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Copper-Catalyzed Decarboxylative/Click Cascade Reaction: Regioselective Assembly of 5-Selenotriazole Anticancer Agents

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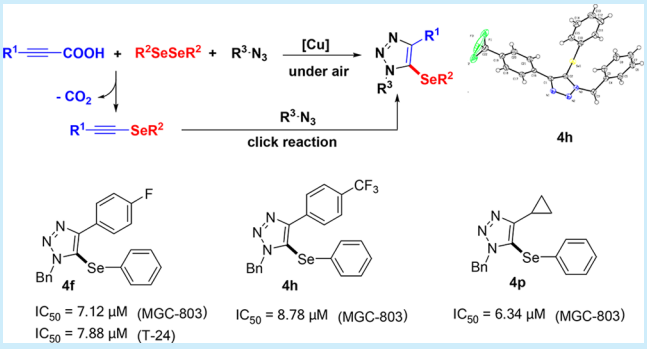
Supporting Information

ABSTRACT: A simple and efficient Cu-catalyzed decarboxylative/click reaction for the preparation of 1,4-disubstituted 5-arylselanyl-1,2,3-triazoles from propiolic acids, diselenides, and azides has been developed. The mechanistic study revealed that the intermolecular AAC reaction of an alkynyl selenium intermediate occurred. The resulting multisubstituted 5-seleno-1,2,3-triazoles were tested for in vitro anticancer activity by MTT assay, and compounds **4f**, **4h**, and **4p** showed potent cancer cell-growth inhibition activities.

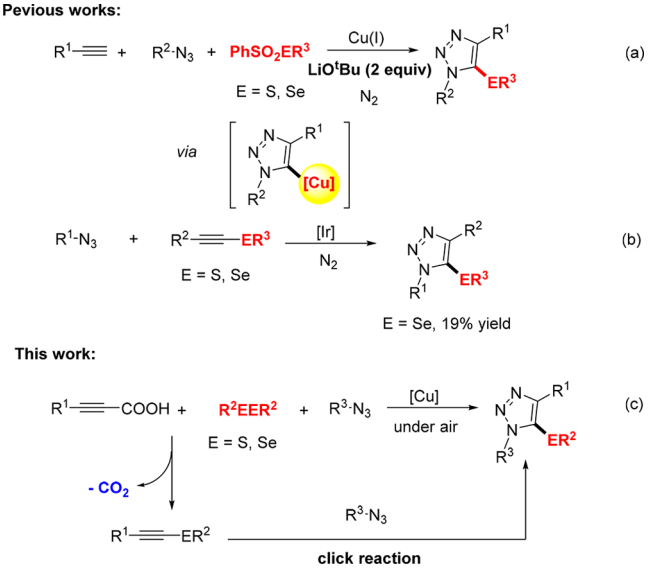


Organoselenium compounds have been extensively studied due to their well-recognized biological activities.[1] The introduction of selenium into organic molecules is widely adopted in drug design and regulation of biological processes.[2] 1,2,3-Triazoles are important versatile N-heterocyclic compounds with diverse pharmacological and biological functions.[3] For example, the multisubstituted 5-heterofunctionalized 1,2,3-triazoles, a kind of privileged triazoles, have been found in a variety of pharmaceutical molecules and drug candidates.[4] It can be anticipated that the functionalization of multisubstituted 1,2,3-triazoles with organoselenium groups would result in profound effects on their biological and pharmacological activities.

In 2002, Sharpless[5] and Meldal[6] reported a copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC) reaction producing 1,4-disubstituted 1,2,3-triazoles with high regioselectivities, where 5-copper(I) triazolide acted as the key reactive intermediate. It was then concluded that the interception of copper intermediates by electrophilic reagents was an effective method for the synthesis of fully substituted 1,2,3-triazoles.[7] Recently, Xu's group[8] reported a Cu-catalyzed interrupted click reaction using electrophilic sulfenylating reagents ($PhSO_2ER$, E = N, S, Se) to trap the 5-copper(I) triazolide intermediate for the preparation of multisubstituted 5-heteroatom functionalized triazoles (Scheme 1a). Although the reaction afforded the target products in high yields, the use of excess strong base significantly limited its application potential.

In contrast to the well-developed Cu-catalyzed AACs of terminal alkynes, the direct reaction of internal alkynes and azides, especially the intermolecular reaction, for the synthesis

Scheme 1. Reported Synthesis Routes to 1,4-Disubstituted 5-Selanyl-1,2,3-triazoles



of fully substituted 1,2,3-triazoles is still a great challenge[9] due to the high activation barrier. Most of the intermolecular AACs of internal alkynes require high temperatures[10] and/or heteroatom-functionalized internal alkynes, such as haloal-

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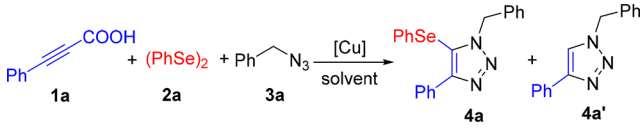
kynes,[11] ynamides,[12] and thioalkyne.[13] For example, Sun and co-workers reported an efficient iridium-catalyzed intermolecular AAC of internal thioalkynes for the synthesis of multisubstituted 5-thio functionalized triazoles under mild reaction conditions.[14] However, the substitution of the S atom with a Se atom led to an unsatisfactory yield of 5-seleno-functionalized triazole (Scheme 1b). With the increasing interest in organoselenium compounds, efficient and practical synthetic methods for constructing multisubstituted 5-seleno-functionalized triazoles are still in high demand. Based on our previous work of click reactions and the formation of C−Se bond,[15] we developed a simple and efficient method for the preparation of 1,4-disubstituted 5-arylselanyl-1,2,3-triazoles from propiolic acids, diselenides and azides, in which alkynyl selenium was formed first via decarboxylative reactions, followed by the intermolecular AAC reaction of azides to afford 5-seleno-triazoles (Scheme 1c).

We initiated our study with the model reaction of 3-phenylpropiolic acid (**1a**), diselenide (**2a**), and benzyl azide (**3a**) under various reaction conditions, and the results are summarized in Table 1. The reaction under the catalysis of 10 mol % of $CuCl_2$ and 1.2 equiv of K_2CO_3 in toluene afforded the desired product **4a** in 20% yield (Table 1, entry 1). Other copper(II) catalysts including $Cu(OAc)_2·H_2O$, $CuBr_2$, and $CuSO_4$ were able to catalyze the reaction, producing **4a** in yields of 50%, 30%, and 48%, respectively (Table 1, entries 2−4). The catalysis of $CuSO_4$/1,10-Phen resulted in a similar yield of **4a** (Table 1, entry 5). Luckily, the yield was dramatically increased to 82% under the catalysis of $Cu(OAc)_2·H_2O$/1,10-Phen (Table 1, entry 6). Further investigations on the model reaction revealed strong effects of reaction solvent on its performance, and toluene was found to be the optimal medium (Table 1, entries 6 vs 7−12). Besides, the reaction performed without Cu catalyst failed to give the desired product of **4a** (Table 1, entry 13). The reaction were performed at room temperature and 60 °C, giving the desired product of 1-benzyl-4-phenyl-5-(phenylselanyl)-1*H*-1,2,3-triazole (**4a**) in 10% and 20% yields, respectively (Table 1, entries 14 and 15). In addition, the reaction was scalable and practical since a satisfactory yield (80%) could be obtained when the reaction was performed on a 1 mmol scale. Therefore, the transformation conditions were optimized as 10 mol % $Cu(OAc)_2·H_2O$, 20 mol % 1,10-Phen, 1.2 equiv K_2CO_3 in toluene, reaction temperature 120 °C, and reaction time 6 h.

Under the optimal reaction conditions, the substrate scopes were explored. The results are summarized in Scheme 2. A series of *para*-substituted aromatic propiolic acids bearing electron-donating and electron-withdrawing groups on the aryl ring were tested first. The results suggest that desired products, 1,4-disubstituted 5-arylselanyl-1,2,3-triazoles, were produced in 71−83% yields (Scheme 2, **4b**−**h**). To our delight, single crystals of **4h** were obtained by gradual crystallization in a

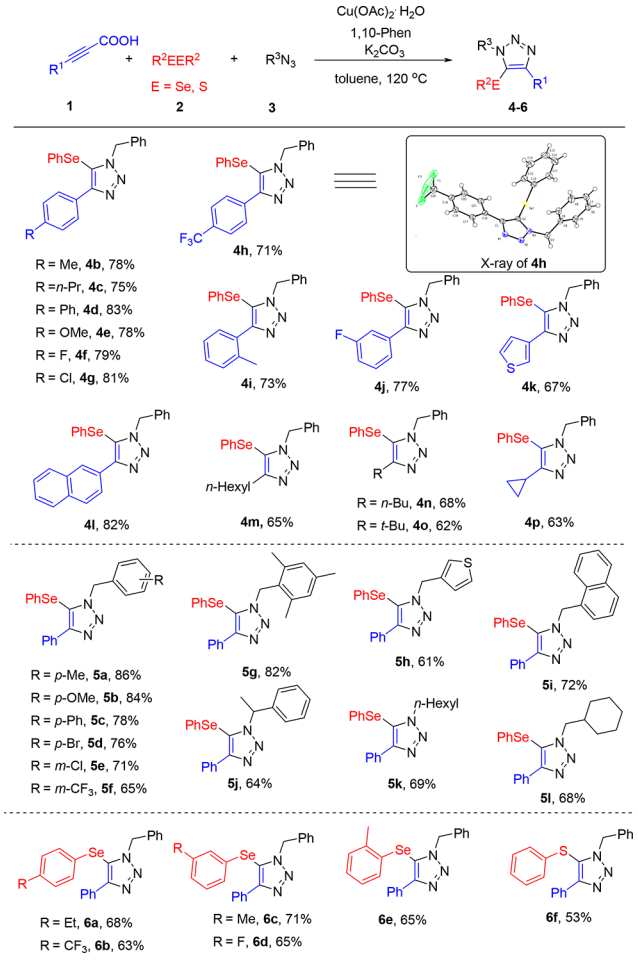
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	ligand	solvent	yield (%) 4a	4a′
1	$CuCl_2$		toluene	20	30
2	$Cu(OAc)_2·H_2O$		toluene	50	30
3	$CuBr_2$		toluene	30	40
4	$CuSO_4$		toluene	48	40
5	$CuSO_4$	1,10-Phen	toluene	50	38
6	**$Cu(OAc)_2·H_2O$**	**1,10-Phen**	**toluene**	**82**	**10**
7	$Cu(OAc)_2·H_2O$	1,10-Phen	DMSO	20	60
8	$Cu(OAc)_2·H_2O$	1,10-Phen	DMF	<5	80
9	$Cu(OAc)_2·H_2O$	1,10-Phen	1,4-dioxane	<5	70
10	$Cu(OAc)_2·H_2O$	1,10-Phen	THF	40	50
11	$Cu(OAc)_2·H_2O$	1,10-Phen	MeCN	<5	75
12	$Cu(OAc)_2·H_2O$	1,10-Phen	H_2O	0	<5
13[b]			toluene	0	30
14[c]	$Cu(OAc)_2·H_2O$	1,10-Phen	toluene	10	20
15[d]	$Cu(OAc)_2·H_2O$	1,10-Phen	toluene	20	60
16[e]	**$Cu(OAc)_2·H_2O$**	**1,10-Phen**	**toluene**	**80**	**10**

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), **3a** (0.2 mmol), catalyst (10 mol %), ligand (20 mol %), K_2CO_3 (0.24 mmol), solvent (2.0 mL), 120 °C, 6 h. Isolated yield. [b]Without $Cu(OAc)_2·H_2O$ and 1,10-Phen. [c]Room temperature. [d]60 °C. [e]Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **3a** (1 mmol), $Cu(OAc)_2.H_2O$ (10 mol %), 1,10-Phen (20 mol %), K_2CO_3 (1.2 mmol), toluene (5.0 mL), 120 °C for 12 h

Scheme 2. Synthesis of 1,4-Disubstituted 5-Arylselanyl-1,2,3-triazoles[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), **3** (0.3 mmol), $Cu(OAc)_2·H_2O$ (10 mol %), 1,10-Phen (20 mol %), K_2CO_3 (0.36 mmol), toluene (2.0 mL), 120 °C. Isolated yield.

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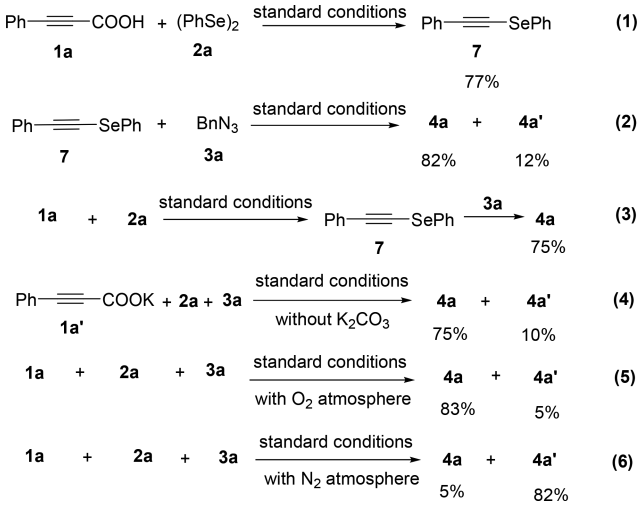
mixture of petroleum ether and ethyl acetate and characterized as 1-benzyl-5-(phenylselanyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole. The reactions of diselenide (**2a**) and benzyl azide (**3a**) with 3-*o*-tolylpropiolic acid or 3-(*m*-fluorophenyl)-propiolic acid afforded the desired products **4i** and **4j** in 73% and 77% yields, respectively, suggesting that this transformation was tolerant toward the electronic and steric effects of aromatic rings. It is worth noting that the reaction of heteroaryl-substituted propiolic acid, 3-(thiophene-3-yl)propiolic acid, also performed well under the optimal conditions and produced 1-benzyl-5-(phenylselanyl)-4-(thiophene-3-yl)-1*H*-1,2,3-triazole (**4k**) in 67% yield. In addition, 3-(naphthalen-2-yl)propiolic acid was well tolerated in this reaction with the formation of **4l** in 82% yield. Non-2-ynoic acid, hept-2-ynoic acid, 4,4-dimethylpent-2-ynoic acid, and 3-cyclopropylpropiolic acid were also found to be suitable substrates for the transformation, and their reaction afforded the corresponding 1,4,5-trisubstituted triazoles **4m**–**p** in 62%–68% yields.

The scope of azidomethyl aromatic substrate was then examined. The reaction was performed on the substituted benzyl azides bearing electron-donating groups, such as Me, OMe, and Ph, or electron-withdrawing groups including Cl, Br, and CF_3 on the aromatic ring, affording the expected 1,4,5-trisubstituted triazoles in 65%–86% yields (Scheme 2, **5a**–**g**). The reactions of benzyl azides with electron-donating groups on the benzene ring gave the corresponding products in higher yields than those of the azides bearing electron-withdrawing groups on the benzene ring. The heteroaryl-substituted azide substrate, 3-(azidomethyl)thiophene, also reacted smoothly, affording the desired product **5h** in 61% yield. In addition, the azide containing a naphthalene moiety was found to be a suitable substrate, and its reaction gave product **5i** in 72% yield. Product **5j** was obtained in the yield of 64% as (1-azidoethyl)benzene treated with 3-phenylpropiolic acid (**1a**) and diselenide (**2a**). The reactions of other substrates including 1-azidohexane and (azidomethyl)cyclohexane also proceeded, giving the desired products **5k** and **5l** in yields of 69% and 68%, respectively. The reaction was also found to be highly tolerant toward the substitutions on diselenides, and the corresponding products **6a**–**e** were isolated in good yields. In addition, the reaction of 1,2-diphenyldisulfane was able to afford the desired product **6f** in 53% yield.

To explore the possible reaction pathway, control experiments were carried out. First, the reaction of **1a** and **2a** worked well under the standard conditions and produced phenyl-(phenylethynyl)selane (**7**) in 77% yield (Scheme 3, eq 1). The reaction of phenyl(phenylethynyl)selane **7** and benzyl azide (**3a**) under the optimal conditions afforded the desired product **4a** in 82% yield (Scheme 3, eq 2). In addition, the mixture of **1a** and **2a** under the standard conditions for 6 h and then addition of **3a** leaded the formation **4a** in 75% yield (Scheme 3, eq 3). These results indicate that **7** is a possible intermediate for the formation of **4a**, and potassium 3-phenylpropiolate (**1a′**) reacted with **2a** and **3a** in the presence of 10 mol % of $Cu(OAc)_2{\cdot}H_2O$, 20 mol % 1,10-Phen, affording the desired product of **4a** in 75% yield (Scheme 3, eq 4). This result suggests that K_2CO_3 play an important role on removes acidic H from propiolic acid, which in turn reacts with Cu and then this new species generated acts on the cleavage of $Ph(Se)_2$. The reaction performed in the different molar ratio of **1a**/**2a**/**3a** such as 1:0.5:1, 1:0.2:1, 0.5:0.5:1, and 0.5:1:1 under the standard conditions, and **2a** always existed (detected by GC–MS) even though the reaction time was prolonged to 24 h. The

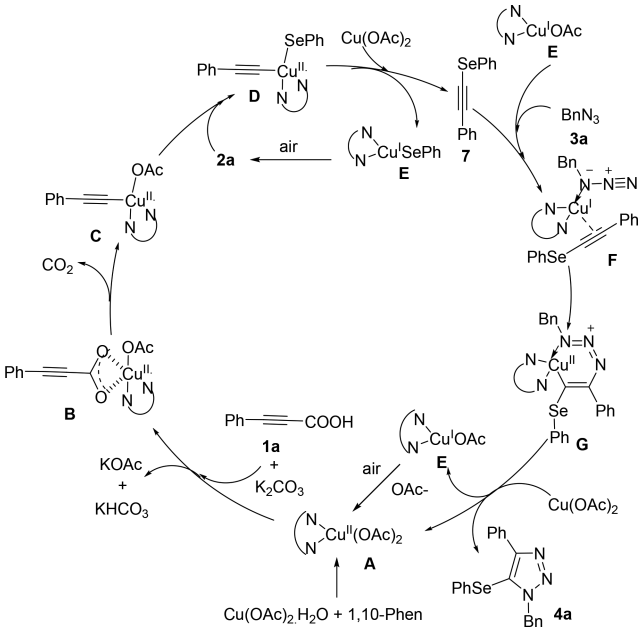
Scheme 3. Control Experiments



reaction under an O_2 atmosphere produced **4a** and **4a′** in 83% and 5% yields, respectively (Scheme 3, eq 5), the same as those obtained under air atmosphere. However, the reaction performed under N_2 atmosphere afforded **4a** and **4a′** in yields of 5% and 82%, respectively (Scheme 3, eq 6). These results demonstrated the important role of O_2 in the reaction.

On the basis of these experimental results and previous reports,[16,17] a plausible mechanism is proposed and depicted in Scheme 4. First, the coordination of 1,10-phenanthroline to

Scheme 4. Proposed Mechanism



$Cu(OAc)_2{\cdot}H_2O$ to form the active copper(II) intermediate **A** that then reacts with phenylacetic acid (**1a**) to afford copper(II) intermediate **B**. The decarboxylation of **B** produces copper(II) intermediate **C** and releases one molecular CO_2.[16] The reaction of **C** with diphenyl diselenide (**2a**) gives intermediate **D**. The reductive elimination of **D** results in phenyl(phenylethynyl)-selane (**7**), as well as copper(I) species **E**. The complexation of **E** with phenyl(phenylethynyl)selane (**7**) and azide (**3a**) generates intermediate **F**, which undergoes oxidative cyclization

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to form intermediate **G**.[17] The reductive elimination of **G** affords the desired product **4a** and copper(I) species **E**. Finally, **E** is converted into **A** under air atmosphere to fulfill the reaction, and another possible pathway for this transformation is a cycloadditions with carboxylic acid and azide, which then undergoes decarboxylation followed by C−Se bond formation with copper catalysis. For details, see the Supporting Information.

The in vitro cytoxicity of all synthetic products **4a−p**, **5a−l**, and **6a−f**, were determined by the methylthiazoltetrazolium (MTT) assay on the human bladder cancer cells (T-24), human ovarian cancer cells (SK-OV-3), human cervical cancer cells (HeLa226), human gastric cancer (MGC-803), and HL-7702 (human liver normal cell line) cell lines with the commercial anticancer drug, 5-fluorouracil (5-FU), as the positive control. The results can be found in the Supporting Information. To our delight, **4f** (IC_{50} = 7.12 μM), **4h** (IC_{50} = 8.78 μM), and **4p** (IC_{50} = 6.34 μM) exhibited potent inhibitory activities against MGC-803 cell lines. Compounds **4f** (IC_{50} = 7.88 μM) were found to be powerful cytotoxic agents against T-24 cell lines (Figure 1). Compound **4f** induced the highest

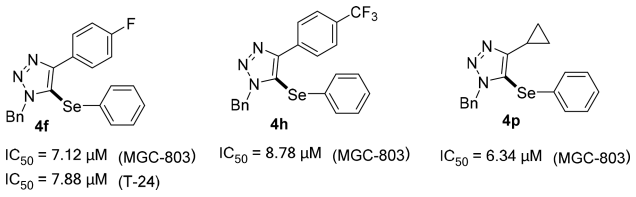

Figure 1. Anticancer activity of 5-selanyl-1,2,3-triazoles.

apoptosis rate of T-24 cells, and it caused cell arrest in the G_2/M phase according to flow cytometric analysis. Further experiments confirmed that **4f** triggered T-24 cells apoptosis by increasing the production of intracellular Ca^{2+} and up-regulating the expression of reactive oxygen species (ROS) (see the Supporting Information for details).

In summary, we report a novel and efficient Cu-catalyzed decarboxylative/click reaction, involving the intermolecular AAC reaction of an alkynyl selenium intermediate, for the preparation of 1,4-disubstituted 5-arylselanyl-1,2,3-triazoles from propiolic acids, diselenides and azides. The catalytic reaction featured with high efficiency and regioselectivity, mild reaction conditions, and easy operation, as well as excellent compatibility with air. The synthesized multisubstituted 5-seleno-1,2,3-triazoles **4f**, **4h**, and **4p** exhibited potent anticancer activities in vitro. In addition, the action mechanism of **4f** on T-24 cells was determined by fluorescence staining assay and flow cytometric analysis to be the induction of G_2/M phase arrest and apoptosis by increasing the production of intracellular Ca^{2+} and up-regulating the expression of reactive oxygen species (ROS).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03734.

Experimental procedures, biological assays, characterization data, and NMR spectra for all products (PDF)

Accession Codes

CCDC 1577235 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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