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Three-Step One-Pot Synthesis of Imidazo[2,1-*b*]chalcogenazoles *via* Intramolecular Cyclization of *N*-Alkynylimidazoles

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Abstract: Imidazo-chalcogenazoles are easily accessible from the corresponding *N*-alkynylimidazoles by a three-step, one-pot chalcogenation reaction. The generality of this reaction has been established with various substituted *N*-alkynylimidazoles as well as elemental chalcogens. By accessing the key intermediate 2-chalcogenolate-*N*-alkynylimidazole it was also possible to prepare dichalcogenide derivatives.

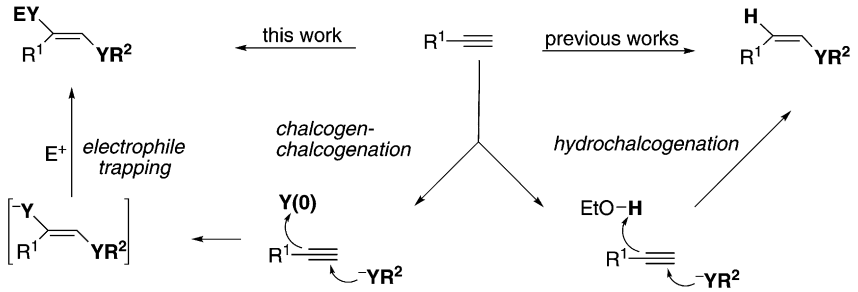
Keywords: *N*-alkynylimidazoles; chalcogen-chalcogenation; heterocycles; imidazoselenazoles; imidazothiazoles

Introduction

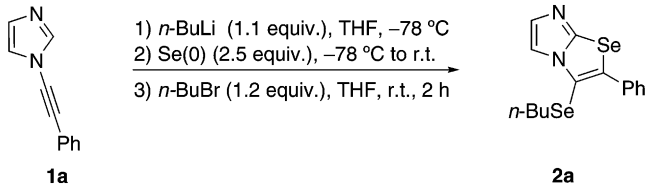
Nitrogen heterocycles are an important class of compounds due to their variety of pharmacological properties, including antifungal, antiviral and antiproliferative activities.[1] In addition, these compounds are very useful synthetic intermediates and can function as suitable building blocks to synthesize some other biologically active compounds, such as natural products.[2] Bicyclic nitrogen compounds have received extensive attention in particular in the natural products and pharmaceutical fields.[3] More specifically, fused imidazo-systems have been used as antibacterial,[4] antifungal[5] and antitumor[6] agents. The chemistry of selenium and tellurium compounds has emerged as a useful and convenient synthetic tool for the construction of more elaborated structures. Consequently, much effort has been spent to study the synthesis of new classes of organochalcogen compounds as well as to study their application as intermediates in organic synthesis. For example, the organochalcogen group is able to be easily removed by using a transmetallation reaction.[7]

There are also reports on the use of organochalcogens as substrates for new carbon-carbon, carbon-metal, carbon-halogen and carbon-heteroatom bond formation *via* lithium intermediates.[8] The organochalcogen class, mainly those with a C(sp^2)–chalcogen bond, can also be applied as electrophiles, similar to vinylic halides, in palladium cross-coupling reactions.[9] Moreover, chalcogen heterocycles are agents widely studied in view of their pharmacological properties which include antibacterial,[10] antiapoptotic,[11] antitumoral,[12] hepatoprotective,[13] anticonvulsant, antioxidant,[14] antinociceptive and anti-allodynic activities.[15]

Although several procedures have been developed for the synthesis of imidazo[2,1-*b*]thiazoles,[16] no examples involving the preparation of the correspinding selenium and tellurium derivatives have been reported in the literature. The hydrochalcogenation of alkynes is the most important and widely employed method for the preparation of vinylic chalcogenides.[17] It differs from the other hydrometallation reactions, since it proceeds in an *anti*-fashion, as a result of an *anti*-addition of an organochalcogenolate anion to the alkyne. This *anti*-addition leads to the *Z*-vinylic chalcogenide, which is stereochemically stable and the isomerization to the *E*-isomer has not been reported to date (Scheme 1, *right*). In continuation of our studies on the preparation of novel heterocycles containing a chalcogen[18] and based on the fact that currently there are no reports in the literature concerning sequential chalcogenation reactions (Scheme 1, *left*), we were encouraged to examine if imidazo[2,1-*b*]chalcogenazoles **2** could be prepared from *N*-alkynylimidazoles **1** *via* a three-step, one-pot chalcogenation sequence (Scheme 2).



Scheme 1. Chalcogen-chalcogenation (*left*) *versus* hydrochalcogenation reactions (*right*).



Scheme 2. Optimized conditions to prepare imidazo[2,1-*b*]chalcogenazoles.

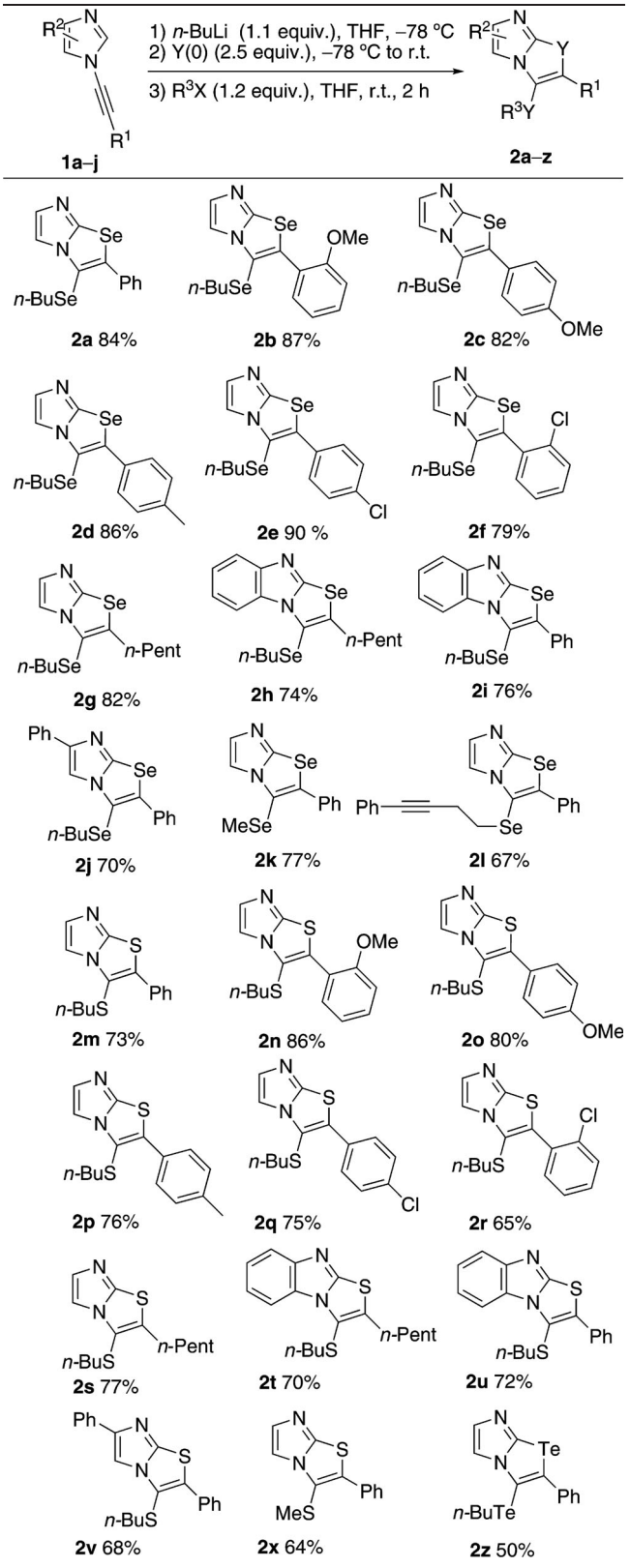
Results and Discussion

The starting *N*-alkynylimidazoles **1** were prepared using previously reported procedures.[19] At first, the anionic 2-lithium-*N*-alkynylimidazole, generated *in situ* by reaction of substrate **1a** (0.5 mmol) with *n*-BuLi (1.1 equiv.) in THF at −78 °C for 30 min, was treated with elemental selenium (2.0 equiv.) at −78 °C. After the mixture had warmed to room temperature, 1-bromobutane (1.2 equiv.) was added and stirring was continued for 2 h. This reaction conditions provided the desired product **2a** in 70% yield. A variety of temperatures for the addition of elemental selenium was tested, and we found that 0 °C gave the product **2a** in 45% yield, while at room temperature the product failed to form. Control experiments indicate that the reaction temperature was an important factor, because the 2-lithium-*N*-alkynylimidazole anion was unstable at above −78 °C. In an effort to better understand the formation of **2a** the amount of elemental selenium was increased to 2.5 and 3.0 equiv. By using this alteration, **1a** was converted to **2a** in 84% yield. A prolonged reaction time only led to a decrease in yield. These findings suggest that the optimum yield of this three-step, one-pot reaction was obtained by reacting *N*-alkynylimidazole with *n*-BuLi (1.1 equiv.) in THF at −78 °C for 30 min, followed by the addition of elemental selenium (2.5 equiv.) at −78 °C. After that, the mixture was warmed to room temperature and 1-bromobutane (1.2 equiv.) was added and the reaction was stirred for 2 h (Scheme 2).

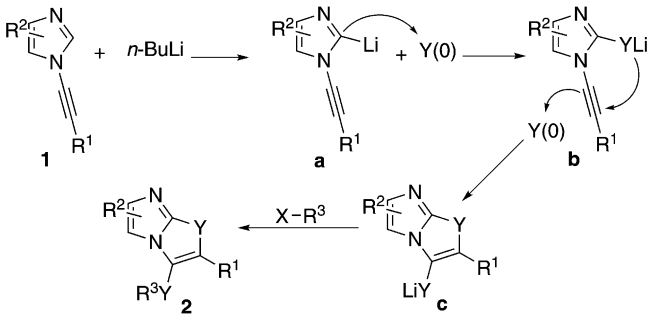
The results in Table 1 indicate the scope and limitations of the cyclization reaction of *N*-alkynylimidazoles with elemental sulfur, selenium and tellurium. In most cases, *N*-alkynylimidazoles were found to work more effectively than *N*-alkynylbenzoimidazoles. For example, compound **2a** was obtained in 84% yield while the corresponding reaction with the benzimidazole derivative gave the cyclized product **2i** in 76% yield. The reaction was not sensitive to either electronic factors or the effective bulk of the aryl group directly bonded to the alkyne. For instance, **2c** having an electron-donating *p*-methoxy group, **2e** having an electron-withdrawing group and **2b** having a hindered *o*-methoxy group showed the same behavior in this reaction. By contrast, in the case of an alkyl group directly bonded to the selenium atom, it was observed that decreasing the length of the alkyl group caused a decrease in the yields (Table 1, compounds **2a** and **2k**). Compounds **2m**–**2x** in Table 1 illustrate the results of the cyclization using elemental sulfur with several *N*-alkynylimidazoles. Compared with the selenium derivatives the reaction employing sulfur was somewhat similar giving the cyclized product in equally good yield. By contrast, the optimized reaction conditions applied to elemental tellurium failed to afford the desired Te-heterocycle derivatives. In attempts to optimize the reaction conditions for tellurium derivatives, the reaction time, after the addition of tellurium, was increased by 5 min until 30 min, at which point samples were taken and analyzed. When the reaction time had reached 30 min the product was obtained in 50% yield. Further increases in the reaction time or changes of the other parameters led to decomposition without any improvement in the yields (Table 1, compound **2z**).

A plausible mechanism for the formation of imidazo-chalcogenazoles **2a**–**z** is shown in Scheme 3. We believe that (i) the removal of hydrogen with *n*-BuLi from *N*-alkynylimidazole gives the 2-lithium-*N*-alkynylimidazole **a**; (ii) the reaction of lithium intermediate **a** with elemental chalcogen affords the chalcogenolate species **b**; (iii) the increase of the reaction temperature leads to the addition of the chalcogenate anion onto the triple bond of the alkyne and the subsequent attack to the other chalcogen atom gives the chalcogenolate species **c**; (iv) trapping of chalcogenolate

Table 1. Scope and generality of the cyclization reaction.[a]



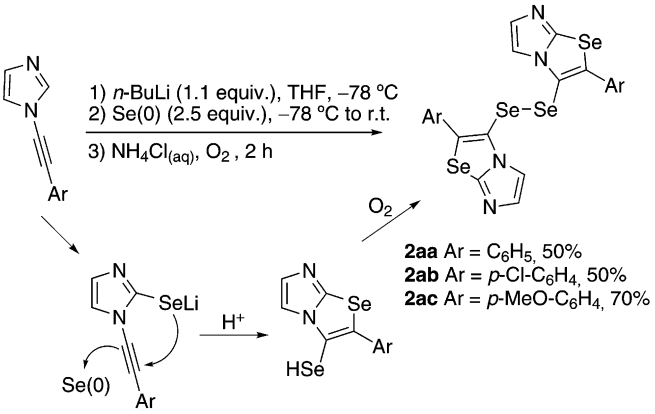
[a] Yields of isolated products.



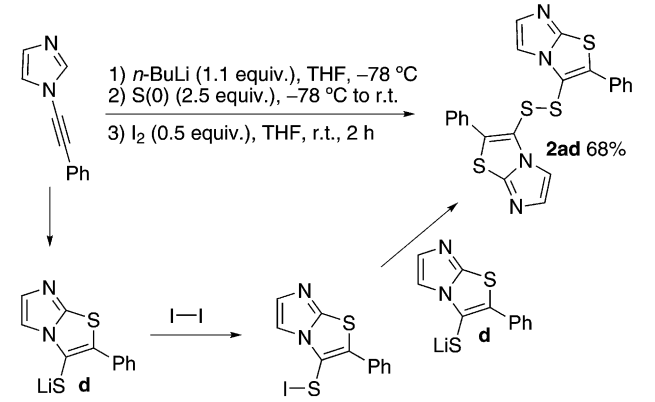
Scheme 3. Proposed mechanism for the synthesis of imidazo-[2,1-*b*]chalcogenazoles **2**.

anion **c** with an electrophile source affords the desired cyclized product **2** (Scheme 3).

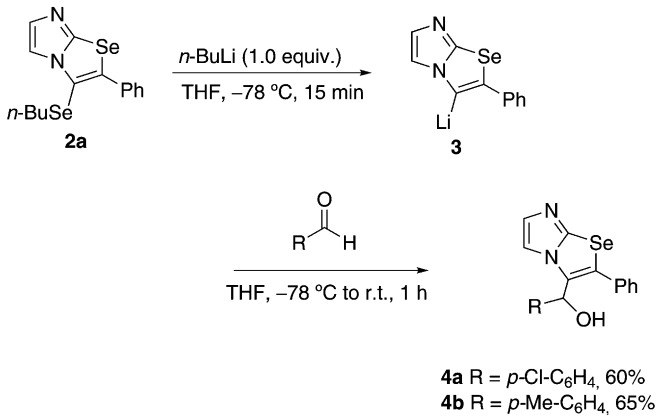
Considering the important role of diorganoyl diselenides[20] and disulfides[21] in biological processes and as synthetic intermediates in organic synthesis, we extend this approach to the synthesis of diselenides and disulfides **2aa**–**ad** (Scheme 4 and Scheme 5). After having shown that the chalcogenolate species **c** (Scheme 3) leads to cyclized product **2** *via* trapping with an electrophile source, we set out to trap the lith-



Scheme 4. Synthesis of diselenides **2aa**–**ac**.



Scheme 5. Synthesis of disulfide **2ad**.



Scheme 6. Reaction of the intermediate 3-lithium-imidazo-[2,1-*b*]selenazole **3** with aldehydes.

ium chalcogenolate intermediate **c** with an aqueous solution of NH_4Cl. The chalcogenol species formed could then be oxidized under air to give the dichalcogenides. We have been successful with our strategy and diselenides derivatives **2aa--ac** were obtained in moderate to good yields (Scheme 4); however, none of the corresponding disulfides were detected. Gratifyingly, disulfide **2ad** was isolated in 68% yield when the lithium thiolate anion **d** was allowed to react with molecular iodine (0.5 equiv.) for 2 h at room temperature (Scheme 5).

The 3-chalcogen imidazo[2,1-*b*]selenazoles obtained appear highly promising as intermediates for the preparation of more highly substituted heterocyclic compounds. To further prove the utility of our methodology, we carried out the selenium-lithium exchange reaction of product **2a** using *n*-butyllithium to prepare the lithium intermediate **3**, which would be trapped with electrophiles. Lithium-selenium exchange reactions have great importance in synthetic organic chemistry, particularly with respect to the formation of new C–C bonds.[22] The lithium intermediate **3** was prepared according to the literature method by deprotonation of 3-(phenylselenyl)-imidazo[2,1-*b*]selenazole **2a** using *n*-butyllithium (1.0 equiv.) in THF (5 mL) at –78 °C.[7a] We found that quenching the resulting lithium intermediate **3** with EtOH afforded the corresponding hydrogenated product in 78% yield. We attempted to extend this reaction to use an aldeyde as the electrophile source. The reaction with *p*-chlorobenzaldeyde and *p*-tolyl aldehyde took place giving the expected secondary alcohols **4** in 60 and 65% yields, respectively (Scheme 6).

Conclusions

In conclusion, we have succeeded in the development of a three-step, one-pot reaction of *N*-alkynylimidazole with elemental sulfur, selenium or tellurium to prepare imidazo[2,1-*b*]chalcogenazoles. In addition, when the reaction was carried out using a proton source instead of organohalides as electrophile source, we obtained dichalcogenides as the products. These results are significant since by using the same reaction conditions we obtained two classes of imidazo[2,1-*b*]chalcogenazoles. For instance, imidazo-[2,1-*b*]selenazoles were treated under selenium/lithium exchange conditions with *n*-BuLi, and trapping the lithium intermediates with aldehydes provided the corresponding secondary alcohols. We have described here a methodology to prepare a new class of organochalcogen compounds. The results of this paper demonstrate that once prepared, the organochalcogen route is a useful and attractive strategy for studies on both synthetic methodology and biologically active compounds. All compounds prepared were characterized by ^1H and ^{13}C NMR spectroscopy, and the structure of **2i** was elucidated by X-ray crystallography[23] (See Supporting Information) which confirmed the formation of the five-membered heterocycle *via* a 5-*endo*-dig cyclization process.

Experimental Section

General Procedure for the *One-Pot* Synthesis of Imidazo[2,1-*b*]selenazoles and Imidazo[2,1-*b*]-thiazoles

To a solution of the appropriate *N*-alkynylimidazole (0.5 mmol) in THF (5 mL) under argon at –78 °C was added *n*-BuLi (0.22 mL of 2.5 M solution in hexane, 0.55 mmol). The reaction mixture was stirred for 30 min at –78 °C prior to the addition of elemental chalcogen (1.25 mmol). After that, the reaction mixture was allowed to stir at room temperature to complete consumption of the chalcogen. The intermediate anionic chalcogenolate was then trapped with an appropriate alkyl electrophile (0.6 mmol). The reaction mixture was stirred at room temperature for 2 h. After this time, the mixture was diluted with ethyl acetate (20 mL) and washed with saturated NH_4Cl solution (3 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent.

3-(Butylselenyl)-2-phenylimidazo[2,1-*b*][1,3]selenazole (2a): Yield: 0.160 g (84%); mp 63–64 °C. ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.71$ (s, 1H), 7.57–7.54 (m, 2H), 7.44–7.38 (m, 3H), 7.30 (s, 1H), 2.73 (t, $J = 7.3$ Hz, 2H), 1.47 (quin, $J = 7.3$ Hz, 2H), 1.22 (sex, $J = 7.3$ Hz, 2H), 0.77 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 136.0$, 133.7, 132.6, 130.0 (2C), 128.9, 128.5, 115.4, 111.8, 32.0, 28.6, 22.4, 13.3; MS (EI, 70 eV): *m/z* (relative intensity) = 384 (7), 328 (19), 248 (5), 168 (100), 89 (36); anal. (%) calcd. for $C_{15}H_{16}N_2Se_2$: C 47.14, H 4.22, N 7.33; found: C 47.31, H 4.29, N 7.40.

3-(Butylthio)-2-phenylimidazo[2,1-*b*]thiazole (2m): Yield: 0.105 g (73%); oil. ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.70$–7.65 (m, 2H), 7.58 (s, 1H), 7.50–7.39 (m, 3H), 7.36 (s, 1H),

2.72 (t, $J=7{,}0$ Hz, 2H), 1.40 (quin, $J=7.3$ Hz, 2H), 1.23 (sex, $J=7.3$ Hz, 2H), 0.75 (t, $J=7.3$ Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=135.0$, 133.6, 131.2, 129.3 (2C), 129.0, 128.5, 118.0, 111.9, 34.0, 31.2, 21.2, 13.3. MS (EI, 70 eV): *m/z* (relative intensity) = 288 (57), 232 (100), 168 (25), 121 (74), 89 (32); anal. (%) calcd. for $C_{15}H_{16}N_2S_2$: C 62.46, H 5.59, N 9.71; found: C 62.60, H 5.64, N 9.80.

General Procedure for the *One-Pot* Synthesis of Imidazo[2,1-*b*]tellurazole 2z

To a solution of 1-(phenylethynyl)-1*H*-imidazole **1a** (0.5 mmol) in THF (5 mL) under argon at −78 °C was added *n*-BuLi (0.22 mL of 2.5 M solution in hexane, 0.55 mmol). The reaction mixture was stirred for 30 min at −78 °C prior to the addition of elemental tellurium (1.25 mmol). After the 30 min at −78 °C, the reaction mixture was allowed to stir at room temperature to complete consumption of the tellurium. The intermediate anionic tellurolate generated *in situ* was then trapped with 1-bromobutane (0.6 mmol). The reaction mixture was stirred at room temperature for 2 h. After this time, the mixture was diluted with ethyl acetate (20 mL) and washed with saturated NH_4Cl solution (3 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. Obs.: The use of tellurium - 200 mesh was required.

3-(Butyltelluronyl)-2-phenylimidazo[2,1-*b*][1,3]tellurazole (2z): Yield: 0.119 g (50%); mp 126–128 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta=7.99$ (s, 1H), 7.39 (s, 5H), 7,27 (s, 1H), 2.72 (t, $J=7.3$ Hz, 2H), 1.57 (quin, $J=7.3$ Hz, 2H), 1.20 (sex, $J=7.3$ Hz, 2H), 0.79 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=139.2$, 131.4, 130.8, 130.0 (2C), 128.4, 128.3, 121.7, 99.2, 33.4, 24.6, 13.2, 10.8; MS (EI, 70 eV): *m/z* (relative intensity) = 480 (22), 424 (22), 298 (64), 168 (100), 89 (72); HR-MS: *m/z* = 506.9352, calcd. for $C_{15}H_{16}N_2Te_2$ ($M+Na^+$): 506.9335.

General Procedure for the *One-Pot* Synthesis of 1,2-Bis[2,1-*b*][1,3]selenazol-3-yl)diselenides

To a solution of the appropriate *N*-alkynylimidazole (0.5 mmol) in THF (5 mL) under argon at −78 °C was added *n*-BuLi (0.22 mL of 2.5 M solution in hexane, 0.55 mmol). The reaction mixture was stirred for 30 min at −78 °C prior to the addition of elemental selenium (1.25 mmol). After that, the reaction mixture was allowed to stir at room temperature to complete consumption of the chalcogen. The reaction mixture was quenched with 5 mL of a saturated NH_4Cl solution and allowed to oxidize under air for 2 h. After this time, the mixture was diluted with ethyl acetate (20 mL) and washed with saturated NH_4Cl solution (3 × 20 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent.

1,2-Bis(2-phenylimidazo[2,1-*b*][1,3]selenazol-3-yl)diselenide (2aa): Yield: 0.081 g (50%); mp 186–188 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta=7.39$ (d, $J=1.3$ Hz, 1H), 7.32–6.96 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=143.3$, 141.3, 132.9, 132.5, 129.4, 129.3, 128.5, 115.2, 109.7. MS (EI, 70 eV): *m/z* (relative intensity) = 652 (4), 571 (15), 493 (10), 325 (22), 169 (84), 89 (100); HR-MS: *m/z* = 676.7781, calcd. for $C_{22}H_{14}N_4Se_4$ ($M+Na^+$): 676.7776.

General Procedure for the Reaction of Intermediate 2-Phenyl-3-lithioimidazo[2,1-*b*]selenazole with Aldehydes

To a two-necked, round-bottomed flask, under argon, containing a solution of **2a** (0.25 mmol) in THF (5 mL) at −78 °C was added *n*-BuLi (0.5 mmol, of a 2.5 M solution in hexane) in one portion. The reaction mixture was stirred for 15 min, and then a solution of appropriated aldehyde (0.3 mmol) in THF (2 mL) at −78 °C was added. The reaction mixture was allowed to stir at room temperature for 1 h. After this, the mixture was diluted with ethyl acetate (20 mL) and washed with saturated solution of NH_4Cl (20 mL). The organic phase was separated, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography and eluted with ethyl acetate/hexane.

(4-Chlorophenyl)(2-phenylimidazo[2,1-*b*][1,3]selenazol-3-yl)methanol (4a): Yield: 0.058 g (60%); mp 228–230 °C. NMR (DMSO-d_6, 400 MHz): $\delta=7.61$(d, $J=8.2$ Hz, 2H), 7.54–7.45(m, 3H), 7.40–7.34(m, 5H), 7.09(s, 1H), 6.70(d, $J=2.4$ Hz, 1H), 5.98 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz): $\delta=143.1$, 138.8, 132.4, 132.3, 132.0, 129.5, 129.3, 129.1, 128.9, 128.4, 127.3, 127.2, 115.7, 65.5; MS (EI, 70 eV): *m/z* (relative intensity)) = 388 (99), 249 (24), 168 (56), 139 (54), 77 (100); HR-MS: *m/z* = 388.9891, calcd for $C_{18}H_{13}ClN_2OSe$ ($M+H^+$): 388.9955.

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[23] CCDC 804627 (**2i**), contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for an ORTEP view of the compound **2i**.

