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ARTICLE

Copper-Catalyzed Generation of Flavone Selenide and Thioether Derivatives Using KSeCN and KSCN via C-H Functionalization

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Flavone selenium or sulfur-containing derivatives are pretty valuable in drug discovery due to their diversity of important bioactivities. Here, two simple Cu-catalyzed methods of constructing C-Se and C-S bonds on flavone skeletal structures via C-H functionalization are reported, which regioselectively afford flavone selenide and sulfide derivatives in good yields using cheap KSeCN or KSCN salts as selenium and sulfur agents. It further enriches current C-Se and C-S bond construction methods.

Introduction

Flavones and their derivatives are highly valued compounds in drug discovery,[1] because many possess various biological activities with low toxicities.[2] Several representative flavone derivatives are shown in figure 1, including examples with anti-oxidant, anti-inflammatory, anti-microbial, anti-cancer, and anti-allergic activities.[3] Substantial research is underway in pharmaceutics, toxicology and pharmacology related to flavones or similar analogs.[4] Previously, flavones and their derivatives were isolated from the extraction of plants.[5] Due to the rapid development of synthetic chemistry, many flavones and their derivatives have recently been synthesized via chemical methods.[6] This has greatly increased access to thevariety and amount of both natural and unnatural flavone derivatives, some with new substituents for bio-screening in drug discovery.[7] New methods to make natural and unnaturalflavones and their derivatives by direct C-H functionalization are especially welcomed,[8] because these methods omit tedious prefunctionalized steps and make synthesis more efficient and more environmentally friendly.

The construction of C-Se and C-S bond via C-H functionalization has become a recent research hot spot,[9] because both are basic bonds in modern organic synthesis. Therefore, any simple and convenient methods of introducing selenium and sulfur into organic compounds via C-H functionalization would be significant.[10] Here, we develop one new method to construct C-Se bond and one to build C-S bonds on flavone skeletons, generating ArSe- and ArS-substitued flavone derivatives.

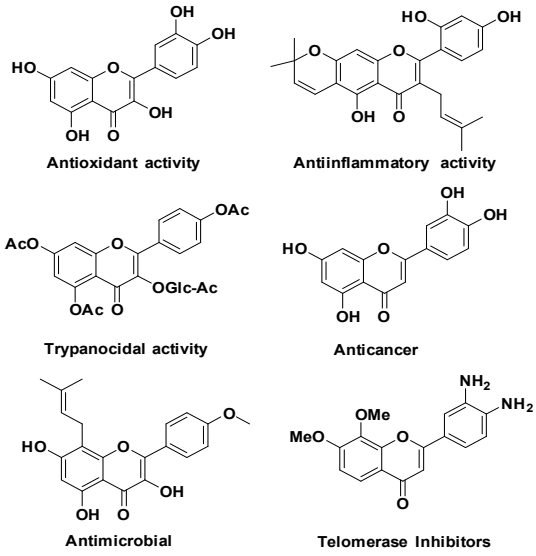

Figure 1. Examples of biologically active flavone derivatives

Flavone derivatives containing selenium have not yet been exploited in drug discovery, so selenium-containing flavone derivatives are of significant interest for bio-screening. In Scheme 1, the current synthetic methods to make flavone selenides are presented, illustrating that ArSeH, ArSeCl and ArSeSeAr have been employed as selenium sources.[11] Here, KSeCN was used as the selenium source to make ArSe-substituted flavones. Compared with ArSeH, ArSeCl, and ArSeSeAr, the KSeCN salt is cheaper, much easier to handle and generates far less odor.

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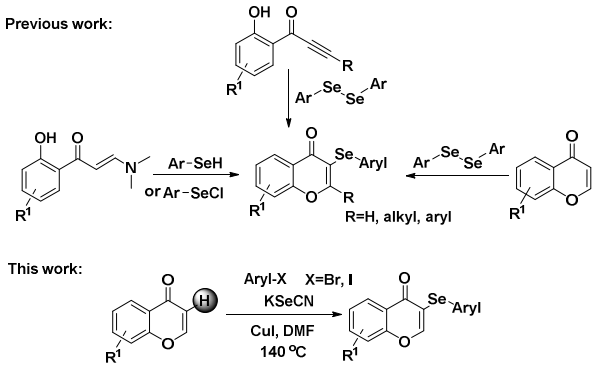


Scheme 1. Previously reported synthetic methods to construct flavone selenides versus our new method

Results and Discussion

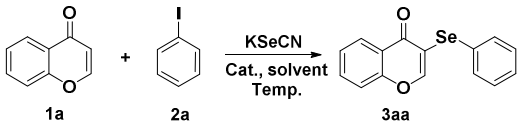
To screen for suitable reaction condition for constructing the C-Sebond on flavone skeletons with KSeCN, flavone **1a** was used as a representative reactant, and iodobenzene **2a** was selected as the representative aryl halide. Based on the literature and our previous research results,[12] copper, iron and nickel catalysts were selected and screened in different solvents at various temperatures in order to find suitable reaction conditions. Representative results are listed in Table 1.

The screening started using CuI as a catalyst in DMF at 90 °C, where the reaction afforded a 21% yield of expected product **3aa** (Table 1, entry 1). Increasing reaction temperature to 115 °C generated a 47% yield of **3aa** (entry 2). When the temperature was raised to 140 °C, the reaction proceeded well and gave an 88% yield of expected product **3aa** (entry 3). Using CH_3CN as the solvent at 140 °C produced a 42% yield (entry 4). Changing solvent from CH_3CN to DMSO at 140 °C decreased the reaction yield to 26% (entry 5). When Dioxane or EtOAc was employed, respectively, **3aa** was generated in a 15% or 20% yield at 140 °C (entries 6, 7). In toluene, the reaction only gave a 23% yield (entry 8). Replacing CuI with CuCN as the catalyst in DMF at 140 °C led to regioselective product **3aa** in a 58% yield (entry 9). Employing CuCl in DMF led to isolation of a 53% yield of **3aa** (entry 10). Using CuBr or $CuCl_2$ as the catalyst in DMF generated **3aa** in a 65% or 55% yields, respectively (entries 11 and 12), while Cu_2O catalyst afforded 57% of **3aa** (entry 13). Using $SnCl_2$ in DMF gave a 32% yield of **3aa** (entry 14). **3aa** was generated using Co(III)oxide (entry 15) and only 5% with $Co(OAc)_2$ (entry 16). Using $FeSO_4 \cdot 7H_2O$ as the catalyst produced 28% of **3aa** (entry 17) and $FeCl_3$ afforded only a trace of **3aa** (entry 18). Finally, using $CuSO_4$ as a catalyst provided a 35% yield of **3aa** (entry 19).

The optimized reaction conditions selected using KSeCN and an iodoarene (or bromoarene) to generate flavone selenide derivatives are: the flavone (1.0 equiv.), KSeCN (1.5 equiv.), iodobenzene or bromobenzene (1.5 equiv.), CuI (20 mol%), and DMF as the solvent at 140 °C for 16 h.

Several flavone analogs were synthesized with electron-donating and electron-withdrawing substituents. These flavones were reacted with KSeCN and different aromatic iodoaroenes containing various functional groups in order to further explore the reaction scope. Under the optimum conditions defined above, the experimental results are shown in Table 2. Most reactions of flavone analogs with iodoarenes proceeded well, giving good yields of the regioselective flavone selenide derivatives via C-H functionalization.Isolated yields of most reactions ranged from 69% to 90%. Even sterically crowded *ortho*-iodotoluene also gave a 78% yield of **3dh**. Bromoarenes were also employed as reactants, but they gave low product yields (10-17%) of **3aa**, **3be**, **3ce**, and **3da**. Clearly, iodoarenes were more reactive than bromoarenes. NMR spectra confirmed that ArSe-substituents were added to the α-position of flavone ketone functions. This regioselectivity was also proved by comparing NMR spectra to those previously reported.[13]

Table 1. Screening for suitable reaction conditions[a]



1a 2a 3aa

Entry	Cat.	Temp (°C)	Solvent	Yield of **3aa** (%)[b]
1	CuI	90	DMF	21
2	CuI	115	DMF	47
3	CuI	140	DMF	88
4	CuI	140	CH_3CN	42
5	CuI	140	DMSO	26
6	CuI	140	Dioxane	15
7	CuI	120	EtOAc	20
8	CuI	110	Toluene	23
9	CuCN	140	DMF	58
10	CuCl	140	DMF	53
11	CuBr	140	DMF	65
12	$CuCl_2$	140	DMF	55
13	Cu_2O	140	DMF	57
14	$SnCl_2$	140	DMF	32
15	Co_2O_3	140	DMF	0
16	$Co(OAc)_2$	140	DMF	5
17	$FeSO_4 \cdot 7H_2O$	140	DMF	28
18	$FeCl_3$	140	DMF	trace
19	$CuSO_4$	140	DMF	35

[a]Reaction conditions: flavone (0.5 mmol, 1.0 equiv.), iodobenzene (1.5 equiv.), KSeCN (1.5 equiv.), Cat. (20 mol%), solvent (0.5 mL). [b] Isolated yield of **3aa** was based on the reactant flavone **1a**. Reaction time: 16 h.

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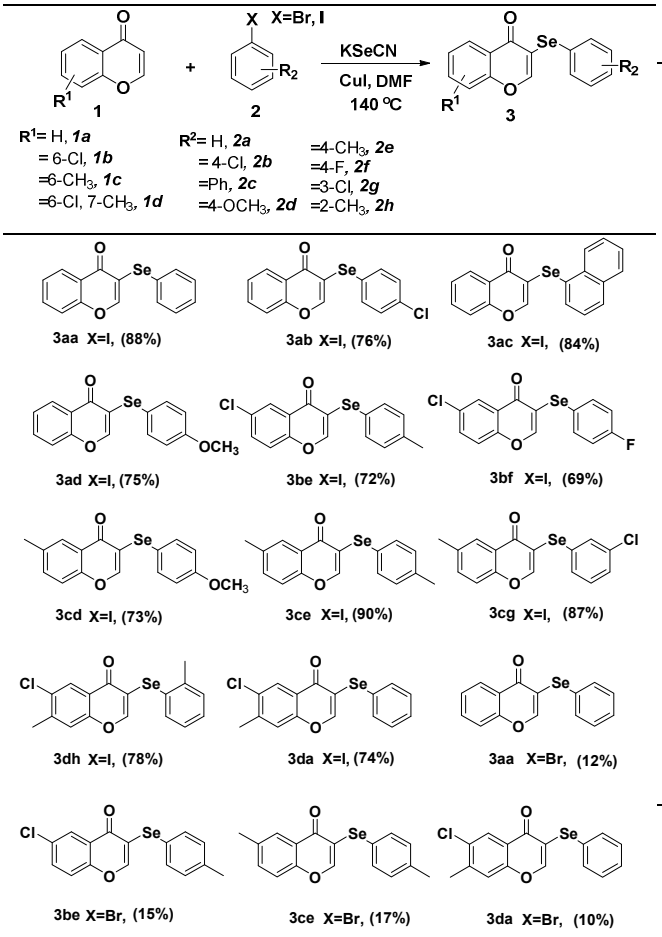
The use of KSeCN as a selenium source might logically be extended to the use of KSCN as a sulfur source to make flavone thiother derivatives because Se and S are both group VI elements. To further develop this chemistry, KSCN was selected as the sulfur source, then reacted with aryl iodides and flavones to make flavone thioethers. Screening reactions similar to those in Table 1 were conducted to establish suitable reaction conditions for KSCN. CuCN was demonstrated to be a better flavone sulfenylation catalyst than CuI, when KSCN was used. Therefore, flavone derivatives and iodoarenes with electron-donating and electron-withdrawing substituents were used to construct flavone thioethers with different substituents in order to partially explore the scope of this sulfenylation. Like the reaction using KSeCN, most reactions of using KSCN went well, giving good yields of ArS-substituted flavone derivatives via regioselective C-H functionalization

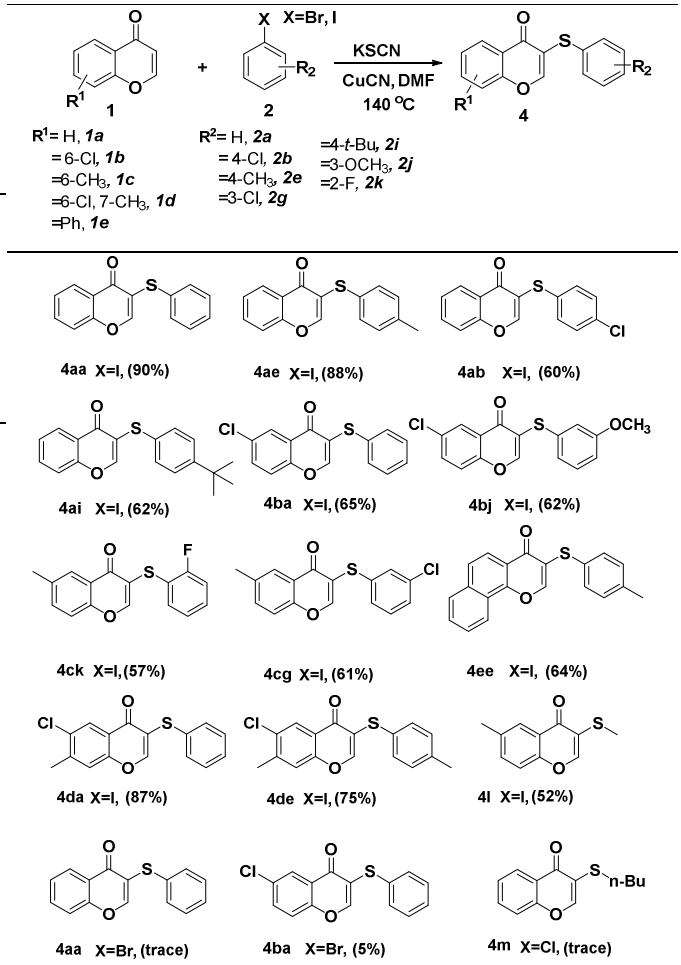
Table 2. Synthesis of selenium-containing flavone derivatives using different iodoarenes (or bromoarenes) and KSeCN[a,b]



[a] Reaction conditions: flavone (0.5 mmol, 1.0 equiv.), iodoarene or bromoarene (1.5 equiv.), KSeCN (1.5 equiv.), CuI (20 mol%), DMF (0.5 mL). [b] Isolated yields are based on reactant **1**, all reactions were run for 16h at 140 °C.

with good regioselectivities to the expected products. *ortho*-Fluoroiodobenzene gave a good yield of **4ck**. Unlike iodoarenes, bromoarenes as reactants generated only very small amounts of **4aa**, **4ba**. Interestingly, iodomethane, an alkyl iodide produced a 52% yield of **4l**, but when the longer-chain 1-chlorobutane was used, only trace amounts of **4m** were found.[14, 15]

Table 3. Sulfenylation of flavones with aryl halides [a,b]



[a] Reaction conditions: flavone (0.5 mmol, 1.0 equiv), iodoarene/ bromoarene/alkyliodide (1.5 equiv.), KSCN (1.5 equiv.), CuCN (20 mol%), DMF (0.5 mL).[b] Isolated yields are based on reactant **1**, all reactions were run for 24 h at 140 °C.

Based on NMR spectra and previous literature reports,[16] all RS-substituents were added to the α-position of flavone ketone function. A speculative but plausible mechanism is

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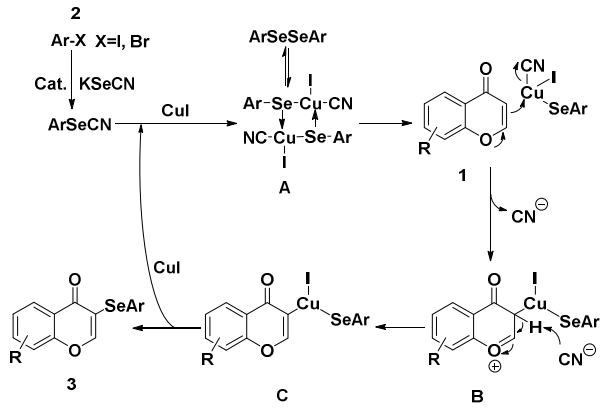
offered in Scheme 2 using KSeCN and Cu(I)I catalyst as an example, using KSCN as a reactant should follow the similar reaction mechanism. Based on the literature[17] and our experimental results. This is a working hypothesis offered to rationalize the results. The reaction between KSeCN and aromatic halides （X=I and Br） **1** could generate ArSeCN intermediates via copper catalysis in DMF. ArSeCN could further react with CuI to insert Cu producing an arylcopper complex intermediate **A**. Intermediate **A** might equilibrate to form a diselenide intermediate ArSeSeAr by Cu(II)ICN elimination. Intermediate **A** or ArSeCu(III)ICN reacts further with flavone **1** to give intermediate **B**. subsequent loss of one proton forms intermediate **C** followed by reductive elimination producing the final ArSe-substituted flavone derivatives product **3**, releasing Cu(I)I for the next cycle.



Scheme 2. Proposed reaction mechanism using KSeCN and CuI catalyst as an example

Conclusions

In summary, new methodsof constructing C-Se and C-S bonds on flavone skeletonsvia C-H functionalization at only the α-position were developed, generatingaryl selenide and sulfide flavone derivatives regioselectively in good yields. CH_3S-substitution was also achieved. These simple methods employed cheap and easy to handle KSeCN and KSCN to regioselectively synthesize ArSe- and ArS-substituted flavone derivatives. Compared with previously reported methods, both methods are more convenient, safer, while reducing odor. These paths have further enriched current C-Se and C-S bond construction methods. Further study to expand the scope of this methodology are under way.

Experimental Section

General: All reactions were carried out in sealed tubes; stirring was achieved with an oven-dried magnetic stirring bar. Solvents were purified by standard methods unless otherwise noted. Commercially available reagents were purchased from Aladdin Company in China and used throughout without further purification other than those detailed below. Flash column chromatography was performed on silica gel (200-300 mesh). All reactions were monitored by TLC analysis. Deuterated solvents were purchased from Cambridge Isotope laboratories.^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz respectively. HRMS spectrometry (LC-HRMS) was recorded on a LXQ Spectrometer (Thermo Scientific) operating in the ESI-TOF mode (MeOH as a solvent).

General procedure for the synthesis of compounds 3.
Flavone **1a** (0.5 mmol, 1.0 equiv.), potassium selenocyanate (1.5 equiv.) and iodobenzene (1.5 equiv.) were added to a dried flask with DMF (0.5 mL), followed by the addition of CuI (0.2 equiv.). The mixture was stirred at 140°C. After 16 h, the reaction was cooled to room temperature, diluted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (Petroleum ether : EtOAc = 100:1) on silica gel to give **3aa** as a colorless oil in an 88% yield. The same procedure was applied to the production of other compounds **3**.
General procedure for the synthesis of compounds 4.
Flavone **1a** (0.5 mmol, 1.0 equiv.), potassium thiocyanate (1.5 equiv.) and iodobenzene (1.5 equiv.) were added to a dried flask with DMF (0.5 mL), followed by the addition of CuCN (0.2 equiv.). The mixture was stirred at 140°C. After 24 h, the reaction was cooled to room temperature, diluted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (Petroleum ether : EtOAc = 100:1) on silica gel to give **4aa** as a colorless oil in a 90% yield. The same procedure was applied to the production of other compounds **4**.

3-(Phenylselanyl)-4H-chromen-4-one (3aa)
Following the general procedure, isolated yield (264.9 mg, 88%) as a colorless oil; IR:3062,2928，1637，1463，1112，762 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.26 (ddd, *J* = 7.7, 1.7, 0.7 Hz, 1H), 7.91 (s, 1H), 7.69 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.65 - 7.59 (m, 2H), 7.44 (td, *J* = 8.0, 7.5, 1.0 Hz, 2H), 7.37 - 7.29 (m, 3H)；^{13}C-NMR ($CDCl_3$, 100 MHz) ： 175.16, 156.35, 155.74, 133.85, 133.81, 129.54, 128.17, 128.12, 126.36, 125.55, 123.17, 118.06, 117.87; HRMS (ESI-TOF) m/z calculated for $C_{15}H_{10}NaO_2Se^+$ 324.9738 $(M+Na)^+$, found 325.0030.

3-((4-Chlorophenyl)selanyl)-4H-chromen-4-one (3ab)
Following the general procedure, isolated yield (255.1 mg, 76%) as a colorless oil; IR: 3039，2926，2360，1635，1461，1077，754 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.25 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.03 (s, 1H), 7.70 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.59 - 7.51 (m, 2H), 7.49 - 7.41 (m, 2H), 7.30 - 7.24 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) ： 175.02, 156.46, 156.36, 134.84, 134.35, 133.96, 129.64, 126.70, 126.40, 125.71, 123.28, 118.10, 117.24; HRMS (ESI-TOF) m/z calculated for $C_{15}H_9ClNaO_2Se^+$ 358.9349 $(M+Na)^+$, found 358.9352.

3-(Naphthalen-1-ylselanyl)-4H-chromen-4-one (3ac)
Following the general procedure, isolated yield (295.7 mg, 84%) as a colorless oil; IR：3064, 1636, 1463, 1311, 758 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz)：δ 8.41 (dt, *J* = 7.4, 1.1 Hz, 1H), 8.29 - 8.24 (m, 1H), 8.02 - 7.83 (m, 3H), 7.67 - 7.49 (m, 3H), 7.49 - 7.32 (m, 4H)； ^{13}C-NMR ($CDCl_3$, 100 MHz) ： δ 175.38, 157.73，

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156.24, 153.38, 135.35,134.29, 134.22, 134.09, 133.72, 130.16, 128.77, 127.70, 127.42, 126.58, 126.14, 126.09, 125.41, 122.72, 118.01; HRMS (ESI-TOF) m/z calculated for $C_{19}H_{12}NaO_2Se^+$ 374.9895 $(M+Na)^+$, found 374.9892.

3-((4-Methoxyphenyl)selanyl)-4H-chromen-4-one (3ad)

Following the general procedure, isolated yield (248.3 mg, 75%) as a colorless oil; IR: 3072，2932，1642，1490，1245，756 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm)8.24 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.70 - 7.59 (m, 4H), 7.41 (dtd, *J* = 8.1, 3.4, 1.1 Hz, 2H), 6.92 - 6.85 (m, 2H), 3.82 (s, 3H)；^{13}C-NMR ($CDCl_3$, 100 MHz)： 175.28, 160.23, 156.30, 153.86, 137.11, 133.67, 126.19, 125.38, 122.90, 119.38, 118.01, 117.08, 115.37, 55.33; HRMS (ESI-TOF) m/z calculated for $C_{16}H_{12}NaO_3Se^+$ 354.9844(M+Na)$^+$, found 354.9868.

6-Chloro-3-(p-tolylselanyl)-4H-chromen-4-one (3be)

Following the general procedure, isolated yield (245.0 mg, 70%) as a colorless oil; IR: 3057，1650，1467，1303，1079，825，810 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.20 (d, *J* = 2.6 Hz, 1H), 7.74 (s, 1H), 7.62 (d, *J* = 2.6 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 2.37 (s, 3H)； ^{13}C-NMR ($CDCl_3$, 100 MHz)：δ 174.13, 154.64, 154.52, 138.78, 134.89, 133.96, 131.36, 130.51, 125.60, 123.81, 123.42, 119.78, 118.95, 21.20; HRMS (ESI-TOF) m/z calculated for $C_{16}H_{11}ClNaO_2Se^+$ 372.9505 $(M+Na)^+$, found 372.9496.

6-Chloro-3-((4-fluorophenyl)selanyl)-4H-chromen-4-one (3bf)

Following the general procedure, isolated yield (244.0 mg, 69%) as a colorless oil; IR: 3057，2926，1634，1489，1464，1081，759 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.20 (d, *J* = 2.7 Hz, 1H), 7.86 (s, 1H), 7.64 (qd, *J* = 6.9, 6.3, 2.3 Hz, 3H), 7.42 (d, *J* = 8.9 Hz, 1H), 7.04 (t, *J* = 8.7 Hz, 2H)；^{13}C-NMR ($CDCl_3$, 100 MHz)：δ 174.05, 163.10 (d, J_{C-F},= 248 Hz), 155.24, 154.66, 136.74（d, J_{C-F},= 8 Hz）, 134.14, 131.56, 125.65, 123.93, 122.05, 119.83, 118.38, 116.87（d, J_{C-F},= 22 Hz）; HRMS (ESI-TOF) m/z calculated for $C_{15}H_9ClFO_2Se^+$ 354.9440 $(M+H)^+$, found 354.9258.

3-((4-Methoxyphenyl)selanyl)-6-methyl-4H-chromen-4-one (3cd)

Following the general procedure, isolated yield (251.9 mg, 73%) as a colorless oil; IR: 3057, 2920, 1644, 1485, 1025, 819 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz)：δ 8.05 - 7.95 (m, 1H), 7.72 - 7.56 (m, 3H), 7.46 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 2.45 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 175.34, 160.16, 154.60, 153.98, 136.98, 135.41, 134.96, 125.41, 122.60, 118.98, 117.76, 117.31, 115.32, 55.32, 20.95. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{14}NaO_3Se^+$ 369.0000 $(M+Na)^+$, found 368.9995.

6-Methyl-3-(p-tolylselanyl)-4H-chromen-4-one (3ce)

Following the general procedure, isolated yield (296.1mg, 90%) as a colorless oil; IR: 3059，2918，2362，1645，1483，1312，757 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.00 (d, *J* = 2.2 Hz, 1H), 7.77 (s, 1H), 7.55 - 7.42 (m, 3H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 2.44 (s, 3H), 2.33 (s, 3H)；^{13}C-NMR ($CDCl_3$, 100 MHz)：δ 175.32, 154.96, 154.62, 138.37, 135.50, 135.01, 134.46, 130.38, 125.52, 124.12, 122.74, 118.18, 117.78, 21.19, 20.97;HRMS (ESI-TOF) m/z calculated for $C_{17}H_{14}NaO_2Se^+$ 353.0051 $(M+Na)^+$, found 353.0027.

3-((3-Chlorophenyl)selanyl)-6-methyl-4H-chromen-4-one (3cg)

Following the general procedure, isolated yield (304.2 mg, 87%) as a colorless oil; IR: 3042，2936，2359，1633，1479，1314 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.11 (s, 1H), 8.07 - 8.01 (m, 1H), 7.55 - 7.49 (m, 2H), 7.45 (dt, *J* = 7.3, 1.5 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.29 - 7.18 (m, 2H), 2.47 (s, 3H)；^{13}C-NMR ($CDCl_3$, 100 MHz)：175.02, 157.27, 154.68, 135.89, 135.26, 134.95, 132.28, 130.78, 130.72, 130.35, 127.91, 125.74, 123.07, 117.88, 116.27, 20.97; HRMS (ESI-TOF) m/z calculated for $C_{16}H_{11}NaO_2Se^+$ 372.9505 $(M+Na)^+$, found 372.9496.

6-Chloro-7-methyl-3-(o-tolylselanyl)-4H-chromen-4-one (3dh)

Following the general procedure, isolated yield (283.7 mg, 78%) as a colorless oil; IR: 3062, 2928, 1627, 1452, 1076, 754 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.20 (s, 1H), 7.63 (s, 1H), 7.49 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.35 - 7.23 (m, 3H), 7.12 (td, *J* = 7.3, 2.1 Hz, 1H), 2.51 (d, *J* = 1.9 Hz, 6H)；^{13}C-NMR ($CDCl_3$, 100 MHz)：δ 174.17, 154.66, 154.41, 143.17, 140.72, 134.63, 132.19, 130.54, 128.69, 128.26, 127.07, 125.82, 121.95, 119.82, 117.33, 22.37, 20.82; HRMS (ESI-TOF) m/z calculated for $C_{17}H_{13}ClNaO_2Se^+$ 386.9662(M+Na)$^+$, found 386.9712.

6-Chloro-7-methyl-3-(phenylselanyl)-4H-chromen-4-one (3da)

Following the general procedure, isolated yield (258.7 mg, 74%) as a colorless oil; IR: 2359, 1645, 1406, 1283, 735, 689 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz)：δ 8.19 (s, 1H), 7.84 (s, 1H), 7.67 - 7.55 (m, 2H), 7.39 - 7.25 (m, 4H), 2.50 (d, *J* = 0.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 174.06, 155.45, 154.61, 143.22, 133.98, 132.23, 129.59, 128.25, 127.89, 125.88, 122.11, 119.83, 117.87, 20.83; HRMS (ESI-TOF) m/z calculated for $C_{16}H_{11}ClNaO_2Se^+$ 372.9505(M+Na)$^+$, found 372.9496.

3-(Phenylthio)-4H-chromen-4-one (4aa)

Following the general procedure, isolated yield (228.6 mg, 90%) as a colorless oil; IR: 3058, 2925, 1653, 1612, 1464, 1309, 1113, 760 cm^{-1}; ^{1}H-NMR ($CDCl_3$，400 MHz)： δ（ppm）8.27 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.18 (s, 1H), 7.72 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.50 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.50 - 7.38 (m, 3H), 7.35 - 7.20 (m, 3H)；^{13}C-NMR (CDCl3，100MHz)：δ175.07, 157.36, 156.35, 134.00, 129.85, 129.80, 129.20, 127.12, 126.47, 125.75, 123.68, 119.95, 118.16; HRMS (ESI-TOF) m/z calculated for $C_{15}H_{11}O_2S^+$ 277.0294 $(M+H)^+$, found 277.0287.

3-(p-Tolylthio)-4H-chromen-4-one (4ae)

Following the general procedure, isolated yield (235.8 mg, 88%) as a colourless oil; **IR**: 3075, 2923, 2359, 1647, 1464, 1114, 758 cm^{-1}; ^{1}H-NMR ($CDCl_3$，400 MHz)： δ（ppm） 8.26 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.07 (s, 1H), 7.70 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.52 - 7.41 (m, 2H), 7.40 - 7.33 (m, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 2.33 (s, 3H)；^{13}C-NMR ($CDCl_3$，100 MHz,)： δ 175.09, 156.26, 137.60, 133.89（2C）, 130.99, 130.06, 129.82, 126.40, 125.61, 123.57, 121.10, 118.11, 21.11; HRMS (ESI-TOF) m/z calculated for $C_{16}H_{12}NaO_2S^+$ 291.0450 $(M+Na)^+$, found 291.0478.

3-((4-Chlorophenyl)thio)-4H-chromen-4-one (4ab)

Following the general procedure, isolated yield (172.8 mg, 60 %) as a colourless oil; IR: 3051,1648，1478，1465，1313，1091，827，758 cm^{-1}; ^{1}H-NMR($CDCl_3$，400 MHz,)： δ （ppm）8.26 (q, *J* = 3.4, 2.6 Hz, 2H), 7.73 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.56 - 7.43 (m, 2H), 7.37 - 7.22 (m, 4H)；^{13}C-NMR ($CDCl_3$，100 MHz)： δ 174.95, 157.91, 156.35, 134.17, 133.10, 132.80, 130.88, 129.27, 126.45, 125.91, 123.72, 119.22, 118.21;HRMS (ESI-TOF)

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m/z calculated for $C_{15}H_9ClNaO_2S^+$ 310.9904 $(M+Na)^+$, found 310.9854.

3-((4-(tert-Butyl)phenyl)thio)-4H-chromen-4-one (4ai)
Following the general procedure, isolated yield (192.2 mg, 62%) as a colourless oil; IR: 3070，2963，1649，1611，1560，1462，1115，846，764cm^{-1}；^{1}H-NMR($CDCl_3$，400 MHz)：δ（ppm）8.27 (dd，*J* = 8.0，1.7 Hz，1H)，8.09 (s，1H)，7.71 (ddd，*J* = 8.7，7.1，1.7 Hz，1H)，7.52-7.44 (m，2H)，7.42-7.32 (m，4H)，1.30 (s，9H)；^{13}C-NMR($CDCl_3$，100MHz)：δ175.16，156.57，150.65，133.90，130.45，129.97，126.42，126.36（2C），125.64，123.59，120.80，118.12，34.55，31.24; HRMS (ESI-TOF) m/z calculated for $C_{19}H_{18}NaO_2S^+$ 333.0920 $(M+Na)^+$, found 333.0927.

6-Chloro-3-(phenylthio)-4H-chromen-4-one (4ba)
Following the general procedure, isolated yield (187.2 mg, 65%) as a colorless oil; IR: 3068，2925，2360，1653，1466，1303，1122，918，821，755cm^{-1}；^{1}H-NMR ($CDCl_3$，400MHz)：δ（ppm）8.22(d，*J* = 2.6 Hz，1H)，8.12 (s，1H)，7.65 (dd，*J* = 8.9，2.6 Hz，1H)，7.49-7.39 (m，3H)，7.35-7.24 (m，3H)；^{13}C-NMR($CDCl_3$，100MHz)：δ173.96，157.00，154.65，134.23，133.39，131.70，130.26，129.31，127.45，125.74，124.46，120.50，119.97; HRMS (ESI-TOF) m/z calculated for $C_{15}H_9ClNaO_2S^+$ 310.9904 $(M+Na)^+$, found 310.9964.

6-Chloro-3-((3-methoxyphenyl)thio)-4H-chromen-4-one (4bj)
Following the general procedure, isolated yield (197.2 mg, 62%) as a colorless oil; IR: 3062, 2924, 1654, 1592,1297, 1038 cm^{-1};^{1}H-NMR ($CDCl_3$，400 MHz)：δ（ppm）8.22 (d, *J* = 2.6 Hz, 1H), 8.14 (s, 1H), 7.65 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.03 - 6.92 (m, 2H), 6.80 (ddd, *J* = 8.4, 2.5, 1.0 Hz, 1H), 3.79 (s, 3H)；^{13}C-NMR ($CDCl_3$，100 MHz)：δ 173.90, 160.06, 157.15, 154.66, 134.72, 134.22, 131.73, 130.08, 125.79, 124.51, 122.21, 120.27, 119.90, 115.56, 113.05, 55.32；HRMS (ESI-TOF) m/z calculated for $C_{16}H_{11}ClNaO_3S^+$ 341.0010，$(M+Na)^+$, found 341.0017.

3-((2-Fluorophenyl)thio)-6-methyl-4H-chromen-4-one (4ck)
Following the general procedure, isolated yield (163.0 mg, 57%) as a colorless oil; IR：3054, 2921, 1644, 1474, 1210, 1114, 812, 743 cm^{-1}; **^{1}H-**NMR ($CDCl_3$，400 MHz)：δ 8.20 (s, 1H), 8.05 - 7.97 (m, 1H), 7.49 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.43 - 7.33 (m, 2H), 7.26 - 7.17 (m, 1H), 7.11 - 7.00 (m, 2H), 2.44 (s, 3H). ^{13}C-NMR ($CDCl_3$，100 MHz)：175.1, 161.1 (d, J_{C-F} = 245 Hz), 157.7, 154.6, 135.9, 135.3, 132.5, 129.2 (d, J_{C-F} = 8 Hz), 125.6, 124.6 (d, J_{C-F} = 4 Hz), 123.3, 121.1 (d, J_{C-F} = 17 Hz), 117.9, 117.8, 115.9 (d, J_{C-F} = 22 Hz), 21.0; HRMS(ESITOF) m/z calculated for $C_{16}H_{11}FNaO_2S^+$ 309.0356 $(M + Na)^+$, found 309.0343

3-((3-Chlorophenyl)thio)-6-methyl-4H-chromen-4-one (4cg)
Following the general procedure, isolated yield (184.2 mg, 61%) as a colourless oil; IR: 3054, 1638, 1313, 1122, 818, 779 cm^{-1}, ^{1}H-NMR ($CDCl_3$，400 MHz)：δ（ppm）8.27 (s, 1H), 8.08 - 7.99 (m, 1H), 7.52 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.29 (t, *J* = 1.8 Hz, 1H), 7.25 - 7.12 (m, 3H), 2.46 (s, 3H). ^{13}C-NMR ($CDCl_3$，100 MHz)：δ 174.93, 158.67, 154.66, 136.92, 136.10（2C）, 135.43, 134.80, 130.04, 128.32, 126.82, 125.73, 123.46, 117.99, 117.94, 20.96; HRMS (ESI-TOF) m/z calculated for $C_{16}H_{11}ClNaO_2S^+$ 325.0060 $(M+Na)^+$, found 325.0030.

3-(p-Tolylthio)-4H-benzo[h]chromen-4-one (4ee)
Following the general procedure, isolated yield (203.5 mg, 64%) as a colourless oil; IR: 3057，2920，2361，1650，1633，1384，1113，886，765cm^{-1}；^{1}H-NMR($CDCl_3$，400 MHz)：δ（ppm）8.40 (dd，*J* = 8.2，1.4 Hz，1H)，8.16 (d，*J* = 8.8 Hz，1H)，8.08 (s，1H)，7.92 (dd，*J* = 7.7，1.4 Hz，1H)，7.80-7.63 (m，3H)，7.43 (d，*J* = 8.2 Hz，2H)，7.16 (d，*J* = 7.9 Hz，2H)，2.35 (s，3H)；^{13}C-NMR ($CDCl_3$,100 MHz)：δ174.79，154.26，153.73，137.98，135.78，131.71，130.21，129.49，129.14，128.12，127.30，125.70，123.80，123.45，122.16，121.04，119.61，21.17;HRMS (ESI-TOF) m/z calculated for $C_{20}H_{14}NaO_2S^+$ 341.0607 $(M+Na)^+$, found 341.0623.

6-Chloro-7-methyl-3-(phenylthio)-4H-chromen-4-one (4da)
Following the general procedure, isolated yield (262.7 mg, 87%) as a colourless oil; IR: 3064, 2921, 1655, 1431, 1106, 917, 795 cm^{-1};^{1}H-NMR ($CDCl_3$，400 MHz)：δ（ppm）8.19 (s, 1H), 8.10 (s, 1H), 7.43 - 7.38 (m, 2H), 7.37 (d, *J* = 0.9Hz, 1H), 7.34 - 7.27 (m, 2H), 7.27 - 7.22 (m, 1H), 2.51 (d, *J* = 0.8 Hz, 3H)；^{13}C-NMR ($CDCl_3$,100 MHz)：δ 173.95, 157.05, 154.59, 143.43, 133.70, 132.43, 130.03, 129.24, 127.28, 125.96, 122.6 , 120.07, 119.93, 20.86. HRMS (ESI-TOF) m/z calculated for $C_{16}H_{11}ClNaO_2S$+ 325.0060 $(M+Na)^+$, found 325.0076.

6-Chloro-7-methyl-3-(p-tolylthio)-4H-chromen-4-one (4de)
Following the general procedure, isolated yield (237.0 mg, 75%) as a colorless oil.IR: 3060, 2924, 1651，1412, 1097, 899, 786 cm^{-1}；^{1}H-NMR ($CDCl_3$，400 MHz)：δ（ppm） 8.19 (s, 1H), 7.98 (s, 1H), 7.36 (d, *J* = 8.2 Hz, 3H), 7.13 (d, *J* = 7.9 Hz, 2H), 2.53 - 2.48 (m, 3H), 2.33 (s, 3H)；**^{13}C-**NMR ($CDCl_3$,100 MHz)：δ 173.96, 155.91, 154.55, 143.28, 137.80, 132.29, 131.20, 130.11, 129.47, 125.90, 122.52, 121.25, 119.88, 21.12, 20.85;HRMS (ESI-TOF) m/z calculated for $C_{17}H_{13}ClNaO_2S^+$ 339.0222 $(M+Na)^+$, found 339.0254.

6-Methyl-3-(methylthio)-4H-chromen-4-one (4l)
Following the general procedure, isolated yield (107.1 mg, 52%) as a colorless oil; IR：3064，2920，1639，1486，1149，1082，872 cm^{-1}；^{1}H-NMR ($CDCl_3$，400 MHz)：δ（ppm）8.06 - 8.01 (m, 2H), 7.52 - 7.44 (m, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 2.46 (s, 3H), 2.40 (s, 3H)；^{13}C-NMR ($CDCl_3$，1010MHz)：δ175.68, 154.55, 153.98, 135.49, 135.05, 125.31, 122.84, 121.47, 117.82, 20.95, 16.38; HRMS (ESI-TOF) m/z calculated for $C_{11}H_{10}NaO_2S^+$ 229.0294 $(M+Na)^+$, found 229.0287.

Conflicts of interest

There are no conflicts to declare.

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Two simple Cu-catalyzed methods of using KSeCN and KSCN to construct C-Se and C-S bonds on flavone skeletal structures via C-H functionalization are developed