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Iron (III)-Promoted Synthesis of Substituted 4*H*-Chalcogenochromenes and Chemoselective Functionalization

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Abstract. The iron(III)-promoted synthesis of densely-substituted 4*H*-chalcogenchromene from organochalcogen propargylamines in the presence of diaryl dichalcogenides is reported. Subsequent C2-functionalization with electrophiles and potassium trifluoroborate salts via Suzuki-Miyaura coupling reaction are also presented. A plausible mechanism based on HRMS experiments is proposed and discussed.

Keywords: Chalcogen, 4*H*-Chalcogenochromenes, Heterocycles, Iron, Propargylamines.

Introduction

Chromene derivatives are an important class of compounds found in natural products and biologically active molecules. Some of the activities described in the literature include anticancer, antiprotozoal, antibacterial, antiviral and insecticidal (Figure 1).[1]

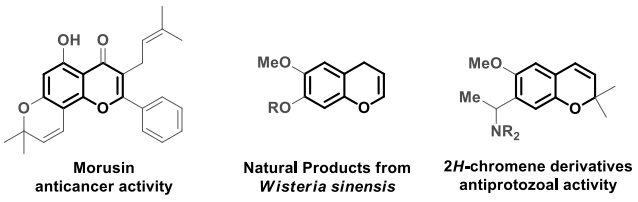


Figure 1. Biologically-relevant chromene derivatives.

The most common members of this family are 4H-chromenes, 2*H*-chromenes, 2*H*-chromen-2-one (coumarins) and 4*H*-chromen-4-one (chromones), whose syntheses have been accomplished via many different routes.[2] Other chalcogenochromenes, such as 4*H*-seleno- and 4*H*-tellurochromenes, are rather unusual, with only very few examples described in the literature (Figure 2).[3]

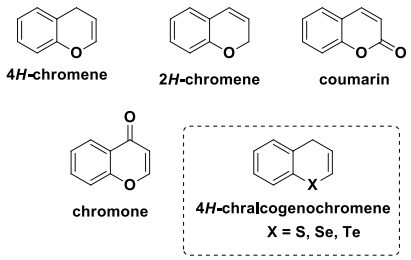


Figure 2. Examples of chromenes.

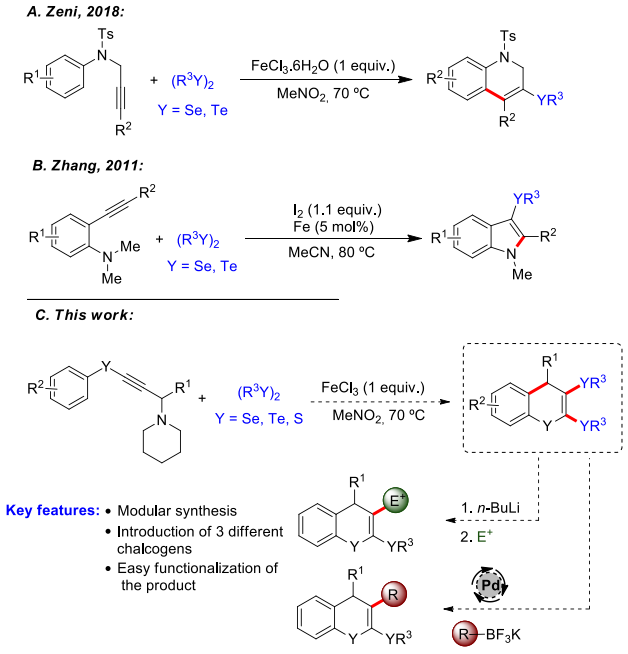
Despite this scarcity, the potential of these molecules cannot be ignored, as many organoselenium and organotellurium compounds have demonstrated pronounced biological activity in previous studies.[4]

With these considerations in mind, we set out to design a useful and operationally simple route to 4*H*-chalcogenochromenes. The proposed methodology should be modular in order to accommodate a wide variety of functional groups, based on simple starting materials and at the same time allow the quick functionalization of the final product. We believed that a rapid cyclization process that at the same incorporated organochalcogenide substituents would meet these criteria as these groups are easily replaced

by carbon-carbon, carbon-halogen and carbon-heteroatom bonds.[5]

These prerequisites led us to investigate iron(III)-promoted cyclization methodologies in which pendant alkynes are cyclized onto carbocyclic rings in the presence of dichalcogenides. These transformations have been explored as a way of introducing organochalcogenide groups into cyclic structures[6] using a non-toxic, environmentally friendly, Earth-abundant element.[7] For example, Zeni and co-workers reported the synthesis of 3-(organoselanyl)-1,2-dihydroquinolines from arylpropargylamines using $FeCl_3$ in nitromethane (Scheme 1A),[8] while Zhang and co-workers obtained functionalized 3-selenylindoles from alkynylanilines in acetonitrile (Scheme 1B)[9] using this approach. Both methodologies rely on simple materials, are highly modular and incorporate organochalcogenide groups in the final heterocyclic product.

Inspired by these methods, we decided to investigate the cyclization of organochalcogen propargylamines (selected for being easily obtained via A^3-coupling chemistry)[10] in the presence of $FeCl_3$ and dichalcogenides. We found that under certain reaction conditions, densely substituted 4*H*-chalcogenochromenes were obtained in a cascade process that concomitantly forged 3 different C–C bonds. Moreover, the organochalcogenide groups installed by this sequence were easily functionalized via coupling chemistry or by electrophilic quench of a lithiated intermediate (Scheme 1C).

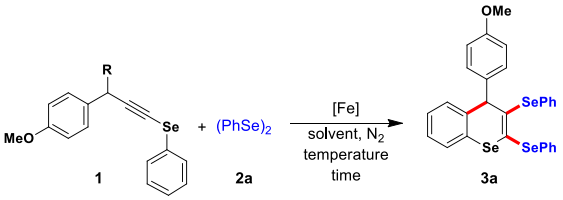


Scheme 1. Synthesis of cyclic chalcogenide species.

Results and Discussion

Our studies initiated with the screening of conditions for the formation of 4*H*-chalcogenochromene **3a** from model substrates **1** and **2a** (Table 1). Reactions were followed by TLC in order to ensure full conversion of **1**.

Table 1. Optimization of reaction conditions.



1 2a 3a

Entry	R	[Fe] (equiv.)	$(PhSe)_2$ (equiv.)	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	piperidinyl	$FeCl_3$ (1)	2	DCE	70	1	71
2	piperidinyl	$FeCl_3$ (0.75)	2	DCE	70	4	n.r.
3	piperidinyl	$FeCl_3$ (0.6)	2	DCE	70	4	n.r.
4	piperidinyl	$FeCl_3$ (1)	1.5	DCE	70	8	73
5	piperidinyl	$FeCl_3$ (1)	1.2	DCE	70	1	87
6	piperidinyl	$FeCl_3$ (1)	1	DCE	70	1	67
7	piperidinyl	$FeCl_3$ (1)	1.2	$MeNO_2$	70	1	94
8	piperidinyl	$FeCl_3$ (1)	1.2	DCM	45	1	20
9	piperidinyl	$FeCl_3$ (1)	1.2	MeCN	80	22	80
10	piperidinyl	$FeCl_3$ (1)	1.2	THF	60	2	traces
11	piperidinyl	$Fe(NO_3)_3$ (1)	1.2	$MeNO_2$	70	2	n.r.
12	piperidinyl	$Fe(acac)_3$ (1)	1.2	$MeNO_2$	70	2	n.r.
13	piperidinyl	$FeCl_2$ (1)	1.2	$MeNO_2$	70	2	n.r.
14	piperidinyl	$FeBr_3$ (1)	1.2	$MeNO_2$	70	2	49
15	piperidinyl	$FeCl_3$ (1)	1.2	$MeNO_2$	70	2	41[b]
16	pyrrolidinyl	$FeCl_3$ (1)	1.2	$MeNO_2$	70	2	72
17	morpholinyl	$FeCl_3$ (1)	1.2	$MeNO_2$	70	2	67
18	acetyl	$FeCl_3$ (1)	1.2	$MeNO_2$	70	1	0
19	methoxy	$FeCl_3$ (1)	1.2	$MeNO_2$	70	1	0
20	methyl	$FeCl_3$ (1)	1.2	$MeNO_2$	70	1	0

Reaction scale: 0.3 mmol; n.r. = no reaction; [a]isolated yields; [b]microwave irradiation.

We began by using 1 equivalent of $FeCl_3$, 2 equivalents of diphenyl diselenide **2a** in DCE at 70 °C obtaining **3a** in 71% yield (entry 1). Lower loadings of $FeCl_3$ were ineffective and no product **3a** was observed with 0.75 or 0.6 equivalents (entries 2 and 3). Next, different amounts of diphenyl diselenide **2a** were screened, with 1.2 equivalents proving optimal (entries 4–6). An increase in the reaction yield was observed when $MeNO_2$ was used as solvent, while DCM, MeCN and THF produced the opposite effect (entries 7–10). The source of iron of choice proved crucial to the reaction outcome, with $Fe(NO_3)_3$, $Fe(acac)_3$, $FeCl_2$ completely failing in delivering product **3a** and $FeBr_3$ giving **3a** in only 49% yield (entries 11–14). The best conditions found were tested under microwave irradiation, however, a lower yield was obtained (entry 15). Finally, the effect of the leaving group R in the organoselenium propargylamine **1** was surveyed: pyrrolidinyl and morpholinyl were tested (entries 16 and 17), however, piperidinyl (entry 7) was confirmed as the best among the amines. Surprisingly, acetyl and methoxy group did not react in a similar way and the starting materials were quickly decomposed under the reaction conditions (entries 18 and 19). Interestingly, a propargylamine containing a methyl group also decomposed when exposed to $FeCl_3$ and no starting material was recovered from this reaction, as it was initially expected (entry 20).

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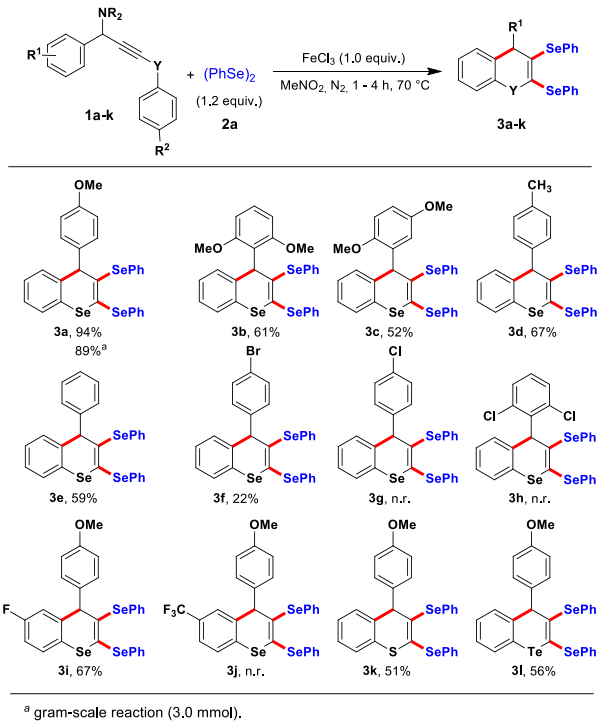
With the optimized conditions in hand, we next explored the scope of this reaction. The results are summarized in Table 2.

Table 2. Scope of organochalcogen propargylamines.



[a] gram-scale reaction (3.0 mmol).

Organoselenium propargylamines bearing electron-neutral (**1e**) and electron-donating substituents such as methyl (**1d**) and methoxy (**1a-c**) smoothly afforded products **3a-e** in good to excellent yields. Reactions involving substrates bearing electron-withdrawing substituents, on the other hand, were sluggish: **1f** gave product **3f** in only 22%, while **1g-h** failed to deliver products **3g-h**. These examples suggest a preference for strongly electron-donating rings with the *ortho* position free. Substitution of the carbocyclic ring was tolerated and product **3i** was obtained in 67% yield. When the strongly deactivating trifluoromethyl group is present in the same position, however, the expected product was not observed (**3j**). Interestingly, phenyltelluryl and phenylthio propargylamines also afforded 4*H*-thiochromene **3j** and 4*H*-tellurochromene **3k** in reasonable yields. A reaction between **1a** and **2a** on a gram scale afforded **3a** in comparable yield, indicating that this protocol is suitable for large-scale processes. Failed (**3g-h, j**) and low-yielding reactions were accompanied by significant decomposition of the starting materials. No relevant by-products or unreacted substrate were isolated after the indicated reaction time.

The structure of **3b** was unambiguously confirmed by single-crystal X-ray analysis. The ORTEP view of this compound is shown in Figure 3.[11] All other compounds were characterized by standard spectroscopic techniques. In addition to that, selenochromenes **3a** and **3b** were also characterized by HMBC (^{77}Se-^{1}H) analysis (see Supporting Information).

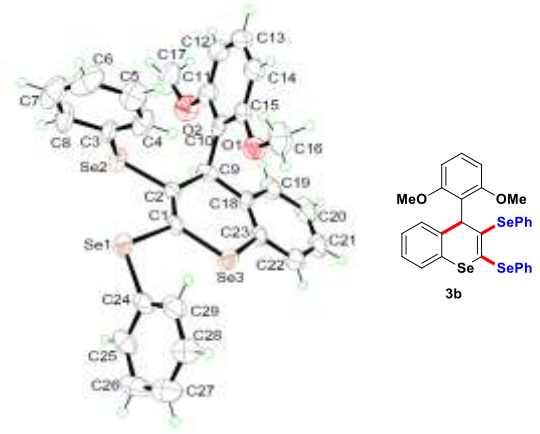
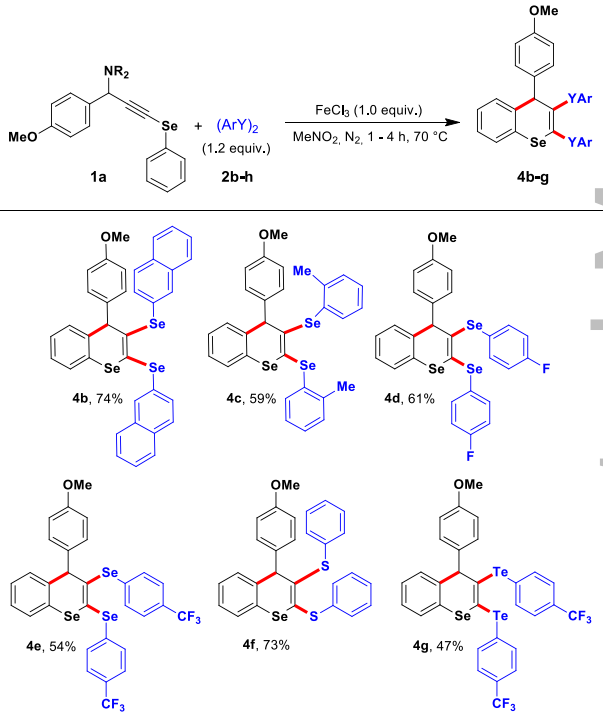


Figure 3. ORTEP view of compound **3b.**

The scope for the diaryl diselenide was next evaluated using **1a** under the same reaction conditions (Table 3).

Table 3. Scope of diaryl diselenides.



The reaction proceeded well with electron-rich diselenides **2b** and **2c**, which allowed the isolation of **4b** and **4c** in 74% and 59%, respectively. Electron-poor propargylamines **2d** and **2e** were also compatible with this reaction, providing **4d** and **4e** in 61% and 54% yield. Gratifyingly, the reaction conditions also tolerated phenyl disulfide **2f** and ditelluride **2g** with products **4f** and **4g** being isolated in 73% and 47%, respectively.

An interesting feature of C(sp^2)-Se bonds is the ability to undergo lithium exchange reactions with organolithium reagents. This approach makes the

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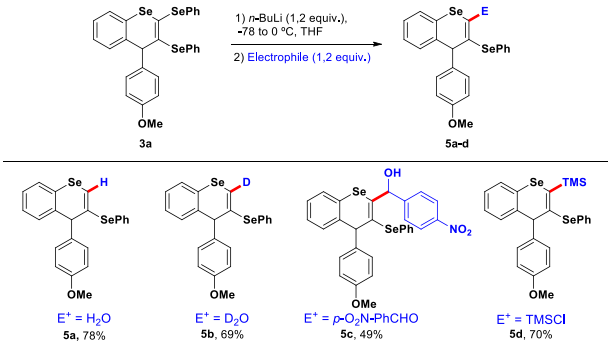
formation of new carbon-carbon, carbon-metal, carbon-halogen and carbon-heteroatom bonds accessible via lithium intermediates.[12] With this objective in mind, we treated **3a** with *n*-butyllithium in THF at -78 °C, followed by the addition of electrophiles (Table 4). The selectivity for the phenylselenyl substituent at position 2 was confirmed by the ^{1}H NMR spectrum of **5a**, which shows a characteristic singlet signal at 3.80 ppm (see supporting information for details). This result is in line with the expected stabilization of the anionic intermediate provided by the adjacent selenium atom.

Table 4. C2-functionalization of **3a** with electrophiles.



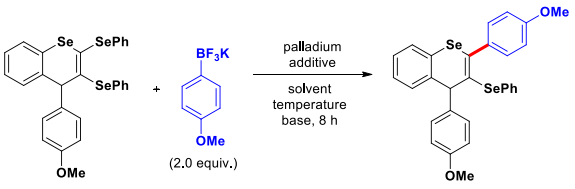
Addition of the electrophiles indicated in Table 4 successfully installed hydrogen (**5a**), deuterium (**5b**), a secondary alcohol (**5c**) and a TMS group (**5d**) at position 2. These examples show the versatility of the phenylselenyl group that is concomitantly installed during the cyclization cascade.

Finally, we wanted to show one more example of the flexibility of this substituent by replacing it by aryl groups via Suzuki-Miyaura cross-coupling reaction, a transformation still unprecedented for –SePh groups.

A screening of reaction conditions was carried out with substrate **3a** and 4-methoxyphenyl-trifluoroborate **6a** (Table 5).

Initially, we used a set of conditions previously described for the Suzuki-Miyaura cross-coupling between aryl tellurides and potassium aryltrifluoroborate salts,[13] obtaining **7a** in encouraging 41% yield (entry 1). Lowering the amount of Ag_2O and Et_3N added increased the isolated yield of **7a** to 52% (entry 2). A survey of some palladium catalysts and ligands showed that $Pd(dppf)Cl_2$ was the most active one (entries 3–7), however, significant amounts of diarylated product were also isolated, which led us to choose PEPPSI-*i*Pr to continue the screening, as this complex provided **7a** as the sole product. Lowering the reaction temperature to 60 °C significantly increased the reaction yield, from 47% to 80% (entry 9). Variations in the additive (entries 11 and 12) or the base (entries 12 and 13) were not productive. Similar outcome was observed with variations in the reaction solvent (entries 14–16).

Table 5. Optimization of reaction conditions for the Suzuki-Miyaura cross-coupling reaction.



Entry	[Pd] (mol%)	Additive (equiv.)	Solvent	Temperature (°C)	Base (eq.)	Yield (%)[a]
1	$Pd(PPh_3)_4$ (10)	Ag_2O (2)	MeOH/DMF	80	Et_3N (4)	41
2	$Pd(PPh_3)_4$ (10)	Ag_2O (1)	MeOH/DMF	80	Et_3N (2)	52
3	$Pd(PPh_3)_2Cl_2$ (10)	Ag_2O (1)	MeOH/DMF	80	Et_3N (2)	40
4	$Pd(dppf)Cl_2$(10)	Ag_2O (1)	MeOH/DMF	80	Et_3N (2)	56
5	$PdCl_2$ (10)/ XantPhos (20)	Ag_2O (1)	MeOH/DMF	80	Et_3N (2)	48
6	$PdCl_2$ (10)/ XPhos (20)	Ag_2O (1)	MeOH/DMF	80	Et_3N (2)	36
7	$PdCl_2$ (10)/ RuPhos (20)	Ag_2O (1)	MeOH/DMF	80	Et_3N (2)	36
8	PEPPSI-*i*Pr (10)	Ag_2O (1)	MeOH/DMF	80	Et_3N (2)	47
9	PEPPSI-*i*Pr (10)	Ag_2O (1)	MeOH/DMF	60	Et_3N (2)	80
10	PEPPSI-*i*Pr (10)	AgOAc (10)	MeOH/DMF	60	Et_3N (2)	41
11	PEPPSI-*i*Pr (10)	CuI (1)	MeOH/DMF	60	Et_3N (2)	n.r.
12	PEPPSI-*i*Pr (10)	Ag_2O (1)	MeOH/DMF	60	K_2CO_3 (2)	n.r.
13	PEPPSI-*i*Pr (10)	Ag_2O (1)	MeOH/DMF	60	DIPEA	51
14	PEPPSI-*i*Pr (10)	Ag_2O (1)	DMF	60	Et_3N (2)	18
15	PEPPSI-*i*Pr (10)	Ag_2O (1)	MeOH/ THF	60	Et_3N (2)	20
16	PEPPSI-*i*Pr (10)	Ag_2O (1)	MeOH/ $PhCH_3$	60	Et_3N (2)	39

[a] *Isolated yield. n.r. = no reaction*

Having established the optimized reaction conditions, various potassium aryltrifluoroborate salts **6** were employed and the results are summarized in Table 6.

The results shown above indicate that the electronic nature of the potassium trifluoroborate salt directly impacts the isolated yields. While electron-rich **6a** cleanly gave **8a** in 80% yield, potassium aryl trifluoroborate salts bearing electron-withdrawing groups such as *p*–Cl (**6b**), *p*–CN (**6c**), *m*–CHO (**6d**) and *p*–COMe (**6e**) afforded 2-aryl-4*H*-selenochromenes **7b-e** in only low to modest yields.

In order to better understand the events leading to the formation of chalcogenochromenes, a control experiment involving propargylamine **1m** containing a methoxy group adjacent to the selenium atom was carried out. Compound **8** bearing a fused 7-membered ring was isolated as the sole product, suggesting a different pathway in the cyclization cascade.

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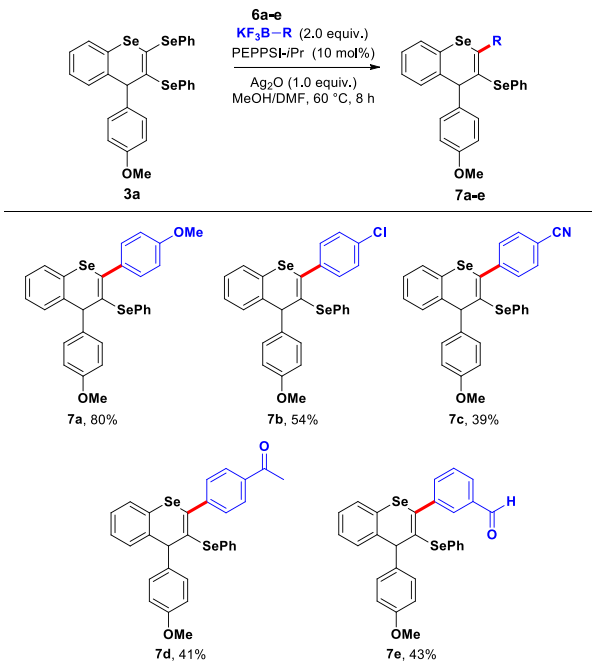
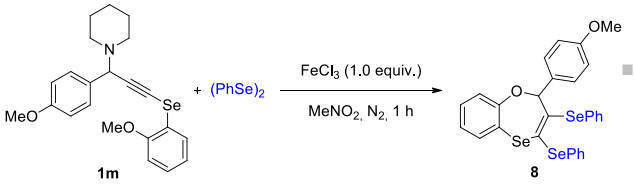
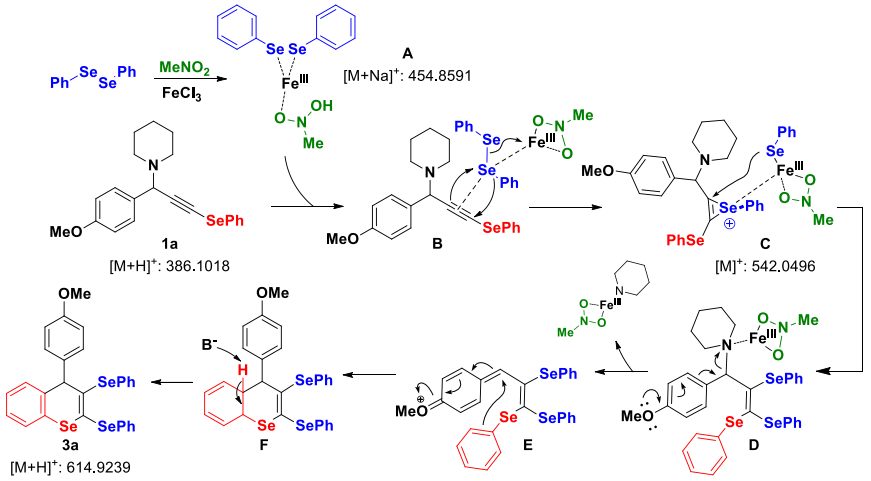
Table 6. Scope for the Suzuki-Miyaura cross-coupling of 3a with potassium aryl trifluoroborate salts.



A plausible mechanism for the cyclization of the organochalcogen propargylamines based on information collected by high-resolution mass spectrometry (see supporting information for details) and the experiments described above is illustrated in Scheme 3. Activation of diphenyl selenide by $FeCl_3$ in $MeNO_2$ generates the activated complex **A** (m/z: 454.8591, $[M+Na]^+$), which is intercepted by **1a** to form seleniranium ion **C** (m/z: 542.0496, $[M]^+$).[14] Attack by phenylselenide leads to intermediate **D**, which then expels the activated piperidinyl leaving group to form the stabilized cation **E**. A quick intramolecular cyclization follows to give **F**. In the final step, the aromaticity is re-established by proton abstraction, delivering product **3a** (m/z: 614.9239 $[M+H]^+$). In the case of compounds **3d-f**, in which a strong activating group is not present in the structure of the starting materials **1d-f**, we speculate that the expulsion of the piperidinyl moiety and the cyclization take place concomitantly (*i.e.* F forms directly from D).



Scheme 2. Control experiment.



Scheme 3. Proposed mechanism for the formation of 4*H*-selenochromens.

This mechanism accounts for some of the experimental observations: strongly electron-donating groups in R^1 (Table 2) facilitate the expulsion of the piperidinyl leaving group in intermediate **D**, while *ortho*-substituents in R^1 introduce steric clash between these groups, the phenyl selenide shown in red and the piperidinyl moiety, making **D** more unstable (Scheme 3). Similarly, the significantly lower yield observed when the piperidinyl moiety was replaced by a morpholinyl group in substrate **1** (Table 1, entry 17) may be due to competitive chelation of the Lewis acid $FeCl_3$ in intermediate **D**. The detection of complex **A** indicates that a polar solvent is required in order to stabilize iron-containing species, which is in agreement with the results observed in entries 7–9 (Table 1). Finally, the control experiment shown in Scheme 2 indicates the trapping of **E** by the *o*-methoxy group adjacent to the selenium atom, strongly suggesting the intermediacy of this species.

Conclusion

In summary, we have described the synthesis of 4*H*-chalcogenochromene prepared via the iron(III)-promoted cyclization of organochalcogen propargylamines in the presence of diaryl dichalcogenides. Products with variations in the

carbocyclic ring and at positions 2, 3 and 4 were obtained in moderate to excellent yields. In addition, we demonstrated the chemoselective C2-functionalization with four different electrophiles as well as the arylation of the same position with potassium aryl trifluoroborate salts via Suzuku-Miyaura reaction, adding nine more examples to the final scope.

Experimental Section

General procedure for the iron-promoted cyclization of organochalcogen propargylamines and diaryl dichalcogenides. A 10 mL-vial was charged with $FeCl_3$ (81 mg, 0.5 mmol, 1.0 equiv.), the appropriate diaryl dichalcogenide (0.6 mmol, 1.2 equiv.) and nitromethane (1 mL). The vial was then flushed with N_2 and then the mixture was stirred at room temperature for 15 min. The appropriate organochalcogen propargylamine **1a-l** (0.5 mmol, 1.0 equiv.) was then diluted in nitromethane (2 mL) and added to the reaction vial via syringe. The mixture was stirred at 70 °C under a N_2 flow until full consumption of the starting material was observed by TLC. The mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography using the mixture of solvents indicated.

4-(4-Methoxyphenyl)-2,3-bis(phenylselanyl)-4*H*-selenochromene (3a): Product **3a** was isolated by column chromatography (hexane:ethyl acetate 95:5) as an orange oil (288 mg, 94%). Reaction time 1h. **IR** ν_{max} (cm^{-1}): 2954, 2853, 2833, 2939, 1525, 1458, 1428, 1391, 1207, 1141, 989, 713, 668. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 2H), 7.46 – 7.41 (m, 2H), 7.26 (m, 7H), 7.18 – 7.11 (m, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.87 (dd, *J* = 7.1, 1.7 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 2H), 4.93 (s, 1H), 3.71 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.3, 137.2, 133.8, 133.8, 132.0, 131.9, 131.5, 130.5, 130.3, 129.7, 129.3, 129.2, 128.7, 128.4, 128.1, 127.9, 127.5, 126.9, 120.2, 113.4, 56.1, 55.2. **^{77}Se NMR** (57 MHz, in $CDCl_3$) δ 484.0, 475.1, 463.6 (d, J_{Se-H} = 7.9 Hz). **HRMS** calcd for $C_{28}H_{24}OSe_3$ (ESI-TOF, [M + H]$^+$): 614.9239. Found: 614.9258.

4-(2,6-Dimethoxyphenyl)-2,3-bis(phenylselanyl)-4*H*-selenochromene (3b): Product **3b** was isolated by column chromatography (hexane:ethyl acetate 90:10) as a yellow solid (196 mg, 61%). mp 162-164 °C. Reaction time 3h. **IR** ν_{max} (cm^{-1}): 2892, 2831, 2738, 1521, 1423, 1387, 1197, 1071, 711, 668. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 2H), 7.39 (d, *J* = 17.0 Hz, 6H), 7.19 (s, 3H), 7.01 (s, 1H), 6.96 – 6.84 (m, 3H), 6.48 (d, *J* = 8.3 Hz, 2H), 5.76 (s, 1H), 3.68 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4, 136.6, 136.1, 132.6, 131.6, 130.6, 129.9, 129.4, 128.9, 128.9, 128.8, 128.3, 127.2, 126.5, 126.3, 126.2, 126.1, 123.4, 120.7, 104.0, 55.6, 46.6. **^{77}Se NMR** (57 MHz, in $CDCl_3$) δ 519.1, 423.7, 415.7 (d, J_{Se-H} = 9.8 Hz). **HRMS** calcd for $C_{29}H_{24}O_2Se_3$ (ESI-TOF, [M]$^+$): 643.9272. Found: 643.9256.

4-(2,5-Dimethoxyphenyl)-2,3-bis(phenylselanyl)-4*H*-selenochromene (3c): Product **3c** was isolated by column chromatography (hexane: ethyl acetate 95:5) as a brown oil (167 mg, 52%). Reaction time 3h. **IR** ν_{max} (cm^{-1}): 2956, 2831, 2738, 1497, 1443, 1391, 1173, 989, 709, 668. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 2H), 7.35 (dd, *J* = 19.3, 6.8 Hz, 5H), 7.19 (dd, *J* = 15.2, 7.5 Hz, 6H), 7.09 – 6.96 (m, 2H), 6.63 (s, 2H), 5.55 (s, 1H), 3.67 (s, 3H), 3.60 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.5, 150.4, 136.8, 135.2, 134.6, 133.5, 130.8, 130.7, 130.2, 129.8, 129.6, 129.3, 129.0, 128.7, 127.9, 127.5, 127.3, 126.7, 122.2, 115.0, 112.8, 111.7, 55.8, 55.7, 51.0. **HRMS** calcd for $C_{29}H_{24}O_2Se_3$ (ESI-TOF, [M]$^+$): 643.9272. Found: 643.9298.

2,3-bis(Phenylselanyl)-4-(*p*-tolyl)-4*H*-selenochromene (3d): Product **3d** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (200 mg, 67%). Reaction time 2h. **IR** ν_{max} (cm^{-1}): 2952, 2823, 2758, 1601, 1585, 1426, 1391, 989, 707, 666. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 6.4 Hz, 2H), 7.38 (d, *J* = 6.6 Hz, 2H), 7.20 (dd, *J* = 13.8, 5.6 Hz, 7H), 7.09 (d, *J* = 7.3 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 1H), 4.88 (s, 1H), 2.18 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.2, 136.7, 136.2, 133.8, 133.6, 132.0, 131.4, 130.5, 130.4, 129.7, 129.3, 129.2, 128.7, 128.4, 128.1, 127.9, 127.5, 127.4, 126.9, 120.4, 56.4, 21.0. **HRMS** calcd for $C_{28}H_{22}Se_3$ (ESI-TOF, [M]$^+$): 597.9217. Found: 597.9235.

4-Phenyl-2,3-bis(phenylselanyl)-4*H*-selenochromene (3e): Product **3e** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (172 mg, 59%). Reaction time 5h. **IR** ν_{max} (cm^{-1}): 2954, 1521, 1426, 1391, 989, 707, 666. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.7, 6.4 Hz, 2H), 7.45 (d, *J* = 6.4 Hz, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.27 – 7.16 (m, 11H), 7.14 (s, 1H), 6.87 – 6.79 (m, 1H), 4.92 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.7, 137.0, 133.8, 133.8, 133.6, 131.6, 130.4, 129.8, 129.3, 129.2, 129.2, 128.8, 128.4, 128.1, 128.0, 127.6, 127.5, 126.9, 126.6, 120.6, 56.7. **HRMS** calcd for $C_{27}H_{20}Se_3$ (ESI-TOF, [M]$^+$): 583.9061. Found: 583.9085.

4-(4-Bromophenyl)-2,3-bis(phenylselanyl)-4*H*-selenochromene (3f): Product **3f** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (73 mg, 22%). Reaction time 5h. **IR** ν_{max} (cm^{-1}): 2950, 2825, 1521, 1426, 1391, 978, 707, 666. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 6.3, 2.9 Hz, 3H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.44 (d, *J* = 6.6 Hz, 2H), 7.34 – 7.29 (m, 5H), 7.20 – 7.15 (m, 3H), 6.99 (d, *J* = 8.2 Hz, 2H), 6.87 (d, *J* = 7.4 Hz, 1H), 4.91 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ: 138.8, 136.6, 134.1, 134.1, 133.8, 132.3, 131.7, 131.2, 129.6, 129.5, 129.4, 129.3, 128.9, 128.6, 128.5, 128.3, 127.9, 127.7, 127.3, 120.7, 56.3. **HRMS** calcd for $C_{27}H_{19}BrSe_3$ (ESI-TOF, [M]$^+$): 661.8166. Found: 661.8143.

6-Fluoro-4-(4-methoxyphenyl)-2,3-bis(phenylselanyl)-4*H*-selenochromene (3i): Product **3i** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a red oil (211 mg, 67%). Reaction time 3h. **IR** ν_{max} (cm^{-1}): 2956, 2900, 2739, 1680, 1529, 1458, 1436, 1184, 1119, 709, 668. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 (q, *J* = 3.0 Hz, 2H), 7.45 – 7.40 (m, 2H), 7.24 (d, *J* = 6.1 Hz, 4H), 7.13 – 7.04 (m, 4H), 6.99 – 6.88 (m, 3H), 6.68 (d, *J* = 8.3 Hz, 2H), 4.93 (s, 1H), 3.67 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.8 (d, *J* = 248.8 Hz), 158.5, 137.3, 136.6 (d, *J* = 8.0 Hz), 136.2 (d, *J* = 8.0 Hz), 133.8 (d, *J* = 4.9 Hz), 133.6, 132.0, 131.7, 129.8, 129.5, 129.3, 128.7, 128.5, 128.0, 127.7, 127.0, 116.7 (d, *J* = 21.7 Hz), 116.6 (d, *J* = 21.7 Hz), 113.6, 56.4, 55.2. **HRMS** calcd for $C_{28}H_{21}FOSe_3$ (ESI-TOF, [M]$^+$): 631.9072. Found: 631.9093.

4-(4-Methoxyphenyl)-2,3-bis(phenylselanyl)-4*H*-thiochromene (3k): Product **3k** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (144 mg, 51%). Reaction time 3h. **IR** ν_{max} (cm^{-1}): 2954, 2739, 1527, 1458, 1393, 1207, 991, 713, 666. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55 (d, *J* = 6.1 Hz, 1H), 7.32 – 7.23 (m, 9H), 7.19 – 7.08 (m, 5H), 6.96 (d, *J* = 3.4 Hz, 1H), 6.73 (d *J* = 8.0 Hz, 2H), 4.81 (s, 1H), 3.72 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.5, 134.8, 133.5, 132.8, 132.3, 131.6, 129.9, 129.7, 129.4, 128.5, 128.1, 128.0, 127.5, 127.4, 126.4, 125.8, 125.7, 124.6, 112.7, 112.6, 54.1, 51.2. **HRMS** calcd for $C_{28}H_{22}OSSe_2$ (ESI-TOF, [M]$^+$): 565.9722. Found: 565.9740.

(4-(4-Methoxyphenyl)-4*H*-tellurochromene-2,3-diyl)bis(phenylselane) (3l): Product **3l** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a brown oil (186 mg, 56%). Reaction time 4h. **IR** ν_{max} (cm^{-1}): 2952, 2739, 1527, 1458, 1391, 1207, 989, 709, 666. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 6.0 Hz, 2H), 7.44 (d, *J* = 6.1 Hz, 2H), 7.33 – 7.20 (m, 7H), 7.14 (t, *J* = 6.0 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 7.0 Hz, 1H), 6.69

(d, *J* = 8.7 Hz, 2H), 4.93 (s, 1H), 3.71 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4, 137.3, 133.8, 133.8, 132.0, 131.9, 131.5, 130.5, 130.4, 129.7, 129.4, 129.3, 128.7, 128.4, 128.2, 127.9, 127.5, 126.9, 120.2, 113.4, 56.1, 55.2. **HRMS** calcd for $C_{28}H_{22}OSe_2Te$ (ESI-TOF, $[M]^+$): 663.9063. Found: 663.9053.

4-(4-Methoxyphenyl)-2,3-bis(naphthalen-2-ylselanyl)-4*H*-selenochromene (4b): Product **4b** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a brown solid (264 mg, 74%); mp: 104-107 °C. Reaction time 5h. **IR** ν_{max} (cm^{-1}): 2944, 2887, 2743, 1456, 1205, 1141, 1000, 782, 715, 670. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.73 (t, *J* = 7.9 Hz, 2H), 7.59 (dd, *J* = 14.4, 8.5 Hz, 2H), 7.54 – 7.37 (m, 7H), 7.33 – 7.23 (m, 4H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 1H), 6.78 – 6.70 (m, 1H), 6.63 (d, *J* = 8.5 Hz, 2H), 5.96 (s, 1H), 3.65 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.3, 134.5, 134.1, 133.8, 133.3, 133.2, 133.1, 132.8, 132.8, 132.0, 131.8, 131.1, 130.9, 130.7, 129.7, 129.3, 129.2, 128.9, 128.6, 128.0, 127.7, 127.7, 127.6, 127.3, 126.6, 126.5, 126.3, 125.4, 125.4, 122.3, 119.9, 113.4, 55.1, 49.4. **HRMS** calcd for $C_{36}H_{26}OSe_3$ (ESI-TOF, $[M]^+$): 713.9479. Found: 713.9265.

4-(4-Methoxyphenyl)-2,3-bis(o-tolylselanyl)-4*H*-selenochromene (4c): Product **4c** was isolated by column chromatography (hexane:ethyl acetate 95:5) as an orange oil (189 mg, 59%). Reaction time 6h. **IR** ν_{max} (cm^{-1}): 2950, 2739, 1458, 1413, 1393, 1207, 1140, 1000, 709, 668. **^{1}H NMR** (300 MHz $CDCl_3$) δ 7.43 – 7.35 (m, 2H), 7.20 – 7.10 (m, 6H), 7.04 – 6.93 (m, 6H), 6.61 (s, 2H), 4.71 (s, 1H), 3.61 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4, 141.3, 137.0, 136.1, 135.3, 133.6, 133.2, 131.9, 130.9, 130.5, 129.4, 129.3, 128.7, 128.6, 128.0, 127.9, 127.4, 127.3, 126.9, 126.8, 126.7, 118.3, 113.5, 113.4, 55.9, 55.2, 22.8, 21.7. **HRMS** calcd for $C_{30}H_{27}OSe_3$ (ESI-TOF, $[M + H]^+$): 642.9552. Found: 642.9563.

2,3-bis((4-Fluorophenyl)selanyl)-4-(4-methoxyphenyl)-4*H*-selenochromene (4d): Product **4d** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a brown oil (198 mg, 61%). Reaction time 5h. **IR** ν_{max} (cm^{-1}): 2959, 2741, 1529, 1458, 1436, 1182, 1119, 981, 799, 711. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H), 7.46 – 7.41 (m, 2H), 7.31 – 7.24 (m, 2H), 7.18 – 7.13 (m, 3H), 7.04 - 6.95 (m, 5H), 6.70 (d, *J* = 7.6 Hz, 2H), 4.87 (s, 1H), 3.72 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.5 (d, *J* = 248 Hz), 161.2 (d, *J* = 248 Hz), 158.4, 137.1, 136.5 (d, *J* = 8.0 Hz), 136.0 (d, *J* = 8.0 Hz), 133.6 (d, J = 18.0 Hz), 131.6 (d, J = 17.7 Hz), 130.4, 129.6, 129.3, 128.5, 128.4, 128.2, 127.6, 127.0, 120.7, 116.6 (d, *J* = 5.1 Hz), 116.3 (d, *J* = 5.1 Hz), 113.5, 56.2, 55.2. **HRMS** calcd for $C_{28}H_{20}F_2OSe_3$ (ESI-TOF, $[M]^+$): 649.8978. Found: 649.8953.

4-(4-Methoxyphenyl)-2,3-bis((4-(trifluoromethyl)phenyl)selanyl)-4*H*-selenochromene (4e): Product **4e** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a brown oil (202 mg, 54%). Reaction time 6h. **IR** ν_{max} (cm^{-1}): 2959, 2743, 1549, 1460, 1277, 1084, 1039, 979, 799, 709. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56 – 7.34 (m, 8H), 7.27 (d, *J* = 6.9 Hz, 1H), 7.14 (t, *J* = 6.9 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 7.1 Hz, 1H), 6.64 (d, *J* = 8.5 Hz, 2H), 4.90 (s, 1H), 3.65 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.8, 136.9, 135.9, 135.4, 135.2, 134.7, 133.1, 132.7, 131.9, 131.6, 131.6, 131.4, 129.8, 128.7 (q, *J* = 32 Hz), 128.5, 128.2, 127.5, 126.2 (q, *J* = 2.3 Hz), 125.9 (q, *J* = 284 Hz), 122.3 (q, *J* = 284 Hz), 113.7, 113.5, 57.1, 55.3. **HRMS** calcd for $C_{30}H_{22}F_6OSe_3$ (ESI-TOF, $[M + H]^+$): 750.8987. Found: 750.8965.

(4-(4-Methoxyphenyl)-4*H*-selenochromene-2,3-diyl)bis(phenylsulfane) (4f): Product **4f** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a brown oil (189 mg, 73%). Reaction time 3h. **IR** ν_{max} (cm^{-1}): 2952, 2739, 1458, 1426, 1391, 1207, 989, 709, 666. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.2 Hz, 2H), 7.44 (d, *J* = 5.7 Hz, 2H), 7.29 – 7.25 (m, 7H), 7.16 (s, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.91 – 6.87 (m, 1H), 6.71 (d, *J* = 8.3 Hz, 2H), 4.82 (s, 1H), 3.73 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.5, 135.4, 135.0, 133.8, 133.6, 133.3, 132.0, 131.6, 129.3, 129.2, 129.0, 128.5, 127.9, 127.8, 127.3, 126.7, 125.7, 123.6, 113.6, 113.4, 55.2, 53.2. **HRMS** calcd for $C_{28}H_{22}OS_2Se$ (ESI-TOF, $[M]^+$): 518.0277. Found: 518.0293.

4-(4-Methoxyphenyl)-2,3-bis((4-(trifluoromethyl)phenyl)tellanyl)-4*H*-selenochromene (4g): Product **4g** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a brown oil (200 mg, 47%). Reaction time 3h. **IR** ν_{max} (cm^{-1}): 2952, 2739, 1458, 1391, 1205, 1140, 989, 709, 606. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 6.7 Hz, 2H), 7.44 (d, *J* = 7.1 Hz, 2H), 7.34 – 7.22 (m, 5H), 7.15 (s, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 6.5 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 2H), 4.93 (s, 1H), 3.73 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4, 137.3, 134.6, 133.8, 133.8, 132.0, 131.9, 131.5, 130.4 (q, *J* = 32 Hz), 130.4, 129.7, 129.5, 129.4, 129.3, 128.7, 128.4, 128.2, 127.9, 127.4 (q, *J* = 2.3 Hz), 126.9 (q, *J* = 284 Hz), 120.2 (q, *J* = 284 Hz), 113.4, 56.1, 55.2. **HRMS** calcd for $C_{30}H_{22}F_6OSeTe_2$ (ESI-TOF, $[M + H]^+$): 850.8781. Found: 850.8778.

General Procedure for the reaction addition of elecrophiles to C-2. A solution of **3a** (0.1 mmol, 1.0 equiv.) in THF (1 mL) was added to a 10 mL pre-flushed flask under nitrogen flow via syringe. The solution was cooled to –78 °C and then *n*-butyllithium 2 M (60 μL, 0.12 mmol, 1.2 equiv.) was added dropwise. The solution was stirred at this temperature for one hour and then the indicated electrophile (0.12 mmol, 1.2 equiv.) was slowly added. The mixture was warmed to RT and stirred for 1 h. The reaction was then diluted with ethyl acetate and the solvent was in sequence removed under reduced pressure. The residue was purified by flash column chromatography using the indicated mixture of solvents as eluent.

4-(4-Methoxyphenyl)-3-(phenylselanyl)-4*H*-selenochromene (5a): Product **5a** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (36 mg, 79%). **IR** ν_{max} (cm^{-1}): 2833, 2739, 1458, 1207, 1140, 998, 711, 668. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 5.2 Hz, 5H), 7.18 (d, *J* = 13.4 Hz, 2H), 7.03 (s, 1H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.90 (s, 1H), 3.80 (s, 1H), 3.77 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.6, 137.0, 133.6, 132.9, 130.3, 129.7, 129.4, 129.1, 128.8, 127.8, 127.5, 127.4, 127.1, 126.9, 117.4, 113.7, 55.2, 54.5. **HRMS** calcd for $C_{22}H_{17}OSe_2$ (ESI-TOF, $[M - H]^+$): 456.9610. Found: 456.9636.

4-(4-Methoxyphenyl)-3-(phenylselanyl)-2-deuterium-4*H*-selenochromene (5b): Product **5b** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (32 mg, 70%). **IR** ν_{max} (cm^{-1}): 2952, 2739, 2501, 1458, 1205, 1140, 1000, 713, 670. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 3.6 Hz, 2H), 7.40 (d, *J* = 6.5 Hz, 1H), 7.31 – 7.19 (m, 6H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.80 – 6.71 (m, 2H), 4.88 (s, 1H), 3.74 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.5, 137.0, 133.6, 132.9, 130.3, 129.7, 129.4, 129.0, 128.7, 127.8, 127.4, 127.4, 126.9, 126.8, 113.7, 55.2, 54.4. **HRMS** calcd for $C_{22}H_{19}DOSe_2$ (ESI-TOF, $[M + H]^+$): 459.9824. Found: 459.9845.

(4-(4-Methoxyphenyl)-3-(phenylselanyl)-4*H*-selenochromen-2-yl)(4-nitrophenyl)metha-nol (5c): Product **5c** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow solid (30 mg, 49%); **MP** 151-153 °C. **IR** ν_{max} (cm^{-1}): 3416, 2831, 1458, 1296, 1208, 1143, 991, 720, 676. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 7.3 Hz, 3H), 7.32 – 7.24 (m, 3H), 7.22 – 7.16 (m, 2H), 7.02 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 6.6 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 2H), 6.51 (s, 1H), 5.02 (s, 1H), 3.72 (s, 3H), 2.74 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.5, 148.2, 147.6, 139.9, 138.0, 133.1, 131.6, 129.6, 129.6, 129.4, 128.8, 128.4, 128.0, 127.7, 127.4, 127.1, 126.9, 126.4, 123.7, 113.5, 75.0, 56.7, 55.2. **HRMS** calcd for $C_{29}H_{21}NO_2Se_2$ (ESI-TOF, $[M - OH]^+$): 591.9930. Found: 591.9946.

(4-(4-Methoxyphenyl)-3-(phenylselanyl)-4*H*-selenochromen-2-yl)trimethylsilane (5d): Product **5d** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (37 mg, 70%). **IR** ν_{max} (cm^{-1}): 2956, 2851, 2831, 1458, 1205, 1140, 1002, 806, 711, 668. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 1H), 7.33 (dd, *J* = 5.5, 2.0 Hz, 2H), 7.25 (d, *J* = 2.1 Hz, 1H), 7.21 – 7.15 (m, 4H), 7.13 – 7.08 (m, 2H), 6.94 – 6.89 (m, 1H), 6.74 – 6.63 (m, 2H), 5.02 (s, 1H), 3.71 (s, 3H), 0.39 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.9, 137.5, 133.3, 133.2, 131.5, 131.2, 131.1, 129.9, 128.9, 128.8, 128.2, 126.9, 126.7, 126.2, 113.3, 113.0, 57.9, 54.7, 0.0. **HRMS** calcd for $C_{25}H_{27}OSe_2Si$ (ESI-TOF, $[M + H]^+$): 531.0156. Found: 531.0138.

General procedure for the Suzuki Coupling Reaction. To a 10 mL vial were added in sequence 3a (122 mg, 0.2 mmol, 1.0 equiv.), potassium organotrifluoroborate (0.4 mmol, 2.0 equiv.), PEPPSI-*i*Pr (14 mg, 20 μmol, 10 mol%), silver (I) oxide (46 mg, 0.2 mmol, 1.0 equiv.), MeOH/DMF (1:3) (4 mL) and triethylamine (56 μL, 0.4 mmol, 2.0 equiv.). The mixture was stirred at 60 °C until total consumption of 3a was observed by TLC. After cooling to RT, the reaction was diluted with EtOAc and washed with saturated of NH_4Cl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was then purified by flash column chromatography.

2,4-bis(4-Methoxyphenyl)-3-(phenylselanyl)-4*H*-selenochromene (7a): Product **7a** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (90 mg, 80%). Reaction time 8h. **IR** ν_{max} (cm^{-1}): 2956, 2741, 1553, 1456, 1205, 1136, 998, 879, 804, 706. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 6.2 Hz, 2H), 7.23 (d, *J* = 8.7 Hz, 2H), 7.18 – 7.11 (m, 5H), 6.87 (d, *J* = 8.6 Hz, 3H), 6.73 (d, *J* = 8.7 Hz, 2H), 5.00 (s, 1H), 3.74 (s, 3H), 3.67 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.0, 158.3, 138.1, 134.3, 133.5, 132.3, 132.3, 131.3, 131.0, 130.6, 129.6, 129.1, 128.7, 128.6, 127.5, 127.3, 126.9, 122.8, 113.7, 113.5, 55.7, 55.3, 55.2. **HRMS** calcd for $C_{29}H_{25}O_2Se_2$ (ESI-TOF, $[M + H]^+$): 565.0180. Found: 565.0162.

2-(4-Chlorophenyl)-4-(4-methoxyphenyl)-3-(phenylselanyl)-4*H*-selenochromene (7b): Product **7b** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (61 mg, 54%). Reaction time 10h. **IR** ν_{max} (cm^{-1}): 2956, 2739, 1680, 1458, 1207, 1140, 981, 715, 668. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 9.1, 5.4 Hz, 2H), 7.35 – 7.32 (m, 3H), 7.25 – 7.17 (m, 9H), 6.96 – 6.89 (m, 1H), 6.75 (d, *J* = 8.6 Hz, 2H), 5.02 (s, 1H), 3.72 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4, 138.4, 137.7, 134.6, 134.0, 133.6, 132.1, 130.9, 130.2, 129.7, 129.2, 129.1, 128.6, 128.4, 127.7, 127.4, 126.9, 124.5, 113.7, 113.6, 55.7, 55.2. **HRMS** calcd for $C_{28}H_{21}ClOSe_2$ (ESI-TOF, $[M]^+$): 567.9611. Found: 567.9640.

4-(4-(4-Methoxyphenyl)-3-(phenylselanyl)-4*H*-selenochromen-2-yl)benzonitrile (7c): Product **7c** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (44 mg, 39%). Reaction time 8h. **IR** ν_{max} (cm^{-1}): 2956, 2741, 2155, 1458, 1393, 1207, 1140, 806, 709, 670. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.55 – 7.45 (m, 3H), 7.31 – 7.17 (m, 9H), 6.98 – 6.92 (m, 1H), 6.76 (d, *J* = 8.7 Hz, 2H), 5.06 (s, 1H), 3.74 (d, *J* = 3.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.5, 144.7, 137.5, 134.0, 133.6, 132.1, 131.8, 130.5, 130.3, 129.8, 129.3, 129.2, 128.5, 128.6, 127.9, 127.6, 127.1, 126.2, 118.6, 113.8, 112.1, 56.0, 55.2. **HRMS** calcd for $C_{29}H_{22}NOSe_2$ (ESI-TOF, $[M + H]^+$): 560.0026. Found: 560.0013.

1-(4-(4-(4-Methoxyphenyl)-3-(phenylselanyl)-4*H*-selenochromen-2-yl)phenyl)ethanone (7d): Product **7d** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (47 mg, 41%). Reaction time 8h. **IR** ν_{max} (cm^{-1}): 2954, 2741, 1626, 1458, 1207, 1141, 802, 715, 670. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 2H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.49 – 7.44 (m, 1H), 7.33 (d, *J* = 7.1 Hz, 2H), 7.25 – 7.17 (m, 7H), 6.94 (q, *J* = 4.2 Hz, 1H), 6.80 – 6.73 (m, 2H), 5.04 (s, 1H), 3.74 (s, 3H), 2.60 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.4, 158.4, 144.8, 137.7, 136.9, 133.6, 133.0, 132.0, 130.8, 130.0, 129.8, 129.7, 129.2, 128.8, 128.6, 128.3, 127.8, 127.5, 127.0, 125.2, 113.6, 55.8, 55.2, 26.7. **HRMS** calcd for $C_{30}H_{24}O_2Se_2$ (ESI-TOF, $[M]^+$): 576.0107. Found: 576.0124.

3-(4-(4-Methoxyphenyl)-3-(phenylselanyl)-4*H*-selenochromen-2-yl)benzaldehyde (7e): Product **7e** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (48 mg, 43%). Reaction time 7h. **IR** ν_{max} (cm^{-1}): 2954, 2739, 2635, 1643, 1458, 1207, 1141, 756, 713, 670. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.91 (s, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.48 (dd, *J* = 6.7, 2.7 Hz, 1H), 7.31 (d, *J* = 6.6 Hz, 2H), 7.27 – 7.16 (m, 7H), 6.95 (dd, *J* = 5.8, 3.2 Hz, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 5.06 (s, 1H), 3.75 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 191.7, 158.4, 141.1, 137.6, 136.4, 135.5, 133.5, 132.8, 131.9, 130.9, 130.7, 130.0, 129.7, 129.5, 129.2, 129.0, 128.6, 128.6, 127.7, 127.5, 127.0, 125.4, 113.6, 55.9, 55.2. **HRMS** calcd for $C_{29}H_{23}O_2Se_2$ (ESI-TOF, $[M + H]^+$): 563.0023. Found: 563.0046.

5-(4-methoxyphenyl)-2,3-bis(phenylselanyl)-5*H*-benzo[e][1,4]oxaselenepine (8): Product **8** was isolated by column chromatography (hexane:ethyl acetate 95:5) as a yellow oil (132 mg, 42%). Reaction time 3h. **IR** ν_{max} (cm^{-1}): 2952, 2803, 2738, 1458, 1391, 1205, 1140, 989, 709, 666. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 7.4 Hz), 7.44 (2H, d, *J* = 6.2 Hz), 7.33 – 7.20 (6H, m), 7.18 – 7.10 (2H, m), 7.06 (2H, d, *J* = 8.6 Hz), 6.90 – 6.84 (1H, m), 6.70 (2H, d, *J* = 8.7 Hz), 4.93 (1H, s), 3,71 (3H, s). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4, 137.3, 133.8, 133.8, 132.0, 131.9, 131.5, 130.5, 130.4, 129.7, 129.4, 129.3, 128.7, 128.4, 128.2, 127.9, 127.5, 126.9, 120.3, 113.4, 56.1, 55.2. **HRMS** calcd for $C_{28}H_{23}O_2Se_3$ (ESI-TOF, $[M + H]^+$): 630.9188 . Found: 630.9152.

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References

[1] a) D. Kumar, P. Sharma, H. Singh, K. Nepali, G. K. Gupta, S. K. Jain, F. Ntie-Kang, *RSC Adv.* **2017**, *7*, 36977-36999; b) D. Harel, D. Schepmann, H. Prinz, R. Brun, T. J. Schmidt, B. Wünsch, *J. Med. Chem.* **2013** *56*, 7442-7448; c) N. F. L. Machado, M. P. M. Marques, *Curr. Bioact. Compd.* **2010**, *6*, 76-89; d) B. Godoi, A. Sperança, D. F. Back, R. Brandão, C. W. Nogueira, G. Zeni, *J. Org. Chem.* **2009**, *74*, 3469-3477; e) W. A. L. van Otterlo, E. L. Ngidi, S. Kuzvidza, G. L. Morgans, S. S. Moleele, C. B. de Koning, *Tetrahedron* **2005**, *61*, 9996-10006. f) D. Joulain, R. Tabacchi, *Phytochemistry* **1994**, 37, 1769-1770.

[2] R. Pratap, V. J. Ram. *Chem. Rev.* **2014**, *114*, 10476-10526.

[3] a) H. Sashida, M. Yoshida, H. Minamida, M. Teranishi, *J. Heterocyclic Chem*. **2002**, 39, 405-409. b) H. Sashida, H. Minamida, *J. Chem. Soc. Perkin Trans.* **1999**, *12*, 1665-1670.

[4] a) J. Sayers, R. J. Payne, N. Winssinger, *Chem. Sci.* **2018**, *9*, 896-903; b) S. Shaaban, F. Sasse, T. Burkholz, C. Jacob, *Bioorg. Med. Chem.* **2014**, *22*, 3610-3619; c) L. Engman, J. Persson, T. K. Vessman, M. Ekstrom, M. Berglund, C.-M. Andersson, *Free Radical Biol. Med.* **1995**, *19*, 441-452; (d) A. Nyska, T. Waner, M. Pirak, M. Albeck, M. Sredni, *Arch. Toxicol.* **1989**, *63*, 386-393.

[5] a) R. Mousa, R. N. Dardashti, N. Metanis, *Angew. Chem. Int. Ed.* **2017**, *56*, 15818-15827; b) I. M. De Oliveira, S. S. N. Vasconcelos, C. S. Barbeiro, T. C. Correra, A. Shamim, D. C. Pimenta, I. Caracelli, J. Zukerman-Schpector, H. A. Stefani, F. Manarin, *New J. Chem.* **2017**, *41*, 9884-9888; c) C. M. Weekley, H. H. Harris, *Chem. Soc. Rev.* **2013**, *42*, 8870-8894; d) I. P. Beletskaya, V. P. Ananikov, *Chem. Rev.* **2011**, *111*, 1596-1636; e) J. V. *J.* Comasseto, *Braz. Chem. Soc.* **2010**, *21*, 2027-2031.

[6] a) A. M. S. Recchi, D. F. Back, G. Zeni, *J. Org. Chem.* **2017**, *82*, 2713-2723; b) B. Godoi, A. Sperança, C. A. Bruning, D. F. Back, P. H. Menezes, C. W. Nogueira, G. Zeni, *Adv. Synth. Catal.* **2011**, *353*, 2042-2050; c) B. Godoi, A. Sperança, C. A. Bruning, D. F. Back, P. H. Menezes, C. W. Nogueira, G. Zeni, *Adv. Synth. Catal.* **2011**, *353*, 2042-2050.

[7] a) X. He, H. Wang, X. Cai, Q. Li, J. Tao, Y. Shang, *Org. Biomol. Chem.* **2018**, *16*, 7191-7202; b) A. Fürstner, *ACS Cent. Sci.* **2016**, *2*, 778-789; c) I. Bauer, H.-J Knölker,. *Chem. Rev.* **2015**, *115*, 3170-3387; d) M. Wang, K. Ren, L. Wang, *Adv. Synth. Catal.* **2009**, *351*, 1586-1594; e) T. Xu, Z. Yu, L. Wang, *Org. Lett.* **2009**, *11*, 2113-2116; f) G. Cantagrel, B. de Carné-Carnavalet, C. Mayer, J. Cossy, *Org. Lett.* **2009**, *11*, 4262-4265.

[8] T. A. C. Goulart, J. A. G. Kazmirski, D. F. Back, G. Zeni, *Adv. Synth. Catal.* **2019**, *361*, 96-104.

[9] H.-A. Du, R.-Y. Tang, C.-L. Deng, Y. Liu, J.-H. Li, X.-G. Zhang, *Adv. Synth. Catal.* **2011**, *353*, 2739-2748.

[10] I. M. De Oliveira, D. C. Pimenta, J. Zukerman-Schpector, H. A. Stefani, F. Manarin, *New J. Chem.* **2018**, *42*, 10118-10123.

[11] CCDC 1903966 (**3b**) contains the supplementary crystallographic data for this paper. These data can obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] a) C. R. B. Rhoden, G. Zeni, *Org. Biomol. Chem.* **2011**, *9*, 1301-1313; b) M. Nakamura, L. Ilies, S. Otsubo, E. Nakamura, *Org. Lett.* **2006**, *8*, 2803-2805; c) M. Nakamura, L. Ilies, S. Otsubo, E. Nakamura, *Angew. Chem. Int. Ed.* **2006**, *45*, 944-947; d) H. J. Reich, M. J. Bevan, B. Ö. Gudmundsson, C. L. Puckett, *Angew. Chem. Int. Ed.* **2002**, *41*, 3436-3439; e) H. J. Reich, M. D. Bowe, *J. Am. Chem. Soc.* **1990**, *112*, 8994-8995.

[13] R. Cella, R. L. O. R. Cunha, A. E. S. Reis, D. C. Pimenta, C. F. Klitzke, H. A. Stefani, *J. Org. Chem.* **2006**, *71*, 244-250.

[14] S. E. Denmark, W. R. Collins, M. D. Cullen, *J. Am. Chem. Soc.* **2009**, *131*, 3490-3492.

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FULL PAPER

Iron (III)-Promoted Synthesis of Substituted 4*H*-Chalcogenochromenes and Chemoselective Functionalization

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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