

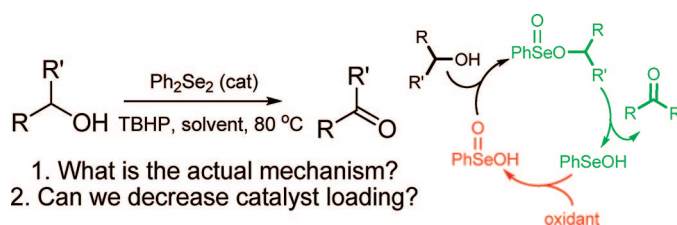
# Diphenyldiselenide-Catalyzed Selective Oxidation of Activated Alcohols with *tert*-Butyl Hydroperoxide: New Mechanistic Insights

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Diselenides are known precatalysts for catalytic oxidations. The use of these widely available compounds as catalysts for the oxidation of alcohols was investigated, still leaving many mechanistic questions to be answered. By using a range of analytical techniques, we found evidence for the unexpected involvement of seleninic anhydride in the catalytic mechanism. The activation time of the diselenide and its influence on the oxidation reaction itself was also investigated. On the basis of these findings, an improved protocol for the selective oxidation of activated alcohols was devised resulting in significantly decreased catalyst loadings (<1%).

## Introduction

Alcohol oxidations are highly relevant reactions in synthetic organic chemistry.<sup>1</sup> The development of catalytic systems for these types of transformations, affording sustainable and atom-efficient methodologies, is still of great interest.<sup>2</sup> Excellent transition-metal catalysts, based on, e.g., Cu, Pd, Ru, and Pt, have been developed which allow the use of molecular oxygen as the terminal oxidant.<sup>3</sup> However, these metal catalysts are often unsuitable for highly functionalized molecules, which are used as intermediates in the pharmaceutical industry. In these cases, organocatalytic methodologies can offer a distinct advantage, due to their high selectivities. A good example of an industrially applied organocatalyst capable of alcohol oxidations is the 2,2,6,6-tetramethylpiperidinyloxy radical (TEMPO), using bleach (sodium hypochlorite) or a hypervalent iodine(III) species as

terminal oxidant.<sup>4,5</sup> Major drawbacks of these systems are the formation of halogenated side products and the use of halogen-rich solvents. Even though the iodine(III) reagents can be used chloride- and bromide-free, their use is accompanied by the formation of 2 equiv of acid.

In our search for other main group elements capable of performing these types of redox reactions with benign oxidants, our interest focused on the use of organoselenium compounds as catalysts.<sup>6–8</sup> Organoselenides are known to be highly selective, mild, and reliable reagents for oxidative transformations.<sup>9</sup> The classical organoselenium reagent for alcohol oxidations is benzeneseleninic acid anhydride (BSA), which was introduced by Barton and co-workers in the late 1970s.<sup>10</sup> They

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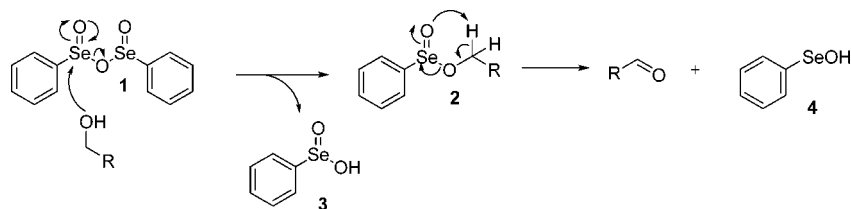
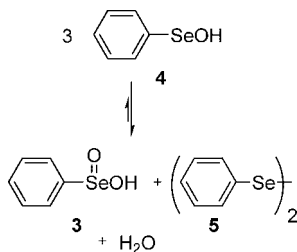
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## SCHEME 1. Mechanism of Alcohol Oxidation by BSA

SCHEME 2. Rearrangement of Benzeneselenate to Benzeneseleninic Acid and Ph<sub>2</sub>Se<sub>2</sub>

proposed a mechanism involving the seleninate ester (compound 2) as the intermediate species (Scheme 1).

Interestingly, if one performs the oxidation of benzyl alcohol with BSA, a yellow color immediately appears upon addition of the alcohol which is attributed to the formation of Ph<sub>2</sub>Se<sub>2</sub>.<sup>10</sup> The formation of Ph<sub>2</sub>Se<sub>2</sub> can be explained by an equilibrium between 3 equiv of benzeneselenate (4) which gives H<sub>2</sub>O and Ph<sub>2</sub>Se<sub>2</sub> and 1 equiv of benzeneseleninic acid (Scheme 2).<sup>11</sup>

We reasoned that diselenides could be introduced as precursors for the active oxidant as several oxidants are known to oxidize aromatic diselenides to the corresponding anhydrides. If this could be done in situ, this would yield a new catalytic process for the oxidation of alcohols.

In the 1970s and 1980s, much effort was directed toward the use of organoselenides as catalysts, of which the work of Kuwajima et al. is the best known. Their best results involved the use of mesitylene diselenide (0.5 equiv) and aqueous *tert*-butyl hydroperoxide (TBHP) (1.5 equiv). This combination was applied to oxidize a variety of primary (benzylic and aliphatic) alcohols to the corresponding aldehydes in high selectivity.<sup>12,13</sup> Two possible mechanisms were proposed, but neither was substantiated with experimental evidence. One possible mechanism involved a seleninate ester, and the other cycle was based upon a seleninate ester as the active intermediate. The catalytic use of simple diphenyl diselenide was also mentioned, but the authors stated that in this case only benzylic (also secondary benzylic) and primary allylic alcohols could be fully oxidized and that using less than 10% mol of this (standard) diselenide did not result in complete conversion of the alcohol. In the literature, the use of different diselenides in combination with sulfonamides as oxidants has been reported with reasonable success.<sup>14,15</sup> The major disadvantage of the use of these sulfonamides is that they are expensive and not readily available.

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TABLE 1. Yields of Benzaldehyde (Aldehyde) and Benzoic Acid (Acid) in Ph<sub>2</sub>Se<sub>2</sub> (5%) Catalyzed Oxidation of Benzyl Alcohol with 1.1 equiv of TBHP (80 °C, 8 h)

solvent	TBHP in H <sub>2</sub> O		TBHP in decane	
	aldehyde (%)	acid (%)	aldehyde (%)	acid (%)
MeCN	67	9	66	16
xylene	61	2	62	6
EtOAc	62	11	49	10
trichloroethane	60	10	48	14
CCl <sub>4</sub>	58	7	70	12
heptane	61	7	61	8
toluene	79	4	86	5

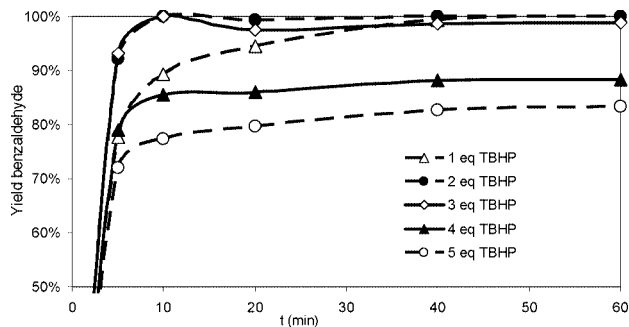
The aim of the present study was to develop a catalytic procedure based on aromatic diselenides as the catalysts and using readily available and stable hydroperoxides as oxidants. Herein, we report our investigation on the mechanism of Ph<sub>2</sub>Se<sub>2</sub>-catalyzed alcohol oxidations which led to the development of a new procedure for alcohol oxidations employing as little as 1 mol % of diphenyl diselenide as the catalyst and TBHP as the terminal oxidant.

## Results and Discussion

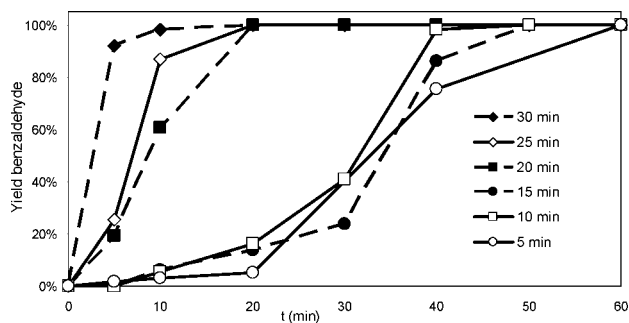
**Ph<sub>2</sub>Se<sub>2</sub>-Mediated Oxidation of Benzyl Alcohol: Catalytic and Stoichiometric Reactions.** Initially we repeated the Ph<sub>2</sub>Se<sub>2</sub>-catalyzed oxidation of benzyl alcohol as described by Kuwajima et al.<sup>12</sup> This involved reactions in chlorobenzene at 80 °C, employing 10 mol % of Ph<sub>2</sub>Se<sub>2</sub> and 1.5 equiv of aqueous TBHP. In agreement with Kuwajima's results, we found that the use of less than 10 mol % of Ph<sub>2</sub>Se<sub>2</sub> resulted in incomplete conversion of benzyl alcohol and the formation of a significant amount of benzoic acid. We also found that the use of TBHP in decane rather than aqueous TBHP led to an increased yield and selectivity of the reaction, depending on the solvent used. In the older reports, chlorobenzene or benzene was the preferred solvent. As we were not interested in these halogenated or carcinogenic solvents, we tested various alternatives (Table 1).

The best results were obtained by using an apolar solvent with a boiling point at or higher than 80 °C, such as heptane or toluene. When using 5 mol % of catalyst and TBHP, an induction period of ca. 1 h was observed, suggesting that a preactivation of the Ph<sub>2</sub>Se<sub>2</sub> catalyst was required. Therefore, we performed a series of experiments under stoichiometric conditions to investigate the origin of this induction period. We found that premixing Ph<sub>2</sub>Se<sub>2</sub> with 1 equiv of TBHP in toluene for 2 h followed by the addition of 1 equiv of benzyl alcohol resulted in complete conversion to benzaldehyde within 40 min (Figure 1). When 2 or 3 equiv of TBHP was added, the rate of benzyl alcohol oxidation increased only slightly.

In theory, the use of 3 equiv of TBHP should result in the formation of 1 equiv of BSA relative to benzyl alcohol. A further increase of the amount of TBHP to 4 or 5 equiv resulted in oxidation of toluene to a mixture of benzyl alcohol and



**FIGURE 1.** Oxidation of benzyl alcohol with  $\text{Ph}_2\text{Se}_2$  preactivated with different amounts of TBHP in toluene.



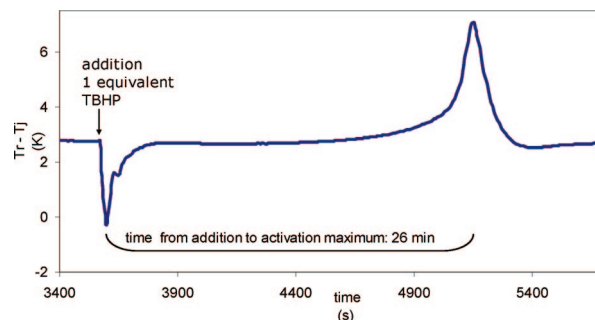
**FIGURE 2.** Influence of activation time length on the oxidation of benzyl alcohol with  $\text{Ph}_2\text{Se}_2$  and 2 equiv of TBHP in toluene.

benzaldehyde, which was confirmed in blank experiments in the absence of alcohol substrate. The oxidation of toluene has been reported previously using BSA as the oxidant, but these reactions are thought to occur at higher temperatures and with longer reaction times.<sup>16</sup> We assume that the excess of TBHP could undergo (selenium-catalyzed) homolytic decomposition to afford *tert*-butoxy and *tert*-butylperoxy radicals which initiate the autoxidation of toluene. We conclude from these experiments that it is important to keep the TBHP concentration low to avoid competing homolytic decomposition of the TBHP and attending autoxidation of toluene.<sup>17</sup>

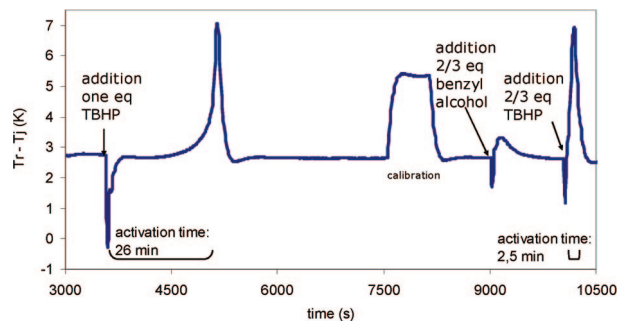
To further understand the preactivation,  $\text{Ph}_2\text{Se}_2$  was activated with 2 equiv of TBHP at different time lengths, followed by the addition of substrate (Figure 2). The oxidation of the substrate was smooth and immediate when the preactivation was performed for 30 min or longer. At shorter preactivation times, an induction period was observed in conversion of the substrate, comparable to results of the preliminary catalytic reactions. With preactivation periods shorter than 15 min, this induction period of the catalyst is even longer, indicating that the substrate hampers the activation of  $\text{Ph}_2\text{Se}_2$  by TBHP.

**Reaction Calorimetry.** The activation period was further investigated by reaction calorimetry. First, the activation of  $\text{Ph}_2\text{Se}_2$  (0.1 M) in toluene with 1 equiv of TBHP was studied (Figure 3).

Upon addition of the cold TBHP there was an expected drop in temperature, but after 20–25 min a sudden increase in reaction temperature was observed. This showed an exothermic reaction with an enthalpy of approximately 150 kJ/mol, and careful analysis of the mixture showed that it consisted of one-third BSA. For the exotherm of this reaction a rough estimation



**FIGURE 3.** Reaction calorimetry profile of the activation of 0.1 M  $\text{Ph}_2\text{Se}_2$  by 1 equiv of TBHP in toluene.



**FIGURE 4.** Reaction calorimetry of the activation of partially oxidized  $\text{Ph}_2\text{Se}_2$ .

of 196 kJ/mol could be made, based on a calculated heat of formation of BSA and known gas-phase values for the other compounds (see the Experimental Section). As there was a huge acceleration in the last part of the reaction, the question arose whether or not this could be attributed to the formed BSA. Therefore, a mixture of  $\text{Ph}_2\text{Se}_2$ /BSA (95/5) was activated with TBHP. This revealed that BSA indeed influences the oxidation of  $\text{Ph}_2\text{Se}_2$  to BSA as in this case the activation period was virtually absent and the enthalpy had the same value (150 kJ/mol). Presumably, mixing BSA with TBHP gives the intermediate *tert*-butyl perseleninic ester, which is possibly a stronger oxidant than either TBHP or BSA.<sup>18</sup> The synthesis of this compound has so far not been successful in our hands, but we were able to show that the oxidation of benzyl alcohol with a mixture of BSA and TBHP proceeded at the same rate as with BSA alone. However, there was a significant difference in selectivity. BSA alone gave no overoxidation of benzaldehyde to the benzoic acid. In contrast, the BSA–TBHP mixture showed substantial conversion to the acid (5% in 20 min). Yet, in the presence of  $\text{Ph}_2\text{Se}_2$ , the aldehyde was not overoxidized, but the diselenide was converted to the anhydride, thereby showing the selectivity of the oxygen transfer.

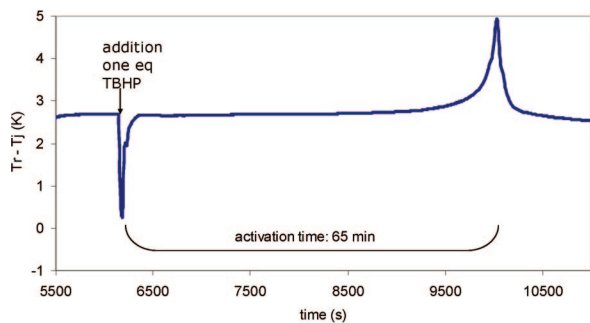
In order to investigate whether the in situ formed BSA could be used for a shorter activation period in a second round of diselenide activation, an experiment was performed in which  $\text{Ph}_2\text{Se}_2$  was activated with 1 equiv of TBHP and was subsequently reacted with  $2/3$  equiv of benzyl alcohol. In this case, some of the BSA or other oxidized selenium intermediates should remain in the reaction mixture. TBHP ( $2/3$  equiv) was subsequently added, and indeed, the preactivation of  $\text{Ph}_2\text{Se}_2$  was instantaneous as indicated by the exotherm (Figure 4).

In a subsequent experiment, the activation of  $\text{Ph}_2\text{Se}_2$  by TBHP was investigated in the presence of 1 equiv of substrate. As

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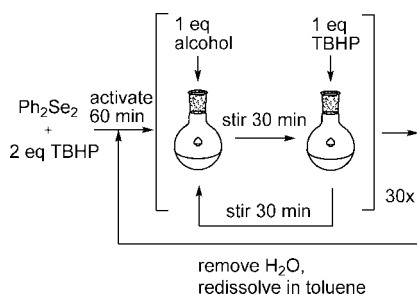
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**FIGURE 5.** Reaction calorimetry of activation of 0.1 M  $\text{Ph}_2\text{Se}_2$  in the presence of 1 equiv of benzyl alcohol.

**SCHEME 3. Experimental Set-up for the Oxidation of Alcohols with  $\text{Ph}_2\text{Se}_2$**



can be deduced from Figure 5, in the presence of substrate the activation of  $\text{Ph}_2\text{Se}_2$  is significantly slower. This can be explained by taking into account that in the presence of benzyl alcohol BSA is immediately consumed by oxidation of benzyl alcohol to benzaldehyde. Therefore, the perester formation is inhibited, thus reducing or precluding its involvement in the oxidation of  $\text{Ph}_2\text{Se}_2$  by TBHP. The latter result also supports the hypothesis that perester is involved in the formation of BSA from  $\text{Ph}_2\text{Se}_2$  and TBHP.

In summary, a number of the above-mentioned findings are of importance for the development of an effective  $\text{Ph}_2\text{Se}_2$ -mediated oxidation of benzyl alcohol with TBHP as the terminal oxidant. First, exposure of more than 3 equiv of TBHP relative to the amount of  $\text{Ph}_2\text{Se}_2$  causes overoxidation of benzaldehyde to benzoic acid and the oxidation of toluene to benzyl alcohol. We attribute this to the formation of the perseleninic ester, which can oxidize benzaldehyde easily to benzoic acid. In addition, a relatively high concentration of TBHP could undergo homolytic cleavage, thereby promoting the latter two reactions via a radical-oxidation process. Therefore, the concentration of TBHP should remain low throughout the process. Second, the preactivation of  $\text{Ph}_2\text{Se}_2$  by reaction with TBHP to afford BSA is autocatalytic, that is, the BSA catalyzes its own formation which we attribute to the formation of the perester, and thus, regeneration of the active species is most effective when a small amount of BSA remains present in the reaction mixture.

These findings have led us to the development of a protocol (Scheme 3) in which first  $\text{Ph}_2\text{Se}_2$  is pretreated with TBHP in order to generate BSA. Next, an amount of an activated alcohol (such as benzyl alcohol or cinnamyl alcohol) is added that is insufficient to consume all of the BSA. Subsequently, after the oxidation of the substrate, another portion of TBHP is added in order to regenerate all of the BSA.

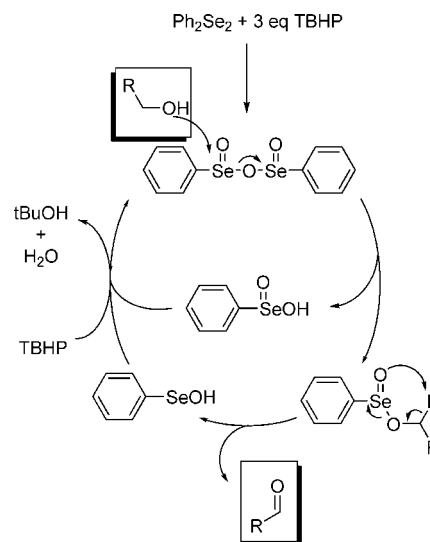
Initial experiments according to this protocol showed that substrate/catalyst ratios above 10 could be achieved. However, the water formed in the oxidation during these cycles showed

**TABLE 2. Results of Optimized Reaction Conditions**

substrate	product	TTN <sup>a</sup>	selectivity (%)
benzyl alcohol	benzaldehyde	115	99.1
cinnamyl alcohol	cinnamaldehyde	180	>99.9

<sup>a</sup> TTN = mmol product/mmol catalyst.

**SCHEME 4. Catalytic Cycle in the Oxidation of Alcohols with TBHP as the Terminal Oxidant and  $\text{Ph}_2\text{Se}_2$  as Catalyst**



a deleterious effect on the reaction, which can be attributed to the hydrolysis of BSA, thus competing with the alcohol substrate. This was overcome by adding a drying agent to the reaction mixture (anhydrous  $\text{MgSO}_4$  or MS 4 Å) enabling substrate to catalyst ratios of more than 100 (Table 2).

Based on the above observations, we propose the following tentative mechanism for the  $\text{Ph}_2\text{Se}_2$ -catalyzed oxidation of alcohols with TBHP (Scheme 4).

**Conclusions**

The  $\text{Ph}_2\text{Se}_2$ -catalyzed oxidation of activated alcohols with TBHP as the terminal oxidant is a reaction that has been known for a long time. The main problem of the methodology was the high loading of catalyst required. We have shown that benzene-seleninic anhydride (BSA) is the active oxidant and that it catalyzes its own formation most likely via the *in situ* formation of a perester. If the concentration of TBHP is too high, homolytic decomposition of this perester results in the autoxidation of solvents containing reactive C–H bonds, such as toluene, and the autoxidation of benzaldehyde to benzoic acid. Based upon these findings, we developed a new catalytic protocol which included the *in situ* removal of water. A drying agent could be added, but alternatively, the reaction can be performed under Dean–Stark conditions, which is more convenient on a larger scale. Two activated alcohols, benzyl alcohol and cinnamyl alcohol, were oxidized by TBHP to the corresponding aldehydes employing <1% of  $\text{Ph}_2\text{Se}_2$  as the catalyst. Compared to other organocatalytic methods, our method is advantageous in that all compounds are cheap and readily available, and the method is completely halogen-free. However, the use of  $\text{Ph}_2\text{Se}_2$  as a catalyst precursor has the disadvantage that only activated alcohols are oxidized smoothly, which was already found previously.<sup>12</sup> Preliminary experiments in the use of this system in the oxidation of 1-decanol (an aliphatic alcohol)



showed that the dehydrogenation step was slow and not complete, thereby prohibiting the practical application of the above-described optimized system. Further investigations are underway with regard to the substrate scope of the system and the effect of electron-donating or -withdrawing groups in the diselenide catalyst on the rate of the reaction.

## Experimental Section

**Materials.** Ph<sub>2</sub>Se<sub>2</sub> (99%), TBHP in decane (5.5 M), benzyl alcohol (99+%), 1,2-dimethoxybenzene (99+%), molecular sieves (4 Å), MgSO<sub>4</sub> (anhydrous 97%), benzeneseleninic anhydride, toluene (reagent grade, stored over molecular sieves 4 Å), and ethyl acetate (p.a.) were all used as received.

**Catalytic Reactions.** To a stirred solution of benzyl alcohol (2 mmol, 216 mg), 1,2-dimethoxybenzene (0.5 mmol, 69 mg, internal standard), and Ph<sub>2</sub>Se<sub>2</sub> (0.1 mmol, 31 mg) in 10 mL of toluene was added TBHP (2.2 mmol, 400 μL) at 80 °C. At several intervals, 50 μL aliquots were withdrawn and quenched with Na<sub>2</sub>SO<sub>3</sub> (100 mg in 1.5 mL of EtOAc), and the solids were filtered off. The mixture was then analyzed by GC.

**Stoichiometric Reactions.** To a stirred solution of Ph<sub>2</sub>Se<sub>2</sub> (1 mmol, 312 mg) and 1,2-dimethoxybenzene (0.5 mmol, 69 mg, internal standard) in 10 mL of toluene at 80 °C was added TBHP (5.5 M solution in decane), and after the appropriate amount of time, benzyl alcohol was added. At several intervals, 50 μL aliquots were withdrawn and quenched with Na<sub>2</sub>SO<sub>3</sub> (100 mg in 1.5 mL EtOAc), and the solids were filtered off. The mixture was then analyzed by GC.

**Catalytic Protocol for the Use of Low Concentrations of Catalyst.** To a solution of Ph<sub>2</sub>Se<sub>2</sub> (1 mmol, 312 mg) and 1,2-dimethoxybenzene (5 mmol, 690 mg) in 15 mL of toluene at 80 °C was added first 2 mmol of TBHP (364 μL) with a pump system (syringe pump equipped with a glass syringe and PTFE 1/16 in. tubing into the reaction), and the mixture was allowed to stand for 1 h. After this, 1 mmol of benzyl alcohol (103 μL) was added with a pump system (programmable syringe pump equipped with a glass syringe and PTFE 1/16 in. tubing into the reaction) which was allowed to react for 30 min. After this, 1 mmol of TBHP (182 μL) was added with the pump system, and the mixture was allowed to stand for 30 min after which benzyl alcohol was added, and this sequence was allowed to loop 30 times. Anhydrous Na<sub>2</sub>SO<sub>4</sub> was added to dry the reaction in case there were no molecular sieves in the reaction. The solids were then filtered off, the solvent was evaporated, and the residue was redissolved in 15 mL of toluene after which the sequence was restarted. This allowed a total of 115 mmol of benzyl alcohol to be converted (0.86% Ph<sub>2</sub>Se<sub>2</sub>) into benzaldehyde, after which benzoic acid formation could no longer be suppressed. Another method of water elimination was to perform a Dean–Stark reflux after 30 cycles of the reaction.

By using this sequence, cinnamyl alcohol could be oxidized to cinnamaldehyde (180 mmol was converted; 0.55% Ph<sub>2</sub>Se<sub>2</sub>) without any byproduct formation. In this case, cinnamaldehyde was dissolved in toluene as a standard solution (2.0 M).

**Reaction Calorimetry.** This was performed in a Multimax apparatus: a programmable 4 parallel reactor box, reaction volume from 25 to 70 mL with overhead stirring, temperature range from –25 to +150 °C, reflux cooler and inter gas purging. Each reactor can be set individually for temperature and stirring. Temperature control modes: Jacket and reactor contents. Reaction calorimetry is done by adding a known amount of heat to the reaction mixture using a calibration probe (150 Ω, 24 V).

To a 100 mM solution of Ph<sub>2</sub>Se<sub>2</sub> at 80 °C was added the appropriate amount of TBHP in decane after which the temperature difference between the internal sensor (*T*<sub>i</sub>; temperature of the reaction) and the external sensor (*T*<sub>j</sub>; temperature of the jacket) was monitored.

**Calculation of Heat of Reaction of Oxidation of Diphenyl Diselenide with *tert*-Butyl Hydroperoxide.** The heat of reaction for the oxidation of diphenyl diselenide into benzeneseleninic acid anhydride (BSA) with *tert*-butyl hydroperoxide can be roughly estimated from the respective heats of formation of the different compounds involved, assuming that solvation enthalpies for substrates and products are equal. For this calculation, the Δ*H*<sub>f</sub> (g) for BSA was calculated with MOPAC using the semiempirical AM1 theory as –117 kJ/mol (in a comparison of known and calculated values for diphenyldiselenide, AM1 gave far better results than PM3; the difference between known and calculation amounted to an overestimation of only 42 kJ/mol in this case). Other values were taken from the *NIST Chemistry Webbook*.<sup>19</sup> Thus the Δ*H*<sub>f</sub> for the reaction:  $\frac{1}{3}\text{Ph}_2\text{Se}_2$  (Δ*H*<sub>f</sub> = 237 kJ/mol) + 1C<sub>4</sub>H<sub>9</sub>OOH (Δ*H*<sub>f</sub> = –235 kJ/mol) →  $\frac{1}{3}\text{PhSe(O)Se(O)Ph}$  (Δ*H*<sub>f,calc</sub> = –117 kJ/mol) + 1C<sub>4</sub>H<sub>9</sub>OH (Δ*H*<sub>f</sub> = –313 kJ/mol) can be estimated as –196 kJ/mol. Taking the calculated value of Ph<sub>2</sub>Se<sub>2</sub> instead of the true value leads to –211 kJ/mol. Given the uncertainty in calculated and liquid phase values, this is in good agreement with the observed heat of reaction of 150 kJ/mol TBHP.

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