Synthesis of Diarylselenides through Rh-catalyzed Direct Diarylation of Elemental Selenium with Benzamides

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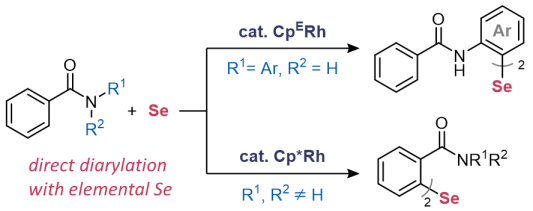
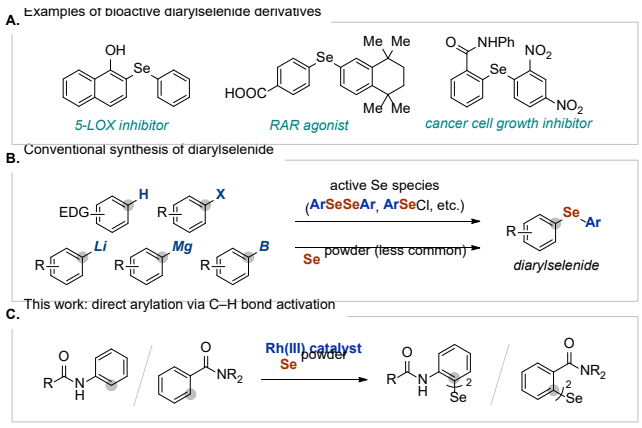


ABSTRACT: Diarylselenides are a representative class of molecules in organoselenium compounds. We herein report a Rh-catalyzed direct diarylation of selenium with benzamide derivatives. The use of elemental selenium as the Se source is intriguing in the view of atom economy, cost, stability, and handling. A series of diarylselenides with amide moieties were readily accessible through the directed C–H activation. The intermediacy of electrophilic Se(IV) species was indicated by the control experiments.

Selenium-containing compounds have gained diverse interests from chemical and pharmaceutical communities due to their versatile therapeutic activity and unique redox behavior.[1-4] Diaryselenide is a representative key structure for various bioactive compounds involving 5-LOX inhibitors, RAR agonists, cancer cell growth inhibitors, etc. (Scheme 1A).[5-6] The redox activity and the nucleophilicity of Se atom can be modulated by changing aryl substituents.

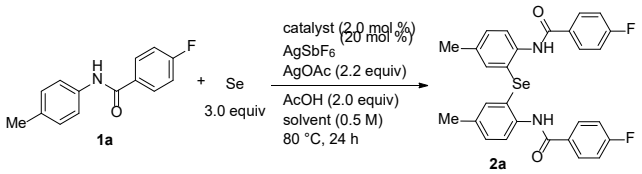
Scheme 1. Synthetic Approaches to Diarylselenides



Conventional synthetic methods have relied on the use of reactive selenium species such as arylselenyl halides,[7] diaryldiselenides,[8] and aryl selenocyanates.[9] These reagents are, however, usually prepared via cumbersome processes, difficult to handle, and of limited function group tolerance (Scheme 1B).[10,11] Thus, development of methods approaching diarylselenides in an efficient and straightforward fashion is highly desired. Undoubtably, utilization of elemental selenium (or selenium powder) as the Se source is intriguing in view of atom economy, cost, stability, and handling.[12] Reported procedures for the arylation of elemental selenium utilize haloarenes,[13] arylboronic acids,[14] or activated electron-rich arenes (electrophilic aromatic substitution)[15] as the aryl sources, while, to the best of our knowledge, there is no report on diarylation through C–H bond cleavage of unactivated aromatic compounds. On the other hand, a first direct catalytic C–H selenium annulation was reported by Nishihara in 2017 with the aid of Ni catalyst and 8-aminoquinoline bidentate directing group.[8b] Our group also established a direct annulation of secondary amides with elemental selenium adopting Rh catalyst.[16] As continuous interest in this field, we herein report a Rh-catalyzed diarylation of selenium with benzamide derivatives (Scheme 1C). For the C–H activation of *N*-arylbenzamides, the site-selectivity is usually not a trivial issue,[17] whereas the developed protocol showed good chemoselectivity and regioselectivity. The intermediacy of electrophilic Se(IV) species was indicated by the control experiments.

At the outset, we examined the reaction of a secondary amide **1a** with selenium powder under the conditions with a standard Cp*Rh catalyst (Table 1). The desired product **2a** was obtained in 15% yield using $[Cp^*RhCl_2]_2$ (2.0 mol %), $AgSbF_6$ (20 mol %), AgOAc (2.2 equiv), and AcOH (2 equiv) in $PhCF_3$ solvent at 80 °C (entry 1). The connectivity of the Se atom and the aniline fragments within **2a** was confirmed by an X-ray crystallographic analysis (CCDC 2182413). The product yield was not considerably improved with other metal catalysts (entries 2–4). To our delight, an electron-deficient Cp^E ligated was effective for this reaction, giving **2a** in 36% yield (entry 5). We then screened the solvent (see the Supporting Information for additional data). Several solvents showed higher productivity and HFIP (hexafluoro-isopropanol) was the most effective to afford **2a** in 56% yield (entry 8). Replacement of AgOAc with AgTFA slightly improved the product yield (entry 9). The reaction could be conducted at 60 °C with comparable efficiency (entries 10–11). This reaction was successfully proceeded in 1.0 mmol scale (Scheme 2).

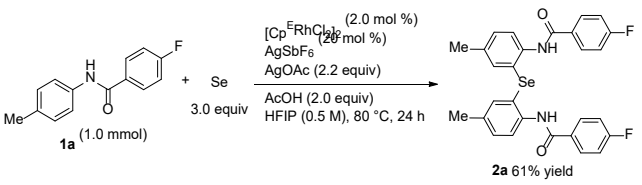
Table 1. Optimization of the Reaction Conditions [a]



entry	cat.	solvent	**2a** (%) [b]
1	$[Cp^*RhCl_2]_2$	$PhCF_3$	15
2[c]	$Cp^*Co(CO)I_2$	$PhCF_3$	18
3	$[Cp^*IrCl_2]_2$	$PhCF_3$	8
4	$[Ru(p\text{-cymene})Cl_2]_2$	$PhCF_3$	13
5	$[Cp^ERhCl_2]_2$	$PhCF_3$	36
6	$[Cp^ERhCl_2]_2$	$CHCl_3$	50
7	$[Cp^ERhCl_2]_2$	TFE	46
8	$[Cp^ERhCl_2]_2$	HFIP	56
9[d]	$[Cp^ERhCl_2]_2$	HFIP	61 (59)
10[d,f]	$[Cp^ERhCl_2]_2$	HFIP	63 (64)
11[d,f,g]	$[Cp^ERhCl_2]_2$	HFIP	65 (68)

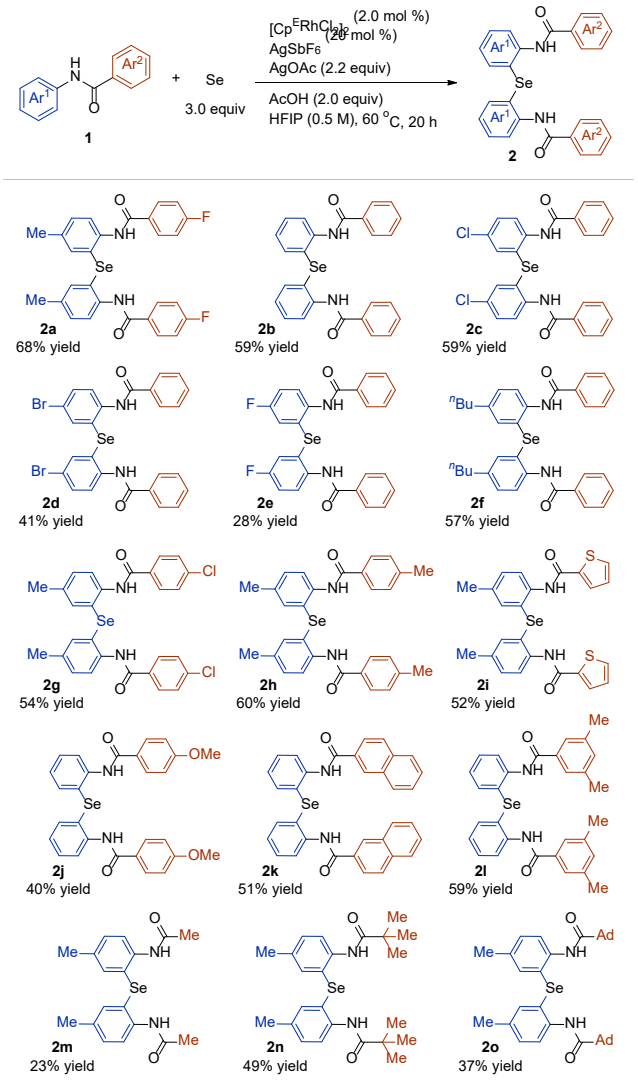
[a] Reaction conditions: **1a** (0.2 mmol), Se (0.6 mmol), catalyst (2.0 mol%), $AgSbF_6$ (0.04 mmol), AgOAc (0.44 mmol), and AcOH (0.4 mmol) in solvent (0.4 mL) at 80 °C for 24 h. [b] Determined by NMR analysis. Isolated yield in parentheses. [c] With 4.0 mol % of catalyst. [d] AgTFA was used instead of AgOAc. [e] With 1.0 mol% of catalyst and 10 mol% of $AgSbF_6$. [f] 60 °C. [g] 20 h.

Scheme 2. Mmol-Scale Synthesis



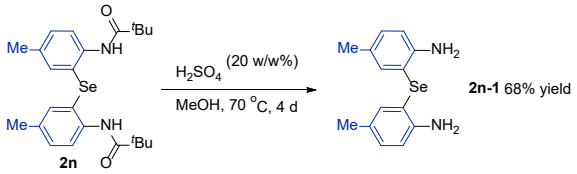
With the optimized conditions of Table 1 entry 11, the scope of secondary *N*-arylbenzamides was evaluated (Scheme 3). *N*-Phenylbenzamide (**1b**) reacted smoothly to afford the desired product **2b** in 59% yield. For the aniline moiety, halogen (**1c**–**1e**) as well as alkyl (**1f**) substituents were compatible to give the corresponding selenides in moderate yields. For the benzoyl fragment, para-substituted (**1g**, **1h**, **1j**), 3,5-dimethyl (**1l**), thienyl (**1i**), and naphtyl (**1k**) substrates were successfully converted to the target products. Interestingly, an acetanilide **1m** was also applicable to the present reaction albeit with lower efficiency. Adopting sterically demanding pivaloyl (**1n**) and 1-adamantanecarbonyl (**1o**) groups, the target compounds were obtained in relatively higher yields. The pivaloyl group could be removed under acidic conditions to afford the corresponding aniline **1n-1** (Scheme 4). Unfortunately, the reaction of meta- and ortho-substituted benzamides resulted in rather complicated, and the product yield could not be determined (not shown).

Scheme 3. Scope of *N*-Arylbenzamides Substrates [a]



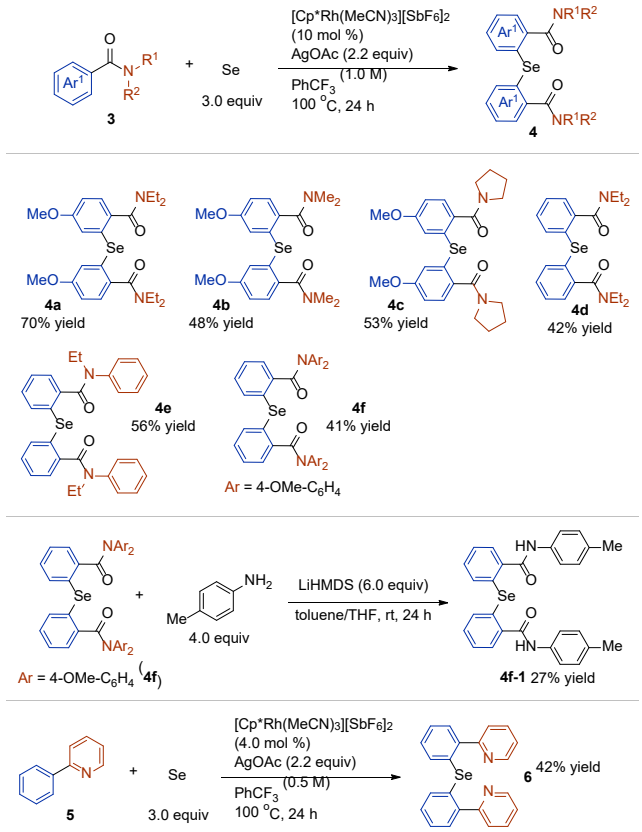
[a] Reaction conditions: **1** (0.2 mmol), Se (0.6 mmol), $[Cp^{E}RhCl_2]_2$ (2.0 mol %), AgTFA (0.44 mmol), and AcOH (0.4 mmol) in HFIP (0.4 mL) at 60 °C for 20 h.

Scheme 4. Protecting Group Removal



Next, we examined the direct selenation of *N,N*-disubstituted benzamides (Scheme 5). For these class of compounds, the standard Cp*Rh catalyst was considerably effective, and a model reaction of **3a** and selenium powder produced the target product **4a** in 70% yield using $[Cp^{*}Rh(MeCN)_3][SbF_6]_2$ (10 mol%) as the catalyst and AgOAc (2.2 equiv) as the oxidant at 100 °C in $PhCF_3$ solvent (see the Supporting Information for the additional data). A series of *N,N*-dialkyl amides **3b**–**3d** were smoothly reacted to give the corresponding selenides **4b**–**4d** in moderate yields. This protocol was also applicable to an *N*-alkyl-*N*-aryl (**3e**) and an *N,N*-diaryl (**3f**) amides. The positional selectivity of selenation for **4f** was confirmed by transamidation: reaction of **4f** with *p*-toluidine afforded **4f-1**. In addition, 2-phenylpyridine (**5**) was successfully coupled with selenium to give the selenide **6** in 42% yield.[18]

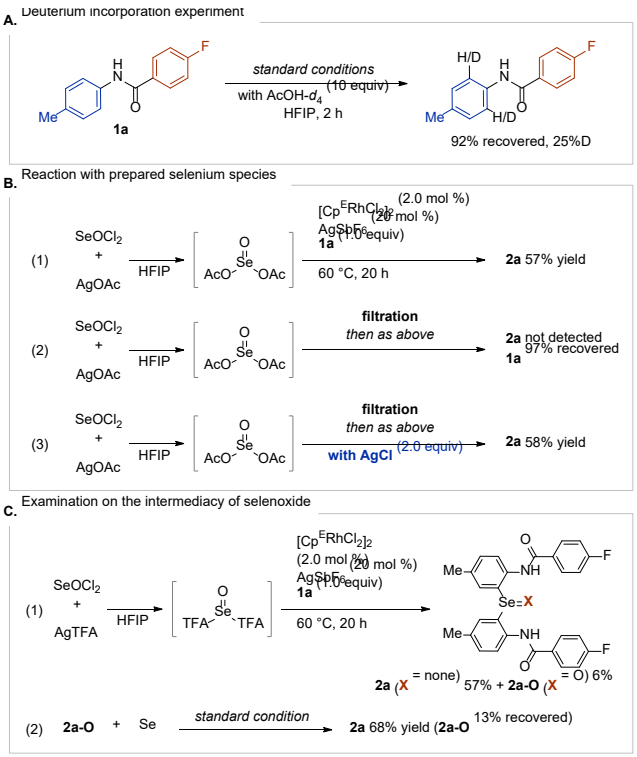
Scheme 5. Scope of *N,N*-Disubstituted Benzamides [a]



[a] Reaction conditions: **3** (0.2 mmol), Se (0.6 mmol) $[Cp^{*}Rh(MeCN)_3][SbF_6]_2$ (10 mol %), and AgOAc (0.44 mmol) in $PhCF_3$ (0.2 mL) at 100 °C for 24 h.

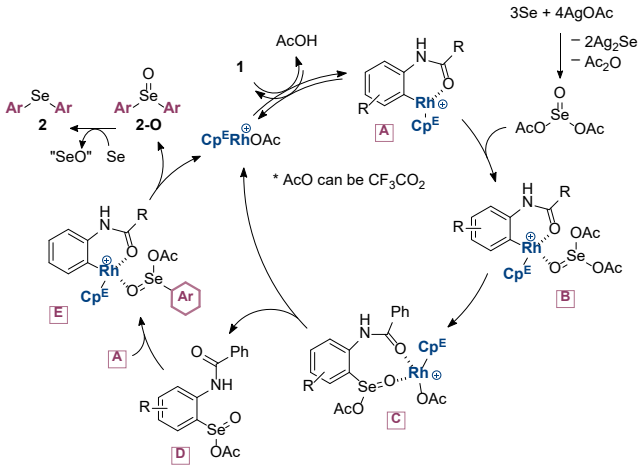
To gain some insights into the reaction mechanism, we conducted several control experiments (Scheme 6). Deuterium incorporation to **1a** under the standard conditions was examined adopting AcOH-d_4 as a deuterium source. After 2 h in the absence of selenium powder, the recovered **1a** had a considerable 25% deuterium content at the ortho positions, indicating the reversibility of C–H bond activation step (Scheme 6A). In our previous report, $SeO(OAc)_2$ formed by treating selenium powder with AgOAc was assumed to be an active electrophile for the direct selenation. To test the intermediacy of this Se(IV) species, we prepared $SeO(OAc)_2$ and subsequently treated it with **1a** under the catalytic conditions. As expected, the product **2a** was obtained in 57% yield (Scheme 6B-1). In sharp contrast, no reaction took place when Ag salts were removed by filtration in prior to react with **1a** (Scheme 6B-2). Addition of extra AgCl after filtration restored the catalytic activity to give **2a** in 58% yield (Scheme 6B-3). These results support the indispensability of Ag(I) salts for the C–Se bond formation while the mechanistic detail is unclear at this stage. In the case AgTFA was used instead of AgOAc for the similar experiment, **2a** was obtained in 57% yield along with the corresponding selenoxide **2a-O** (6% yield). Additionally, conversion of this selenoxide to **2a** under the reaction conditions was confirmed (Scheme 6C), which indicated that **2a-O** was involved in the mechanism as an intermediate.[16c]

Scheme 6. Control Experiments



On the basis of these results and information from reported literatures, a possible catalytic cycle for the reaction of **1** with selenium is proposed as shown in Scheme 7. Thus, a catalytically active species, which is assumed to be [$Cp^ERh(OAc)$][SbF_6] (OAc may be $OCOCF_3$) formed through anion exchange in the reaction medium, induces the coordination-assisted C–H activation of **1** to form a six-membered metallacycle **A**. Meanwhile, $SeO(OAc)_2$ (OAc may be $OCOCF_3$) is given by the disproportionation of elemental selenium and coordinates to the complex **A**. The nucleophilic carbon atom within **B** substitutes the leaving group on the Se atom to give **C**. This step should be facilitated by Ag salts according to the Scheme 6B while the detail is still unclear. The liberated **D** coordinate to another rhodacycle species **A** to form an intermediate **E**. The nucleophilic carbon atom would replace the OAc leaving group on the Se atom, eventually affording the primary product selenoxide **2-O**. This would be reduced to the desired diarylselenide **2** by low valent selenium species.

Scheme 7. A Proposed Reaction Mechanism



In conclusion, we have developed a Rh-catalyzed diarylation of elemental selenium with benzamide derivatives. A series of diarylselenides are readily accessible through the directing-group-assisted C–H activation. The reaction shows high regioselectivity, and the mechanistic study suggests that Se(IV) species are involved in the reactions in contrast to well-established Se(-II) species as active intermediates in the reported literatures. This work represents a new reaction mode in chalcogen chemistry and related works are performing in our laboratories.

EXPERIMENTAL SECTION

Nuclear magnetic resonance spectra were measured at 400 MHz (^{1}H NMR), at 100 MHz ($^{13}C\{^1H\}$ NMR), at 376 MHz ($^{19}F\{^1H\}$ NMR), and at 76 MHz ($^{77}Se\{^1H\}$ NMR) in 5 mm NMR tubes. ^{1}H NMR chemical shifts were reported in ppm relative to the resonance of TMS (δ 0.00) or the residual solvent signals at δ 2.50 for DMSO-d_6. $^{13}C\{^1H\}$ NMR chemical shifts were reported in ppm relative to the residual solvent signals at δ 77.2 for $CDCl_3$ and at δ 39.5 for DMSO-d_6. $^{77}Se\{^1H\}$ NMR chemical shifts were reported in ppm relative to the external standard diphenyldiselenide at δ 460.0. High resolution mass spectra (HRMS) were recorded by APCI-TOF. Preparative gel permeation chromatography (GPC) was conducted with two in-line YMC-GPC T2000 preparative columns. Thin layer chromatography analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck silica gel $60F_{254}$. Silica gel column chromatography was performed using Wakosil® C-200 (64~210 μm).

All manipulations were performed under N_2 using standard Schlenk techniques unless otherwise noted. Amide compounds were prepared by standard condensation of the corresponding acid chlorides and amines similarly to the literature:[19] all **1** and **3** are known in literatures.[20] [Cp^ERhCl_2]$_2$ was prepared according to the literature procedure.[21] All other reagents were purchased from suppliers and used without further purification.

Rh-catalyzed Synthesis of Diarylselenides 2a (Scheme 2). To a screw-top glass tube were added [Cp^ERhCl_2]$_2$ (17.0 mg, 0.02 mmol, 2.0 mol%), $AgSbF_6$ (68.7 mg, 0.2 mmol, 20 mol%), anilide **1a** (229 mg, 1.0 mmol), Se (237 mg, 3.0 mmol, 3.0 equiv), and AgTFA (480 mg, 2.2 mmol, 2.2 equiv). HFIP (2.0 mL) and AcOH (114 μL, 2.0 mmol, 2.0 equiv) were added via syringe. The suspension was stirred at 60 °C using aluminum heating blocks for 20 h under N_2. The resulting mixture was diluted with $CHCl_3$ and filtered through a pad of Celite eluting with $CHCl_3$ and EtOAc. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc/$CHCl_3$ = 7/1/1) to give **2a** as white solid (163.2 mg, 61% yield).

General Procedure for the Rh-catalyzed Synthesis of Diarylselenides 2 (Scheme 3). To a screw-top glass tube were added [Cp^ERhCl_2]$_2$ (3.4 mg, 4.0×10^{-3} mmol, 2.0 mol%), $AgSbF_6$ (13.7 mg, 0.04 mmol, 20 mol%), anilide **1** (0.2 mmol), Se (47.4 mg, 0.6 mmol, 3.0 equiv), and AgTFA (97.2 mg, 0.44 mmol, 2.2 equiv). HFIP (0.4 mL, 0.5 M) and AcOH (23 μL, 0.4 mmol, 2.0 equiv) were added via syringe. The suspension was stirred at 60 °C using aluminum heating blocks for 20 h under N_2. The resulting mixture was diluted with $CHCl_3$ and filtered through a pad of Celite eluting with $CHCl_3$ and EtOAc. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography or preparative TLC and, if indicated, by GPC.

***N,N'*-(selenobis(4-methyl-2,1-phenylene))bis(4-fluorobenzamide) (2a)** Purified by silica gel column chromatography (*n*-hexane/EtOAc/$CHCl_3$ = 7/1/1), white solid (36.6 mg, 68% yield), single crystals suitable for the X-ray crystallographic analysis were obtained by slow evaporation from the $CHCl_3$ solution, m.p. 193-194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 2H), 8.06 (d, J = 8.0 Hz, 2H), 7.79-7.57 (m, 4H), 7.30-7.23 (m, 2H), 7.17 (dd, J = 8.4, 1.6 Hz, 2H), 7.14-7.03 (m, 4H), 2.20 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.1 (d, J = 251.5 Hz), 164.5, 136.1, 136.0, 135.0, 130.9, 130.7 (d, J = 3.1 Hz), 129.6 (d, J = 9.0 Hz), 123.2, 120.6, 116.0 (d, J = 22.0 Hz), 20.8; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -107.1; $^{77}Se\{^1H\}$ NMR (76 MHz, $CDCl_3$) δ 264.1; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{28}H_{23}F_2N_2O_2Se$ 537.0887; Found 537.0879.

***N,N′*-(selenobis(2,1-phenylene))dibenzamide (2b).** Purified by silica gel column chromatography (*n*-hexane/EtOAc/$CHCl_3$ = 7/1/1), white solid (27.8 mg, 59% yield), m.p. 165-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 2H), 8.31 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.78-7.70 (m, 4H), 7.57-7.49 (m, 2H), 7.49-7.36 (m, 8H), 7.04 (td, *J* = 7.6, 1.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.7, 138.6, 134.8, 134.5, 132.3, 130.2, 129.0, 127.2, 125.9, 122.9, 120.9; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{21}N_2O_2Se$ 473.0763; Found 473.0764.

***N,N′*-(selenobis(4-chloro-2,1-phenylene))dibenzamide (2c).** Purified by silica gel column chromatography (*n*-hexane/EtOAc/$CHCl_3$ = 3/1/1), white solid (31.7 mg, 59% yield), m.p. 220-221 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 2H), 8.25 (d, *J* = 8.8 Hz, 2H), 7.77-7.68 (m, 4H), 7.59-7.52 (m, 2H), 7.51-7.44 (m, 6H), 7.38 (dd, *J* = 8.4, 2.4 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.6, 137.3, 134.2, 134.1, 132.5, 130.8, 130.6, 129.1, 127.1, 124.1, 121.6; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{19}Cl_2N_2O_2Se$ 540.9983; Found 540.9999.

***N,N′*-(selenobis(4-bromo-2,1-phenylene))dibenzamide (2d).** Purified by silica gel column chromatography (*n*-hexane/EtOAc/$CHCl_3$ = 6/1/1 to 3/1/1), white solid (26.0 mg, 41% yield), m.p. 231-233 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 2H), 8.21 (d, *J* = 8.8 Hz, 2H), 7.75-7.68 (m, 4H), 7.62 (d, *J* = 2.0 Hz, 2H), 7.60-7.43 (m, 8H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.6, 137.9, 137.0, 134.1, 133.6, 132.6, 129.2, 127.1, 124.4, 121.7, 118.3; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{19}Br_2N_2O_2Se$ 628.8973; Found 628.8965.

***N,N′*-(selenobis(4-fluoro-2,1-phenylene))dibenzamide (2e).** Purified by silica gel column chromatography (*n*-hexane/EtOAc/$CHCl_3$ = 6/1/1 to 4/1/1), white solid (14.1 mg, 28% yield), m.p. 198-199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 2H), 8.15 (dd, *J* = 8.4, 5.2 Hz, 2H), 7.82-7.69 (m, 4H), 7.59-7.50 (m, 2H), 7.50-7.42 (m, 4H), 7.18-7.06 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 159.7 (d, *J* = 249.6 Hz), 134.6 (d, *J* = 3.0 Hz), 134.1, 132.4, 129.1, 127.2, 125.1 (d, *J* = 7.8 Hz), 123.1 (d, *J* = 7.1 Hz), 121.0 (d, *J* = 24.0 Hz), 117.2 (d, *J* = 22.1 Hz); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -114.8; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{19}F_2N_2O_2Se$ 509.0574; Found 509.0558.

***N,N′*-(selenobis(4-butyl-2,1-phenylene))dibenzamide (2f).** Purified by silica gel column chromatography (*n*-hexane/EtOAc/$CHCl_3$ = 20/1/1 to 10/1/1), white solid (33.4 mg, 57% yield), m.p. 175-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 2H), 8.18 (d, *J* = 8.0 Hz, 2H), 7.76-7.68 (m, 4H), 7.56-7.48 (m, 2H), 7.47-7.37 (m, 4H), 7.28 (d, *J* = 2.0 Hz, 2H), 7.18 (dd, *J* = 8.4, 2.0 Hz, 2H), 2.42 (t, *J* = 7.6 Hz, 4H), 1.54-1.34 (m, 4H), 1.24 (h, *J* = 7.2 Hz, 4H), 0.85 (t, *J* = 7.2 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.5, 140.7, 136.4, 134.7, 134.6, 132.1, 130.2, 128.9, 127.2, 122.7, 120.4, 34.9, 33.4, 22.3, 14.0; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{34}H_{37}N_2O_2Se$ 585.2015; Found 585.2015.

***N,N′*-(selenobis(4-methyl-2,1-phenylene))bis(4-chlorobenzamide) (2g).** Purified by silica gel column chromatography (*n*-hexane/EtOAc/$CHCl_3$ = 7/1/1), white solid (30.8 mg, 54% yield), m.p. 251-252 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 2H), 7.89 (d, *J* = 8.8 Hz, 4H), 7.57 (d, *J* = 8.8 Hz, 4H), 7.39 (d, *J* = 7.6 Hz, 2H), 7.25-7.07 (m, 4H), 2.19 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 164.5, 136.5, 136.3, 135.5, 134.3, 132.8, 129.5, 129.1, 128.6, 128.1, 126.3, 20.4; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{28}H_{23}Cl_2N_2O_2Se$ 569.0296; Found 569.0283.

***N,N′*-(selenobis(4-methyl-2,1-phenylene))bis(4-methylbenzamide) (2h).** Purified by silica gel column chromatography (*n*-hexane/EtOAc/$CHCl_3$ = 7/1/1), white solid (31.8 mg, 60% yield), m.p. 215-217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 2H), 8.16 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 4H), 7.29 (d, *J* = 1.2 Hz, 2H), 7.21 (d, *J* = 7.6 Hz, 4H), 7.17 (dd, *J* = 8.4, 1.6 Hz, 2H), 2.39 (s, 6H), 2.19 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.5, 142.6, 136.4, 135.4, 135.2, 131.8, 130.9, 129.5, 127.1, 122.7, 120.3, 21.6, 20.8; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{29}N_2O_2Se$ 529.1389; Found 529.1402.

***N,N′*-(selenobis(4-methyl-2,1-phenylene))bis(thiophene-2-carboxamide) (2i).** Purified by preparative TLC (*n*-hexane/EtOAc = 3/1), white semisolid (26.8 mg, 52% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 2H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.51 (dd, *J* = 4.8, 1.2 Hz, 2H), 7.47 (dd, *J* = 3.6, 1.2 Hz, 2H), 7.30 (d, *J* = 1.6 Hz, 2H), 7.16 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.08 (dd, *J* = 4.8, 3.6 Hz, 2H), 2.21 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.0, 139.0, 135.84, 135.81, 135.2, 131.1, 130.9, 128.7, 128.0, 123.1, 120.6, 20.8; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{21}N_2O_2S_2Se$ 513.0204; Found 513.0184.

***N,N′*-(selenobis(2,1-phenylene))bis(4-methoxybenzamide) (2j).** Purified by silica gel column chromatography (*n*-hexane/EtOAc/$CHCl_3$ = 5/1/1), white solid (21.2 mg, 40% yield), m.p. 191-193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 2H), 8.31 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.76-7.67 (m, 4H), 7.45 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.42-7.35 (m, 2H), 7.03 (td, *J* = 7.6, 1.2 Hz, 2H), 6.95-6.88 (m, 4H), 3.85 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.2, 162.8, 138.8, 134.8, 130.2, 129.1, 126.7, 125.6, 122.7, 120.8, 114.2, 55.6; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{28}H_{25}N_2O_4Se$ 533.0974; Found 533.0959.

***N,N′*-(selenobis(2,1-phenylene))bis(2-naphthamide) (2k).** Purified by silica gel column chromatography (*n*-hexane/EtOAc/$CHCl_3$ = 6/1/1 to 5/1/1), white solid (29.2 mg, 51% yield), m.p. 215-216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 2H), 8.33 (d, *J* = 9.2 Hz, 2H), 8.19 (d, *J* = 1.2 Hz, 2H), 7.89-7.82 (m, 6H), 7.76 (dd, *J* = 8.8, 1.6 Hz, 2H), 7.60-7.49 (m, 6H), 7.46-7.40 (m, 2H), 7.05 (td, *J* = 7.6, 1.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 138.6, 135.0, 134.8, 132.6, 131.6, 130.2, 129.2, 128.9, 128.1, 127.89, 127.87, 127.0, 126.0, 123.5, 123.1, 121.2; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{34}H_{25}N_2O_2Se$ 573.1076; Found 573.1076.

***N,N′*-(selenobis(2,1-phenylene))bis(3,5-dimethylbenzamide) (2l).** Purified by silica gel column chromatography (*n*-hexane/EtOAc = 6/1 to 5/1), white solid (31.2 mg, 59% yield), m.p. 179-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 2H), 8.30 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.46 (dd, *J* = 7.6, 1.2 Hz, 2H), 7.43-7.37 (m, 2H), 7.29 (s, 4H), 7.14 (s, 2H), 7.04 (td, *J* = 7.6, 1.2 Hz, 2H), 2.33 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.1, 138.7, 138.6, 134.8, 134.6, 133.9, 130.1, 125.8, 124.9,

122.9, 120.8, 21.4; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{29}N_2O_2Se$ 529.1389; Found 529.1381.

***N,N'*-(selenobis(4-methyl-2,1-phenylene))diacetamide (2m).** Purified by preparative TLC (*n*-hexane/EtOAc = 1/1), colorless oil (7.0 mg, 23% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.65 (s, 2H), 7.22 (s, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 2.26 (s, 6H), 2.05 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.9, 136.0, 135.8, 134.7, 130.4, 124.0, 121.8, 24.2, 20.9; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{21}N_2O_2Se$ 377.0763; Found 377.0767.

***N,N'*-(selenobis(4-methyl-2,1-phenylene))bis(2,2-dimethylpropanamide) (2n).** Purified by preparative TLC (*n*-hexane/EtOAc = 3/1), colorless oil (22.4 mg, 49% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.89 (s, 2H), 7.14 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.11 (d, *J* = 1.6 Hz, 2H), 2.23 (s, 6H), 1.24 (s, 18H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.8, 135.7, 135.4, 134.2, 130.4, 122.8, 120.5, 40.0, 27.6, 20.9; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{33}N_2O_2Se$ 461.1702; Found 461.1714.

***N,N'*-(selenobis(4-methyl-2,1-phenylene))bis(adamantane-1-carboxamide) (2o).** Purified by preparative TLC (*n*-hexane/EtOAc = 5/1), colorless oil (22.9 mg, 37% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 2H), 7.84 (s, 2H), 7.20-7.07 (m, 4H), 2.23 (s, 6H), 2.05 (s, 6H), 1.88-1.83 (m, 12H), 1.80-1.62 (m, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.2, 135.8, 135.1, 134.2, 130.4, 122.5, 120.1, 41.9, 39.3, 36.5, 28.2, 20.9; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{36}H_{45}N_2O_2Se$ 617.2641; Found 617.2659.

Removal of the Protecting Group (Scheme 4). To a screw-top glass tube were added **2n** (54.6 mg, 0.12 mmol), 20 w/w% aqueous H_2SO_4 (3.5 mL), and MeOH (3.5 mL). The suspension was stirred under N_2 atmosphere at 70 °C for 4 d. The resulting mixture was poured into water and washed with $CHCl_3$. The aqueous phase was neutralized with $NaHCO_3$aq and extracted with $CHCl_3$ three times. The combined organic extracts was concentrated in vacuo and purified by preparative TLC (*n*-hexane/EtOAc = 3/1) to give **2n-1** as yellow oil (23.5 mg, 68% yield).

2,2'-selenobis(4-methylaniline) (2n-1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 1.6 Hz, 2H), 6.92 (dd, *J* = 8.0, 1.6 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 2H), 3.60 (br, 4H), 2.18 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.0, 135.8, 130.5, 128.7, 115.6, 114.5, 20.4; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{17}N_2Se$ 293.0551; Found 293.0543.

General Procedure for the Rh-catalyzed Synthesis of Diarylselenides 4 (Scheme 4). To a screw-top glass tube were added $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (16.6 mg, 0.02 mmol, 10 mol%), amide **3** (0.2 mmol), Se (47.4 mg, 0.6 mmol, 3.0 equiv), and AgOAc (73.4 mg, 0.44 mmol, 2.2 equiv.). $PhCF_3$ (0.2 mL, 1.0 M) was added via syringe. The suspension was stirred at 100 °C using aluminum heating blocks for 24 h under N_2. The resulting mixture was diluted with $CHCl_3$ and filtered through a pad of Celite eluting with $CHCl_3$ and EtOAc. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography or preparative TLC and, if indicated, by GPC.

2,2'-selenobis(4-methoxy-*N,N*-diethylbenzamide) (4a). Purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/1 to 1/2), colorless oil (34.3 mg, 70% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 2.8 Hz, 2H), 6.81 (dd, *J* = 8.4, 2.4 Hz, 2H), 3.72 (s, 6H), 3.63-3.08 (m, 8H), 1.36-0.97 (m, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.8, 159.9, 133.0, 129.8, 127.6, 119.8, 113.7, 55.5, 43.2, 39.2, 14.4, 12.9; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{33}N_2O_4Se$ 493.1600; Found 493.1603.

2,2'-selenobis(4-methoxy-*N,N*-dimethylbenzamide) (4b). Purified by silica gel column chromatography (EtOAc to EtOAc/MeOH = 20/1), colorless oil (20.8 mg, 48% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 2.4 Hz, 2H), 6.83 (dd, *J* = 8.4, 2.4 Hz, 2H), 3.73 (s, 6H), 3.16-2.78 (m, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.4, 160.1, 132.5, 130.0, 128.3, 120.0, 113.8, 55.6, 39.1, 35.0; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{25}N_2O_4Se$ 437.0974; Found 437.0969.

(selenobis(4-methoxy-2,1-phenylene))bis(pyrrolidin-1-ylmethanone) (4c). Purified by silica gel column chromatography (EtOAc/MeOH = 20/1 to 10/1), colorless oil (25.9 mg, 53% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 2.4 Hz, 2H), 6.81 (dd, *J* = 8.4, 2.4 Hz, 2H), 3.72 (s, 6H), 3.59 (t, *J* = 6.8 Hz, 4H), 3.27 (t, *J* = 6.4 Hz, 4H), 1.99-1.79 (m, 8H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.6, 160.1, 133.5, 130.2, 128.1, 119.9, 113.6, 55.5, 49.0, 45.8, 26.2, 24.6; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{29}N_2O_4Se$ 489.1287; Found 489.1287.

2,2'-selenobis(*N,N*-diethylbenzamide) (4d). Purified by preparative TLC (*n*-hexane/EtOAc = 1/1), colorless oil (18.2 mg, 42% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.41 (m, 2H), 7.33-7.17 (m, 6H), 3.57 (q, *J* = 6.8 Hz, 4H), 3.19 (q, *J* = 7.2 Hz, 4H), 1.27 (t, *J* = 7.2 Hz, 6H), 1.07 (t, *J* = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.7, 140.6, 134.9, 129.6, 128.5, 127.7, 126.5, 43.1, 39.1, 14.3, 12.9; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{29}N_2O_2Se$ 433.1389; Found 433.1376.

2,2'-selenobis(*N*-ethyl-*N*-phenylbenzamide) (4e). Purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/1), colorless oil (32.2 mg, 56% yield, 0.219 mmol scale); ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-6.90 (m, 18H), 3.99 (s, 4H), 1.25 (t, *J* = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.7, 142.2, 140.1, 133.8, 130.6, 129.3, 129.1, 128.3, 128.2, 127.2, 126.5, 44.8, 13.2; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{29}N_2O_2Se$ 529.1389; Found 529.1388.

2,2'-selenobis(*N,N*-bis(4-methoxyphenyl)benzamide) (4f). Purified by silica gel column chromatography (*n*-hexane/EtOAc/$CHCl_3$ = 3/1/1 to 3/3/2), white foam (30.5 mg, 41% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 7.6, 1.2 Hz, 2H), 7.28-7.05 (m, 10H), 7.01 (td, *J* = 7.2, 1.6 Hz, 2H), 6.95 (dd, *J* = 8.0, 1.2 Hz, 2H), 6.74 (br, 8H), 3.73 (s, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.3, 158.0, 140.1, 136.1, 134.4, 130.6,

129.6, 128.7, 127.9, 126.9, 114.3, 55.5; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{42}H_{37}N_2O_6Se$ 745.1811; Found 745.1858.

bis(2-(pyridin-2-yl)phenyl)selane (6). Purified by silica gel column chromatography (*n*-hexane/EtOAc = 1/1), white foam (16.1 mg, 42% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (ddd, *J* = 4.8, 1.6, 0.8 Hz, 2H), 7.65 (td, *J* = 7.6, 1.6 Hz, 2H), 7.57-7.48 (m, 4H), 7.45 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.31 (td, *J* = 7.6, 1.2 Hz, 2H), 7.24-7.14 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.0, 148.7, 142.6, 136.0, 135.1, 133.5, 129.8, 129.1, 127.3, 123.5, 122.0; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{17}N_2Se$ 389.0551; Found 389.0557.

Transamidation (Scheme 5). To a screw-top glass tube were added **4f** (43.1 mg, 0.058 mmol), *p*-tolidine (45.3 mg, 0.232 mmol, 4.0 equiv.), LiHMDS (58.2 mg, 0.348 mmol, 6.0 equiv.), THF (0.2 mL), and toluene (0.6 mL) in glove-box. The suspension was stirred at rt for 24 h. After quenched with saturated NH_4Claq, the resulting mixture was extracted with $CHCl_3$ and concentrated in vacuo. The obtained crude material was purified by preparative TLC (hexane/EA = 10/1) to give **4f-1** as colorless oil (7.7 mg, 27% yield).

2,2'-selenobis(N-(*p*-tolyl)benzamide) (4f-1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 2H), 7.67 – 7.59 (m, 2H), 7.54 – 7.48 (m, 2H), 7.40 – 7.28 (m, 4H), 7.23 (d, *J* = 8.4 Hz, 4H), 7.05 (d, *J* = 8.4 Hz, 4H), 2.31 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 138.1, 135.2, 135.0, 134.3, 131.5, 131.0, 129.5, 129.1, 128.2, 120.1, 21.1; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{28}H_{25}N_2O_2Se$ 501.1076; Found 501.1065.

***N,N'*-(seleninylbis(4-methyl-2,1-phenylene))bis(4-fluorobenzamide) (2a-O)** To a $CHCl_3$ solution of **2a** (26.8 mg, 0.05 mmol in 1.0 mL) was added dropwise H_2O_2 (17.0 mg, 0.15 mmol, 30% w/w in water). The mixture was stirred at room temperature 18 h. After complete conversion of **2a** (monitored by TLC) the resulting mixture was diluted with $CHCl_3$ and washed by saturated $Na_2S_2O_3$aq and brine. The combined organic extracts was dried over Na_2SO_4 and concentrated in vacuo to give the title compound as white solid (27.5 mg, >99% yield). m.p. 223 °C (decomposed); ^1H NMR (400 MHz, DMSO-d_6) δ 11.37 (s, 2H), 8.07-7.89 (m, 4H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.49-7.39 (m, 6H), 7.20 (dd, *J* = 8.4, 1.6 Hz, 2H), 1.84 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 164.8 (d, *J* = 250.2 Hz), 163.9, 136.5 (d, *J* = 3.8 Hz), 134.3, 132.4, 130.7 (d, *J* = 9.3 Hz), 130.6, 130.1, 129.0, 124.6, 116.1 (d, *J* = 22.0 Hz), 20.2; $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ -108.0; HRMS (APCI) *m/z*: $[M+H]^+$ Calcd for $C_{28}H_{23}F_2N_2O_3Se$ 553.0836; Found 553.0836.

ASSOCIATED CONTENT

The Supporting Information is available free of charge athttps://pubs.acs.org.xxx

^1H, $^{13}C\{^1H\}$, $^{19}F\{^1H\}$, and $^{77}Se\{^1H\}$ NMR spectra for all products, detailed optimization studies, and X-ray crystallographic analysis (PDF)

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Notes

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