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# **Copper-Catalyzed Decarboxylative Alkylselenation of Propiolic Acids with Se Powder and Epoxides**

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**Abstract:** A copper-catalyzed decarboxylative alkylselenation of propiolic acids with Se powder and epoxides leading to alkynyl selenides is developed. This protocol not only provides an approach to obtain alkynyl selenides with the formation of double C–Se bonds, but also expands the applicability of alkynyl carboxylic acid.

Keywords: Alkylselenation; Copper-Catalyzed; Se powder; Decarboxylation; Tandem reaction

# Introduction

Alkynyl selenides compounds are intriguing fragments, that served as building blocks transformed into various polyfunctionalized vinyl selenides<sup>[1]</sup> and precursors for anti-inflammatory drug molecules.<sup>[2]</sup> Therefore, various methodologies were developed to construct novel alkynyl selenides with the formation of new C-Se bonds.<sup>[3]</sup> One representative reaction is the coppercatalyzed decarboxylative C-Se cross-coupling, where highly reactive selenating reagents such as phenyl selenocyanate<sup>[4]</sup> and seleno Bunte salts<sup>[5]</sup> were used (Scheme 1A). However, issues are accompanied by unstable selenating reagents, expensive catalytic systems and narrow scope of substrates, limiting the of selenium-containing development pharmaceuticals.<sup>[6]</sup> Pan et al. described a three-component reaction to prepare 5-arylselanyl-1,2,3-triazoles from propiolic acids, diselenides and azides via decarboxylative selenation and subsequent intermolecular click reactions.<sup>[7]</sup> However, a prevailing challenge in copper-catalyzed decarboxylative selenation of propiolic acids with diselenides is the chemo-and region-selectivity to generate tri-selenide alkenes<sup>[8]</sup> (Scheme 1B). Thus, a new approach for transfering alkynyl carboxylic acids into  $C_{sp}$ -Se bonds would be significant to organic synthesis and pharmaceutical science.

Given our long-term interest in the difunctionalization of elemental selenium,<sup>[9]</sup> we aimed to find a new pathway for the alkylation of alkynylselenyl anions. This approach could nicely address the polyselenation of alkynyl carboxylic acids by avoiding the use of electrophilic diselenides.<sup>[8]</sup> Therefore, we proposed a copper-catalyzed three-component cascade coupling of alkynyl carboxylic acids, Se powder and epoxides (Scheme 1C). As a blueprint of our design, we assumed that copper-catalyzed decarboxylative selenation of alkynyl carboxylic acids with elemental selenium could generate alkynylselenylcopper species. Moreover, intermolecular nucleophilic ring-opening reactions could appear by these key intermediates with asc.wiley-vch.de



(A) Previous works: single C-Se bond formation Cu(OAc)<sub>2</sub> (5 mol%) Ag<sub>2</sub>CO<sub>3</sub> (1.0 equiv) Ph SePh Ph-CO<sub>2</sub>H Ph-SeCN NMP, 100 °C, 10 h Cul (20 mol%) Ag<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub> NaO<sub>3</sub>S-Se-R<sup>2</sup> R1-Se-R2 DMF, 130 °C , 12 h prior preparation of selenating reagent poor functional groups tolerance narrow substrate scope expensive catalytic system (B) Challenge: over-selenation ArSe SeA Cul(10 mol%) R-----CO<sub>2</sub>H ArSeSeAr Cs<sub>2</sub>CO<sub>2</sub> (2.0 equiv) SeA Ŕ NMP, 120 °C (C) Our work; double C-Se bonds formation CuCl<sub>2</sub> ·ОН −CO<sub>2</sub>H Se H₂O, 50 °C decarboxylatior R -CuL R SeCul insertion coupling nucleophilid ring-opening Se as selenating reagent green catalytic system water as solvent Spectrum functional group tolerance

**Scheme 1.** Copper-catalyzed decarboxylative selenation of alkynyl carboxylic acids.

epoxides to access  $\beta$ -alkynylselenyl alcohols. As a result, this transformation could provide a straightforward and efficient protocol to access structurally diverse alkynylalkyl selenides by forming two C–Se bonds, expanding the new applicability of alkynyl carboxylic acid.

## **Results and Discussion**

Phenylpropiolic acid 1a, Se powder and glycidyl phenyl ether 2 a were chosen as substrates to verify the feasibility of copper-catalyzed three-component decarboxylative C-Se cross-coupling reactions. After the extensive screening of reaction parameters, it was found that the expected product 3a was isolated in 91% yield when using CuCl<sub>2</sub> as the catalyst, 1,10-phen as an efficient ligand, Cs<sub>2</sub>CO<sub>3</sub> as base and TBAI as phase transfer catalyst in H<sub>2</sub>O at 50°C (Table 1, entry 1). CuCl<sub>2</sub> was essential to this reaction (entry 15), but other copper salts, such as Cu(OAc)<sub>2</sub> CuBr<sub>2</sub>, CuCl or CuI showed relatively low efficiency, and only  $Cu(OAc)_2$  gave comparable yields (entries 2–5). The pK<sub>b</sub> of base greatly influenced this transformation (entries 6–8). Presumably, base plays an essential role in the deprotonation of carboxylic acid and activation of elemental selenium. Next, the effect of reaction solvent was investigated, whether strong polar, weak coordination or apolar solvent were unsuitable for current three-component reactions (entries 9–11). It was found that switching TBAI to TBAB significantly affected the reaction outcome (entries 12). Besides, 2,2'-bipyridine instead of 1,10-Phen did not enhance the product yield (entry 13). Moreover, the trans-

		Table	1.	Reaction	optimization.	[a]
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PhCO2	H + Se + 🕰	OPhTBAI,	, phen, Cs₂CO₃ H₂O, 50 ºC, air	OH PhOSePh
1a	2a			3a
Entry	[Cu]	Base	Solvent	Yield (%) <sup>[b]</sup>
1	CuCl <sub>2</sub>	$Cs_2CO_3$	$H_2O$	91
2	$Cu(OAc)_2$	$Cs_2CO_3$	$H_2O$	77
3	CuBr <sub>2</sub>	$Cs_2CO_3$	$H_2O$	32
4	CuCl	$Cs_2CO_3$	$H_2O$	56
5	CuI	$Cs_2CO_3$	$H_2O$	41
6	CuCl <sub>2</sub>	Li <sub>2</sub> CO <sub>3</sub>	$H_2O$	22
7	CuCl <sub>2</sub>	Na <sub>2</sub> CO <sub>3</sub>	$H_2O$	25
8	CuCl <sub>2</sub>	$K_2CO_3$	$H_2O$	38
9	CuCl <sub>2</sub>	$Cs_2CO_3$	DMSO	14
10	CuCl <sub>2</sub>	$Cs_2CO_3$	CH <sub>3</sub> CN	22
11	CuCl <sub>2</sub>	$Cs_2CO_3$	toluene	0
12 <sup>[c]</sup>	CuCl <sub>2</sub>	$Cs_2CO_3$	$H_2O$	68
13 <sup>[d]</sup>	CuCl <sub>2</sub>	$Cs_2CO_3$	$H_2O$	83
14 <sup>[e]</sup>	CuCl <sub>2</sub>	$Cs_2CO_3$	$H_2O$	0
15 <sup>[f]</sup>	CuCl <sub>2</sub>	$Cs_2CO_3$	$H_2O$	80
16	CuCl <sub>2</sub>		$H_2O$	0
17		$Cs_2CO_3$	$H_2O$	0

<sup>[a]</sup> Reaction conditions unless specified otherwise: **1a** (0.2 mmol), Se (0.6 mmol), **2a** (0.6 mmol), CuCl<sub>2</sub> (0.02 mmol), 1.10-phen (0.02 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.6 mmol), TBAI (0.4 mmol), H<sub>2</sub>O (2.0 mL), under air, 50 °C, 24 h.

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup> TBAB instead of TBAI.

<sup>[d]</sup> 2,2'-bipyridine instead of 1,10-phen.

<sup>[e]</sup> The absence of TBAI.

<sup>[f]</sup> The absence of 1.10-phen.

formation was completely shut down, when the reaction was performed in the absence of a phase transfer catalyst (entry 14). Besides, the yield of product **3a** was slightly decreased in the absence of ligand (entry 15). Finally, when the reaction was performed in the absence of copper salts or base, no target product was detected, suggesting that these factors played indispensable roles in promoting decarboxylation and in the formation of double C–Se bonds (entries 16–17). It is worth mentioning that vinyl selenides via copper-catalyzed decarboxylative C–Se cross-coupling,<sup>[10a]</sup> ring-opening halogenating reaction<sup>[10b]</sup> of epoxides with TBAI and oxidative decarboxylative homocoupling<sup>[10c]</sup> of aryl propiolic acids were not observed in all cases.

With the optimized reaction conditions in hand, we set out to examine the scope of propiolic acids for copper-catalyzed three-component decarboxylative alkylselenations (Scheme 2). Generally, it was noted that arylpropiolic acids bearing electron-donating substituents (**3a**, **3b**, **3d** and **3f**) showed much higher reactivity than those bearing electron-deficient substituents (**3g**, **3l**, **3m**–**3o**). This observation suggested that the high efficiency of current transformation relies

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<sup>a)</sup> Reaction conditions unless specified otherwise: **1** (0.2 mmol), Se (0.6 mmol), **2a** (0.6 mmol), CuCl<sub>2</sub> (0.02 mmol), phen (0.02 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.6 mmol), TBAI (0.4 mmol), H<sub>2</sub>O (2.0 mL), under air, 50 °C, 24 h. Isolated yields are given.

Scheme 2. Propiolic acids scope.<sup>[a]</sup>

on substituents' innate electronic effect on the benzene ring. To our delight, various important functional groups, such as alkyl (3b-3d), halogen (3g-3k), phenyl (3e), cyano (3l), ester (3m) and trifluoromethyl (3n, 3o) were well-tolerated, which indicated good compatibility of this protocol. It was delightful to observe that sterically hindered 3-mesitylpropiolic acid (3 c) could smoothly undergo decarboxylative alkylselenation to give a corresponding product with high efficiency. Besides, heteroaromatic propiolic acid (3p) was also viable and provided the expected product in a good yield. However, 2-butynoic acid could not be accommodated under the standard reaction conditions. Unfortunately, the current catalytic system could not be extended to the alkynyllkylation of sulfur or tellurium, even after systematic optimization of reaction conditions.

Subsequently, various epoxides were also evaluated to investigate their role in this methodology, and the results were summarized in Scheme 3. Generally, various glycidyl aryl ethers were successfully engaged in these transformations to access the targeted alkynylalkyl selenides with moderate to good yields. Also, the copper-catalyzed ring-opening alkynylselenation of epoxides displayed a broad-spectrum functional group tolerance, such as different halogen (4b, 4c and 4l), trifluoromethoxy (4e), thiomethyl (4f) and amine (4h), providing a useful platform for further transformation of selenium-containing products. Notably, the substrate (4g) bearing nitro group that could



<sup>a)</sup> Reaction conditions unless specified otherwise: **1a** (0.2 mmol), Se (0.6 mmol), **2** (0.6 mmol), CuCl<sub>2</sub> (0.02 mmol), phen (0.02 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.6 mmol), TBAI (0.4 mmol), H<sub>2</sub>O (2.0 mL), under air, 50 °C, 24 h. Isolated yields are given.

Scheme 3. Epoxides scope.<sup>[a]</sup>

undergo the nucleophilic substitution with chalcogen<sup>[11]</sup> also worked well and afforded the corresponding product with satisfactory yield. Heterocycle substituted oxirane (4m) was also a feasible substrate for alkynylselenation with good efficiency. Furthermore, this protocol could be applied to an array of structurally more-complicated molecules, such as carvacrol (4n), guaiacol (4o) and estrone (4p) derivatives, which indicated the applicability and versatility of current catalytic systems. Encouraged by the versatility of our catalytic alkynylselenation of epoxides, we turned our attention to examine other commonly used nucleophiles, such as indole, benzoxazole, arylboronic acid as cross partners, to achieve the new type cascade of three-component reaction. Regrettably, the preparation of the target compound has not vet been obtained.

As shown in Scheme 4, the prominent feature of this reaction is that the large-scale reaction makes the



Scheme 4. Gram-scale reaction and late-stage selenation of bioactive molecules.

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research strategy more reliable and immense application prospects. This protocol was also further applied to the late-stage selenation of bioactive molecules, alkynyl carboxylic acid from estrone, which is one of the major mammalian estrogens, which has shown selective decarboxylative alkylselenation to give the corresponding product in good yield.

A series of controlled experiments were designed to elucidate the reaction mechanism and the sequence of multi-component cascade reactions (Scheme 5). With the addition of 3.0 equivalents of TEMPO to perform a radical-probing experiment (eq. 1), it was found that the efficiency of the reaction was not significantly affected, which excluded the radical-mediated progress. Two sets of blank tests were conducted and investigated by GC-MS, and a mixture of phenyl propionic acid with selenium powder under the standard reaction condition (eq. 2), a certain amount of 1,4-diphenylbuta-1,3-diyne cis-5-phenyl-2and (phenylmethylene)-1,3-diselenole<sup>[12]</sup> were detected. It is worth noting that the reaction of epoxides with Se powder under the optimized reaction conditions (eq. 3), only gave the vicinal diol product via nucleophilic ring-opening reactions. This result suggested that the possibility in situ formation of alkynylcopper intermediate could undergo the selenium insertion reaction. When using 10 mol% phenylethynyl copper as catalyst (eq. 5), 61% yield of corresponding product was isolated, which suggested the alkynylcopper may be the key intermediate, which was further supported by the stoichiometric reactions (eq. 4). Furthermore, cesium 3-phenylpropiolate reacted with Se powder and epoxide under the standard reaction condition to give the target compound in good yield (eq. 6). This reaction showed that cesium carbonate played an essential role in the deprotonation of alknyl acids and promoted the activation of selenium with copper salts.

Based on the above experimental results and relevant works of literature, a plausible reaction mechanism for copper-catalyzed three-component de-





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carboxylative alkylselenation reaction was proposed (Scheme 6). The decarboxylation of the alkynyl carboxylic acid with the copper catalyst appears first to produce alkynylcopper species **A** with the release of equivalent CO<sub>2</sub>. Then, this intermediate **A** undergoes the ligand exchange with Se<sup>2-</sup> and disproportionation to form the key intermediate C,<sup>[9,13]</sup> and reductive elimination and recoordination of alkynylselenyl anions with copper salt to generate alkynylselenylcopper species **D**. Finally, the critical complex **D** undergoes nucleophilic ring-opening reactions with epoxide<sup>[14]</sup> to provide the target compounds and release the copper catalyst.

#### Conclusion

The first example of copper-catalyzed decarboxylative alkylselenation of alkynyl carboxylic acids with Se powder and epoxides were described. It provides a concise and distinct protocol to access a variety of functionalized alkynyl selenides. Meanwhile, cheap and readily available elemental selenium was used as a selenating reagent. Moreover, copper catalyst playing a multi-role in this reaction, effectively broadened the scope of difunctionlization of Se atom with the formation of two C-Se bonds. Furthermore, this transformation's apparent feature was the use of water as solvent, sustainable catalytic system, excellent functional group compatibility and late-stage alkynylselenation of small bioactive compounds, which would advance the synthetic applications and new drug development.

### **Experimental Section**

General experimental procedures of copper-catalyzed decarboxylative alkylselenation of propiolic acids with Se powder and epoxides: in a 25 mL Schlenk tube equipped with a stir bar were placed propiolic acids (0.2 mmol), Se (0.6 mmol), epoxides (0.6 mmol), CuCl<sub>2</sub> (0.02 mmol), 1,10-phen (0.02 mmol), TBAI (0.4 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.6 mmol) in H<sub>2</sub>O (2 mL), then the Schlenk tube was plugged with a Teflon screwcap. The reaction mixture was stirred at 50 °C for 24 h. After it was cooled, the reaction mixture was diluted with 10 mL of ethyl acetate, and filtered through diatomaceous earth, followed by washing the pad of silica gel with the same solvent (20 mL). The organic



Scheme 6. Proposed mechanism.



phase was dried over  $Na_2SO_4$ , filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel to provide the corresponding product.

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