

Ultrasound-assisted synthesis of alkali metals diselenides (M_2Se_2) and their application for the gram-scale preparation of 2,2'-diselenobis(benzoic acid)

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This article is dedicated to Professor Lorenzo Testaferri on the occasion of his retirement

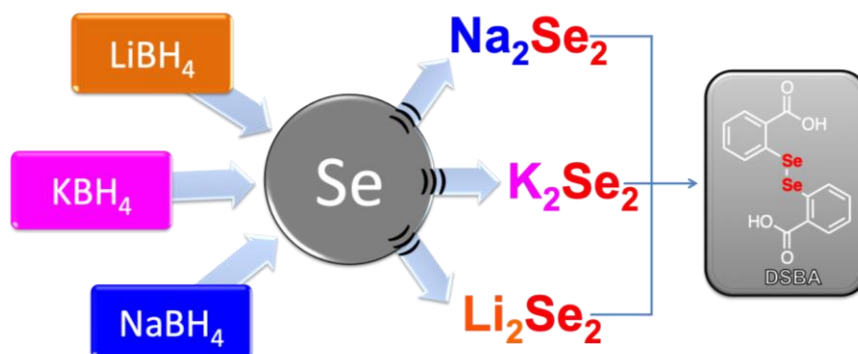
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Abstract

A simple and efficient method to convert elemental selenium into alkali metal diselenide was developed. The use of selenium and metal borohydride in a molar ratio of 1 to 0.125 in the presence of base, under “on water” conditions and ultrasound activation permitted the reduction of Se into Se_2^{2-} to be completed within minutes. Thus obtained metal diselenide aqueous solution was then used in the multigram scale synthesis of 2,2'-diselenobis(benzoic acid) (DSBA) a valuable building block for the development of diverse and pivotal selenorganic compounds.



Keywords: Alkali metal diselenides, borohydrides, hydrazine, ultrasound

Introduction

Among selenium containing compounds, diselenides are surely valuable since they represent the starting point for the preparation of nucleophilic,^{1,2} electrophilic,³ radical selenium-centered reagents^{4,5} and catalysts for oxidative transformations.⁶⁻⁹ In addition, aromatic diselenides exert interesting biological activities.^{10,11} As shown in Figure 1, the methods reported for their synthesis can be clustered into three groups: **(A)** decomposition of selenides,¹² selenyl azides,¹³ selenocyanates¹⁴ and selenyl halides;¹⁵ **(B)** nucleophilic displacement of leaving units, as exemplified in electron withdrawing group (EWG)-containing aromatic halides or diazonium salts, both operated by alkali metal diselenides (M_2Se_2) and **(C)** reaction between a carbon nucleophile, either an organolithium¹⁶ or a Grignard reagent,¹⁷ and elemental selenium.

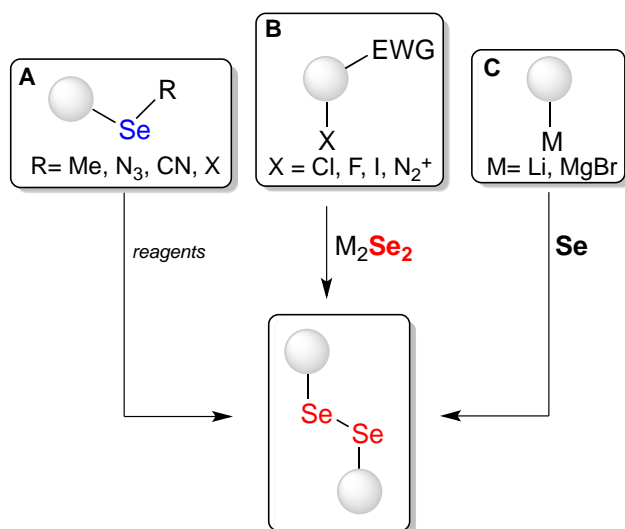


Figure 1. Synthetic approaches to obtain organic diselenides.

Among the three pathways we focused our attention to route B. In this context the synthesis of M_2Se_2 , where M is an alkali metal i.e. lithium, sodium or potassium, is usually accomplished right before the reaction with the organic electrophile since none of M_2Se_2 is commercially available. Among the three salts, the sodium containing one is surely the most frequently used and synthetically explored, while there are scarce examples of K and Li diselenide in literature (Figure 2).

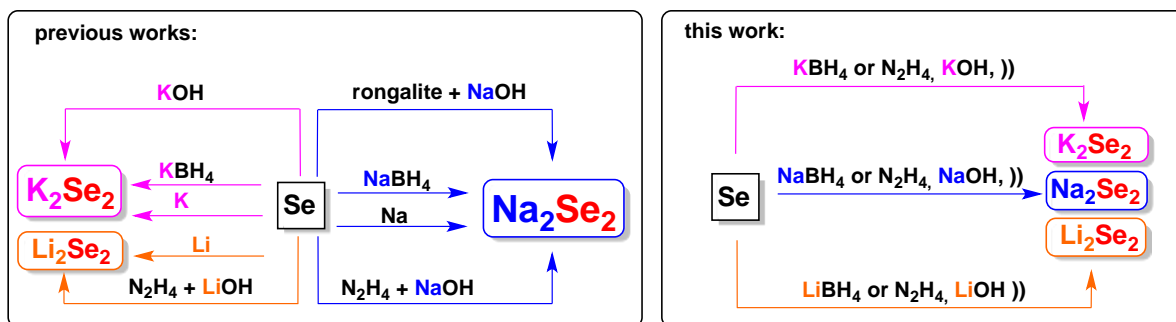
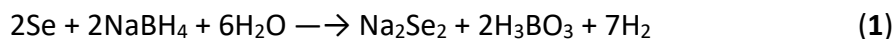


Figure 2. Strategies to obtain M_2Se_2 and summary of the present investigation.

Sodium diselenide can be obtained alternatively by the reduction of grey selenium with sodium hydroxymethylsulfinate (rongalite) in the presence of sodium hydroxide in water suspension for 2-5 hours.^{18,19} Other reducing agents utilized for the preparation of Na₂Se₂ are: sodium metal reacting in dry and refluxing THF for 6 hours,²⁰ or hydrazine, provided that the reduction is carried out at 80 °C in water for 1 hour²¹ or in methanol at room temperature for 24-60 h.^{22,23} Given the number of examples, NaBH₄ is the reagent of choice for converting elemental selenium into a Na₂Se₂ solution. Starting from the seminal paper of Klayman who first developed a two step procedure to convert Se first into NaHSe and then to Na₂Se₂ by using equimolar amounts of NaBH₄ in protic solvents at reflux,²⁴ other authors implemented this protocol, with few modifications^{25,26}(equation 1).

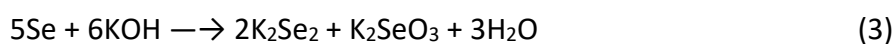


The amount of NaBH₄ was dramatically reduced by Yang and coworkers who found, by chance, that the addition of NaOH permits to use a 1 : 0.125 Se:NaBH₄ stoichiometry (equation 2) in the presence of catalytic amounts of hexadecyltrimethylammonium bromide, as a phase transfer catalyst.²⁷



This procedure represents the greenest alternative reported to date in terms of atom economy (93% Vs 75%, comparing Equations 2 and 1), solvent impact (since the reaction is carried out in water) and time (1.5 hours). For this reason it was adopted by us^{10,28} and others²⁹ in selenium-related research projects.

Lithium and potassium diselenides are much less explored and a fewer number of articles have been published regarding their synthesis. According to equation 3, the solvent free, thermally activated (240 - 360 °C) reaction between potassium hydroxide and elemental selenium affords K₂Se₂ along with K₂SeO₃, through a disproportionation reaction in which selenium is reduced and oxidized at the same time. This procedure reported for the first time as early as 1919,³⁰ was then slightly modified by other authors.^{31,32}



In 1988, the one-to-one reaction between Se and potassium metal in THF was published,³³ then in 2011, the procedure with an overstoichiometric amount of potassium borohydride was reported by Chen and coworkers.³⁴

The synthesis of Li₂Se₂, on the other hand, was accomplished by the reaction of Li metal and Se in the presence of electron transfer reagents in dry THF,³⁵ or through the Se reduction using hydrazine hydrate and LiOH.³⁶

In this paper, we report a green protocol for the preparation of M₂Se₂ using alkali metal borohydrides as reducing agents that benefits from being conducted under ultrasonic activation and “on water” conditions. The results of the studies on the use of hydrazine hydrate in the ultrasound-assisted synthesis of M₂Se₂ are also included. Sonochemistry is a subject of intense research in the chemistry community since it is emerging as a valid alternative to conventional heating; the interested reader is directed to recently published reviews^{37,38} and books.^{39,40}

The prepared alkali metal diselenides were then challenged in the aromatic nucleophilic substitution of the 2-carboxybenzenediazonium salt, leading to the preparation of 2,2'-diselenobis(benzoic acid) (DSBA, Figure 3). The yield of such reaction was then used to infer the reactivity of M₂Se₂ salts and the reduction efficiency of both MBH₄ or of hydrazine.

DSBA is a valuable building block since it is used as a key substrate to prepare ebselen, the most studied selenorganic compound known to date,⁴¹⁻⁴³ ethaselen that is under clinical investigation for the treatment of thioredoxin reductase overexpressing non-small cell lung cancers⁴⁴ and DiSeBAs, potent anti-HIV agents¹⁰ due to their ability to inhibit NCp7.^{45,46} Besides, DSBA itself showed promising biological activities being recognised by some of us as a hormetine.⁴⁷

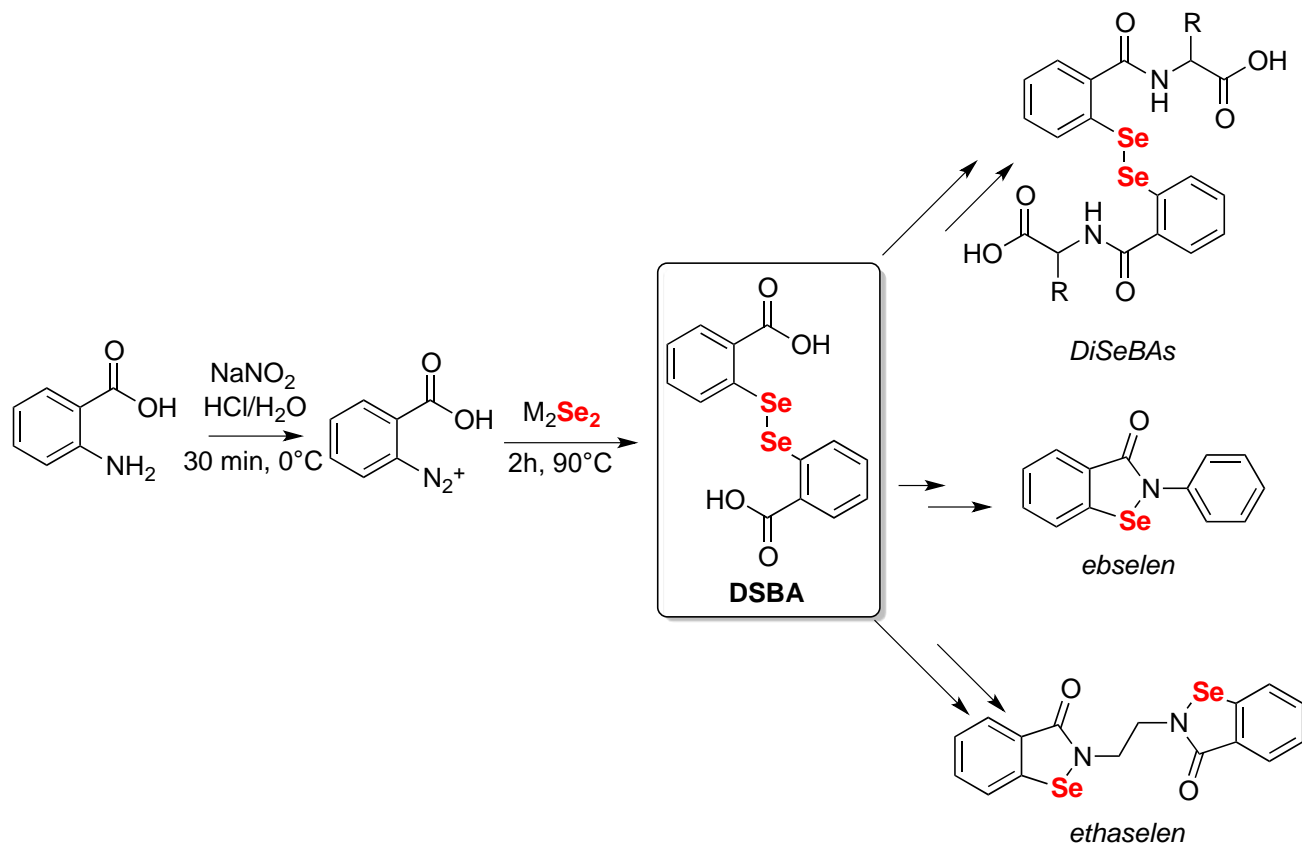


Figure 3. Procedure for preparing DSBA and its transformations to ebselen, ethaselen and DiSeBAs.

Results and Discussion

We started our investigation from the synthesis of sodium diselenide in alkaline aqueous solution following the method reported by Yang in 2002 with few modifications, i. e. removing the phase transfer catalyst, using ultrasound activation, shortening the reaction time from 1.5 hours to 1 hour and maintaining the temperature below 30°C instead of 90°C . After 1 hr sonication a dark reddish brown solution was formed and then transferred by dropping into a freshly prepared aqueous solution of 2-carboxybenzenediazonium salt²⁸ (Figure 3). For the diazonium salt displacement, after a deep literature analysis,^{29,34,48} we set the reaction time at two hours and the temperature at 90°C as we intended to employ the already optimized conditions leading to the highest possible conversion in a reasonable time. DSBA was thus obtained in 91% yield, clearly indicating that the ultrasound induced formation of metal diselenide in water is a viable alternative to conventional heating for this sort of reaction (Table 1, entry 1). Then, we attempted to synthesize sodium diselenide by reducing the reaction time to 30 and 15 min (entry 2 and 3 respectively). The selenium nucleophilic species were subsequently treated with 2-carboxybenzenediazonium salt to be transformed into the diaryl diselenide under

the established conditions. The product of the substitution was obtained in lower yields as a result of a shorter time and less efficient sodium diselenide formation.

Then we proceeded in examining potassium borohydride as reducing agent by using 0.125 moles of KBH_4 for each moles of selenium under sonochemical activation. If compared to the procedure reported in literature, where equimolar amounts were used³⁴ this method is much more atom economical. As reported in Table 1, entries 4-6 the reactions led to the target product in very good (entry 6, 86%) to excellent yields (entry 4 and 5, 91 and 94% respectively). Head to head comparison between the reactions to produce K_2Se_2 and Na_2Se_2 within 15 min reveals that KBH_4 gives better results (entry 6) than NaBH_4 (entry 3).

Finally, the same investigations were carried out using LiBH_4 (entries 7-9) and also in these cases DSBA was synthesized in excellent yields. To the best of our knowledge, the use of LiBH_4 for the preparation of Li_2Se_2 was never reported before.

Table 1

$$8\text{Se} + \text{MBH}_4 + 8\text{MOH} \xrightarrow[\text{H}_2\text{O}]{\text{RT,)))}} 4\text{M}_2\text{Se}_2 + \text{MBO}_2 + 6\text{H}_2\text{O}$$

Entry	M	Time (min)	Yield of DSBA
1	Na	60	91%
2	Na	30	81%
3	Na	15	50%
4	K	60	91%
5	K	30	94%
6	K	15	86%
7	Li	60	91%
8	Li	30	90%
9	Li	15	90%

All the reactions were carried out in water as a solvent using the following scale: Se = 2.19 mmoles, MBH_4 = 0.275 mmoles, MOH = 3.29 mmoles, H_2O = 2ml. The diazonium salt displacement was carried out using the following scale diazonium salt = 2.19 mmoles, H_2O = 4 ml, 90 °C, 2 hours. The yield refers to isolated product.

We were interested in examining the effect of ultrasound on the formation of metal diselenides produced by the reduction of selenium using hydrazine hydrate in alkaline aqueous solution. The yields of the reactions were estimated by the same chemical correlation based on the reaction of the diselenide with diazonium salt. We choose to set the reaction time to 1 hour since it is reported in literature that this time is sufficient at 80°C in water.²¹ As reported in Table 2, entry 1, trace amount of DSBA were obtained by using NaOH as metal source after 1 hour of sonication. Lithium and potassium gave slightly better results, which however were far from the expected yields if compared with any alkali metal borohydride mediated reduction.

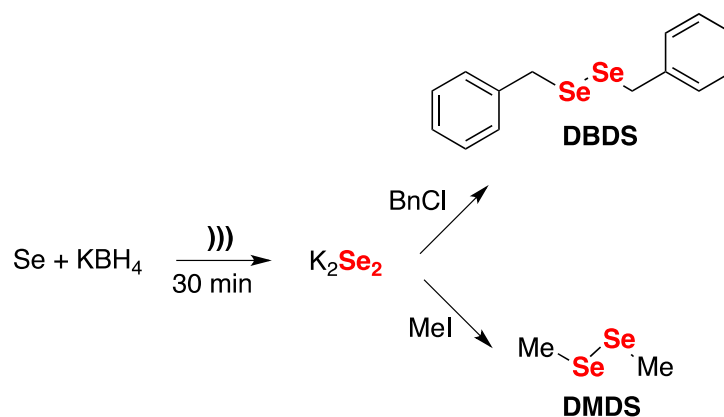
Table 2

$$4\text{Se} + \text{N}_2\text{H}_4 + 4\text{MOH} \xrightarrow[\text{H}_2\text{O}]{\text{RT,)))}} 2\text{M}_2\text{Se}_2 + \text{N}_2 + 4\text{H}_2\text{O}$$

Entry	M	Time (min)	Yield
1	Na	60	5%
2	K	15	7%
3	K	30	13%
4	K	60	17%
5	Li	60	10%

All the reactions were carried out in water as a solvent using the following scale: Se = 2.19 mmol, N₂H₄ = 17.5 mmol, MOH = 3.29 mmol; H₂O = 2 ml. The diazonium salt displacement was carried out using the following scale diazonium salt = 2.19 mmol, H₂O = 4 ml, 90 °C, 2 hours. The yield refers to isolated product.

On the basis of this investigation we selected as best condition to synthesize M₂Se₂ those displayed in Table 1, entry 5. In the DSBA synthesis KBH₄ indeed granted 94% yield after just 30 minutes of reaction time where sodium borohydride gave 81%. Lithium was as effective as potassium but it is much more expensive. According to Sigma-Aldrich supplier sodium and potassium borohydrides have comparable costs (approximately 30 € for 25 g with ≥ 97.0% purity). With the best conditions in our hands we briefly tested the “on water” synthesis of other synthetically relevant organic diselenides, i. e. dimethyl diselenide (DMDS) and dibenzyl diselenide (DBDS) (Scheme 1 and Table 3).



Scheme 1. Synthesis of DMDS and DBDS.

DBDS was synthesized in excellent yield performing the nucleophilic substitution reaction under conventional heating at the temperature of 90 °C (Table 3, entry 1). The same reaction carried out by adding benzyl chloride to the sonicating aqueous solution of K₂Se₂ did not afford the desired diselenide. On the contrary, the addition of stoichiometric amounts of methyl iodide led to the formation of the desired DMDS in 40% yield (entry 5). Interestingly the same reaction performed under conventional heating at 50 and 90 °C led to the DMDS formation in lower yields (entry 3 and 4). In all the cases DMDS was obtained as a mixture of

selenide and polyselenides. The DSBA synthesis under sonication (entry 7) occurred, even though with a lower efficiency if compared to the standards conditions (entry 6).

Table 3

Entry	Product	Condition	Yield
1	DBDS	90°C	94%
2	DBDS)))	traces
3	DMDS	90°C	20%
4	DMDS	50°C	23%
5	DMDS)))	40%
6	DSBA	90°C	94%
7	DSBA)))	60%

All the reactions were carried out in water as a solvent using the following scale: Se = 2.19 mmoles, KBH_4 = 0.275 mmoles, KOH = 3.29 mmoles, H_2O = 2ml. The reaction time is 2 hours in each case. The yield refers to isolated product.

Finally, having selected the best the conditions (Table 1 entry 5) we tested the scalability of the DSBA synthesis by doubling each time the amount of reactants for four consecutive reactions (Figure 4).

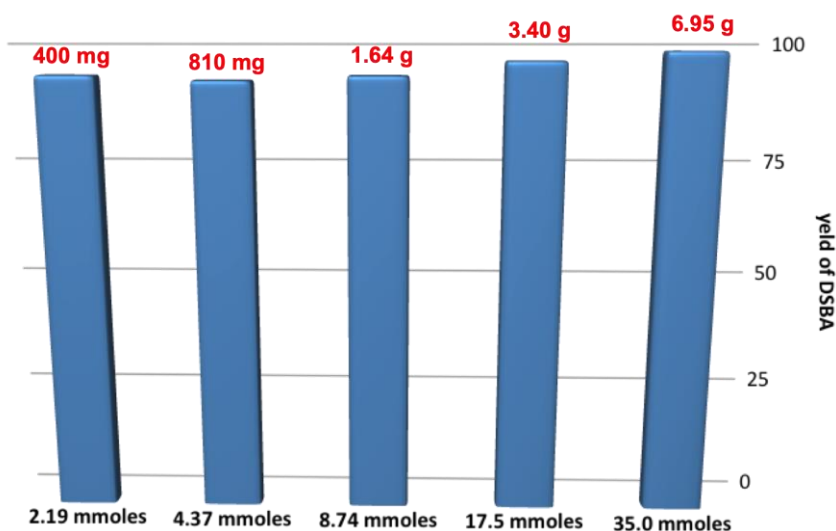


Figure 4. Scalability of the DSBA synthesis, in red the amount of DSBA obtained.

As shown in Figure 4, we demonstrated that the reported procedure is scalable for at least 35 mmoles of selenium (2.8 grams) and anthranilic acid (4.8 grams) allowing us to prepare almost 7 grams of DSBA in one shot. This point is really important for a future industrial application of such valuable compound.

Conclusions

Alkali metal diselenides are pivotal reagents to install the diselenide functional group onto organic substrates. In this paper we demonstrated that ultrasonic activation is a valid alternative to normal heating in the borohydride-mediated reduction of elemental selenium. The procedure allows for the convenient syntheses of alkali metal diselenides using potassium and lithium borohydrides in a molar ratio of 1:8 to selenium, which requires only 15- 30 minutes of sonication. For the high yielding reduction of selenium by sodium borohydride the longer reaction time, 60 minutes of sonication, is required. On the contrary, sonochemistry is not appropriate when hydrazine hydrate is the reductant. In addition we proved also that, beside NaBH_4 and KBH_4 also LiBH_4 is suitable to convert selenium into diselenide. Finally, the multigram scale synthesis of DSBA was demonstrated by using potassium diselenide as selenium source, which is also suitable for the preparation of DBDS.

Experimental Section

General. Reactions were conducted in Schlenk tubes or round bottom flasks and were stirred with Teflon-coated magnetic stirring bars. The reactions under ultrasound irradiation were performed in a Polsonic[®] sonic bath (model Sonic-3) with 80 W and 40 KHz of effective sonication power and frequency, respectively. Commercially available organic and inorganic reagents were used without further purification. NMR experiments were conducted at 25 °C with a Bruker Avance 200 spectrometer operating at 200.16 MHz for ^1H , or with a Bruker Avance III 500 spectrometer operating at 500.13 MHz for ^1H , 125.76 MHz for ^{13}C and 95.43 MHz ^{77}Se experiments. ^1H , ^{13}C and ^{77}Se chemical shifts (δ) are reported in parts per million (ppm), and are cited with respect to TMS ($\delta = 0.0$ ppm), as internal standard (^1H) and the residual solvent peak of $\text{DMSO}-d_6$ ($\delta = 2.50$ and 39.53 ppm in ^1H and ^{13}C NMR, respectively) or Ph_2Se_2 (^{77}Se $\delta = 463$ ppm) as the external standard. Data are reported as: chemical shift (multiplicity, coupling constants where applicable, number of hydrogen atoms, and assignment where possible). Abbreviations are: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), tt (triplet of triplet), m (multiplet), bs (broad singlet). Coupling constant (J) quoted in Hertz (Hz) to the nearest 0.1 Hz. High-resolution mass spectrometry (HRMS) measurements were performed using Synapt G2-Si mass spectrometer (Waters) equipped with an APCI source and quadrupole-Time-of-Flight mass analyzer. The mass spectrometer was operated in the positive and negative ion detection modes with discharge current set at 4.0 μA . The heated capillary temperature was 350 °C. The results of the measurements were processed using the MassLynx 4.1 software (Waters) incorporated with the instrument. Melting points (m.p.) were determined on Mel-Temp[®] apparatus and are uncorrected.

General procedure A, preparation of alkali metal diselenide solution with MBH_4 . A Schlenk tube was charged with elemental selenium (175 mg, 2.19 mmoles) and filled with argon. A solution of alkali metal hydroxide (3.29 mmoles) and borohydride (0.275 mmoles) in 2 ml of distilled water was prepared in a test tube, cooled to room temperature and added at once to the Schlenk tube which was allowed to sonicate for the amount of time indicated in Table 1. Then a dark solution is formed and used without further purifications.

General procedure B, preparation of alkali metal diselenide solution with hydrazine hydrate. A Schlenk tube was charged with elemental selenium (175 mg, 2.19 mmol) and then filled with argon. A solution of alkali metal hydroxide (3.29 mmol) in 2 ml of distilled water along with hydrazine monohydrate (0.85 ml, 17.5

mmol) was added dropwise. The Schlenk tube was allowed to sonicate for the amount of time indicated in Table 2. Then a dark suspension is formed and used without further purifications.

2-Carboxybenzenediazonium chloride. 2-Carboxybenzenediazonium chloride aqueous solution (2.19 mmol) was prepared just before use through the reaction of anthranilic acid (200 mg, 2.29 mmol), sodium nitrite (185 mg, 2.63 mmol) and 0.1 ml of HCl 37 % in 4 ml of distilled water.²⁸ The colourless solution so obtained was used without further purifications.

Preparation of 2,2'-diselenobis(benzoic acid) (DSBA). The freshly prepared solution of alkali metal diselenide (1.095 mmol) in water (2 mL) was added dropwise to the solution of 2-carboxybenzenediazonium chloride (2.19 mmol) at 0°C. The reaction mixture was allowed to reach room temperature with a continuous stirring and then heated at 90 °C for 2 hours. After this period the solution was passed through a filter with a thin pad of Celite, and water was used to rinse the Celite. The filtrate was acidified (ca. 7 ml of 1M HCl aq solution) until a beige precipitation appeared. The formed solid was separated by filtration, solubilized with hot methanol and evaporated in vacuo to yield the target product as beige solid. Analytically pure samples can be obtained by recrystallization from dioxane. Mp 290-292 °C (289-292 °C ref²⁸); ¹H NMR (DMSO-*d*₆) δ = 13.73 (bs, 1H, OH), 8.02 (d, *J* 7.8 Hz, 1H, ArCH), 7.66 (d, *J* 8.17 Hz, 1H, ArCH), 7.48 (t, *J* 7.87 Hz, 1H, ArCH), 7.35 ppm (t, *J* 7.56 Hz, 1H, ArCH); ¹³C NMR (DMSO-*d*₆) = 169.04, 134.08, 133.90, 132.06, 129.93, 129.19, 127.04 ppm. ⁷⁷Se NMR (DMSO-*d*₆) = 439.60 ppm. HRMS calculated for C₁₄H₁₀O₄NaSe₂ = 424.8807, found = 424.8818.

Scale up experiments: Scale up experiments were carried out using K₂Se₂ prepared within 30 min according the general procedure A using 30 minutes of sonication time. The amounts adopted are listed in Table 4.

Table 4

Se	KBH ₄ mmol	KOH	H ₂ O ml	Antranilic Acid mmol	NaNO ₂	HCl 37% ml	H ₂ O
2.19	0.275	3.29	2	2.19	2.63	0.1	4
4.38	0.55	6.60	4	4.38	5.27	0.25	8
8.74	1.10	13.11	8	8.74	10.50	0.55	16
17.50	2.20	26.25	16	17.50	21.00	1.20	32
35.00	4.40	52.50	32	35.00	42.00	2.60	64

Preparation of dibenzyl diselenide (DBDS). To a solution of K₂Se₂ freshly prepared according to the general method A using 30 minutes of sonication time, benzyl chloride (2.19 mmoles, 0.25 ml) was added at once. The reaction was allowed to react for 2h under conventional heating at 90°C or under ultrasonic irradiation. The reaction was then diluted with water (30 ml) and extracted three times with dichloromethane (3 X 30 ml). The combined organic extracts were dried over magnesium sulphate, filtered and concentrated in vacuo. The resulting orange oil was purified by silica gel column chromatography using petroleum ether: ethyl acetate 95:5 as eluent. The compound was isolated as a yellow solid in the yields indicated in Table 3. Mp = 84-86 °C (87-88 °C ref⁴⁹); ¹H NMR (CDCl₃) δ = 7.25 – 7.13 (m, 5H, ArCH), 3.76 (s, 2H, CH₂); ¹³C NMR (CDCl₃) δ = 139.08, 129.10, 128.52, 127.18, 32.66 ppm; ⁷⁷Se NMR = 402.37 ppm.

Preparation of dimethyldiselenide (DMDS). To a solution of K₂Se₂ freshly prepared through the general method A using 30 minutes of sonication time, methyl iodide (2.19 mmoles, 0.14 ml) was added at once. The

reaction was allowed to react for 2 hours under conventional heating at 90°C or under ultrasonic irradiation. The reaction was allowed to react for 2 hours under conventional heating at 90°C or under ultrasonic irradiation. The reaction mixture was then diluted with water (30 ml) and extracted three times with diethyl ether (3 X 30 ml). The combined organic layers were dried over magnesium sulphate, filtered and the solvent was evaporated in vacuo. A dark orange oil was obtained. ¹H NMR analysis carried out in CDCl₃ revealed a mixture of DMDS, dimethyl triselenide and tetraselenide, which was not separated.

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Supplementary Material

Supplementary data associated with this article can be found in the online version.

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