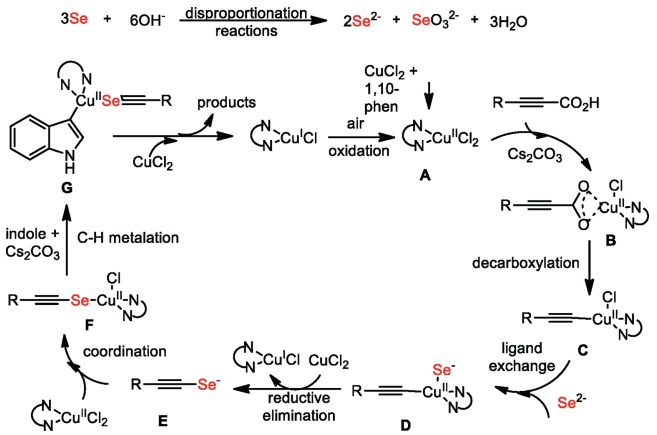
Scheme 4. Synthetic application.



Scheme 5. Preliminary mechanism investigation.

Encouraged by the novel reactivity of propiolic acids underlying this multi-component coupling, and we wanted to gain reliable insight into this mechanism and elucidate the role of each substrate (Scheme 5). At first, 1.0 equiv. of TEMPO was added (Eq. 1), the yield of **3a** was dramatically reduced, while phenylpropiolic acid was completely consumed, and no TEMPO-captured product was detected by HRMS and NMR. This result suggested that a radical pathway could be excluded, and the reason for the steep decrease in the product yield was that the coordination of TEMPO with copper salt mainly inhibited the Se insertion reaction [44]. Subsequently, the reaction of phenylpropiolic acid with selenium powder under the standard reaction conditions (Eq. 2), 1,2-bis(phenylethynyl)diselane and 1,4-diphenylbuta-1,3-diyne were detected by HRMS. However, the reaction between indole and selenium powder was not observed, and 92% of the raw indole was recovered (Eq. 3). The sluggishness of this reaction indicates that decarboxylative selenation of propiolic acids followed by the alkynylselenation of indoles is likely to be a possible pathway for the current transformation. This proposed reaction path could be supported by the following step-by-step reaction (Eq. 6). In addition, we also made two controlled experiments to explain the effect of IBAI. We prepared alkynyl iodide and tried a three-component reaction, but there was no product except a large amount of indole raw material and homo-coupling of (iodoethynyl)benzene byproduct (Eq. 4). Under standard reaction conditions, the reaction of phenylpropargylic acid and tetrabutylammonium iodide could not generate (iodoethynyl)benzene (Eq. 5). These experimental results indicate that (iodoethynyl)benzene is not a key intermediate. Finally, when stoichiometric (phenylethynyl)copper was used as substrate in the absence of $CuCl_2$, the expected product **3a** was isolated in 42% (Eq. 7). Meanwhile, a catalytic amount of (phenylethynyl)copper was used as catalyst under the optimized reaction conditions, the reaction was carried out smoothly (Eq. 8). These results clearly show that alkynylcopper is a competent intermediate in current transformation.

A plausible reaction mechanism for copper-catalyzed three-component decarboxylative Se insertion coupling was proposed based on the above important experimental results and precedent literature (Scheme 6). Initially, the coordination of $CuCl_2$ with 1,10-phen to generate an active copper catalyst **A**, then ligand exchange with alkynyl carboxylic acids and decarboxylation to generate the alkynylcopper species **C** and releases CO_2 [45]. Meanwhile, selenium anions and selenates are formed by the disproportionate reaction of selenium powder in the presence of base. The ligand exchange between intermediate **C** with Se^{2-} afforded **D**, which was disproportionated with $CuCl_2$ or oxidation by O_2 to give Cu(III) species [46], and then reductive elimination to afford alkynylseleno anion **E**. Subsequently, the recombination of **E** with copper catalyst



Scheme 6. Proposed mechanism.

generates capable alknylselenocopper intermediate **F**. Then, the reaction of **F** with indoles produces the critical intermediate **G** in the presence of base [47,48]. Finally, the reductive elimination of **G** provides the desired products in the presence of $CuCl_2$ and the generation of CuX catalyst to fulfill the catalytic cycle.

In summary, we have developed a concise and straightforward copper-catalyzed decarboxylative alkynylselenation of indoles with propiolic acids using Se powder as selenating reagent. The key success of these multicomponent reactions was found to be the generation of nucleophilic alkynylseleno anions as the competent intermediate to suppress the unwished electrophilic polyselenation side reactions of propiolic acids. The transformation featured the use of air as an oxidant and alcohol as a greent solvent, prominent functional group compatibility and late-stage indolylselenation of small bioactive compounds, which would advance the research and development of selenium-containing drug molecules.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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