# Synthesis of nitroarenes and azoxyarenes through the selenium-mediated on water oxidation of aryl amines

**Synthesis of nitroarenes and azoxyarenes through the selenium-mediated *on water* oxidation of aryl amines**

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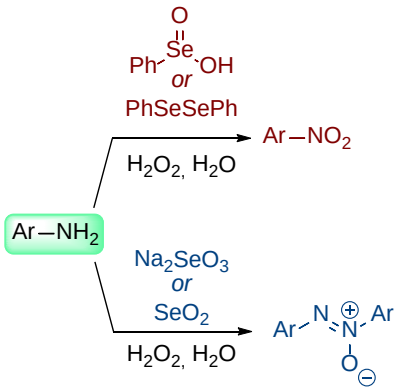
**Abstract**

Selenium-promoted oxidations enable a broad range of valuable oxidative functional group interconversions. Anilines are oxidised with hydrogen peroxide in water in the presence of selenium catalysts. The selenium catalyst determines the nature of the oxidation product; whereas nitroarenes are obtained employing diphenyl diselenide or benzeneseleninic acid, azoxyarenes are formed using selenium dioxide or sodium seleninate. The reaction mechanism relies on the reactivity of Se(IV) active oxidants, while Se(VI) species have been demonstrated not to be involved in.

**Graphical Abstract**

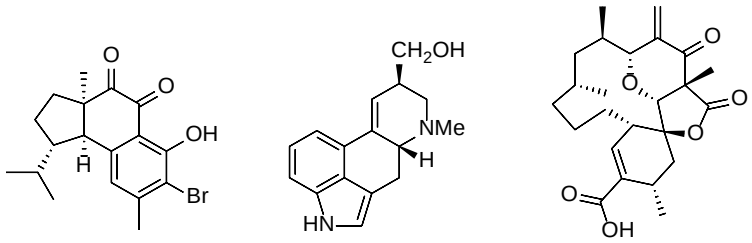



Selenium-promoted oxidative functional group interconversions occupy a privileged position in organic chemistry.[1-4] Both organic and inorganic selenium species are employed as catalysts for these reactions. While diselenides, seleninic acids, anhydrides, as well as other derivatives are used as organoselenium catalysts,[5] selenium(IV) oxide is arguably the most widely employed inorganic selenium species.[6] Hydrogen peroxide and tertbutyl hydroperoxide (TBHP) are the oxidant of choice in selenium-mediated oxidations.

A wide variety of organoselenium-catalysed methodologies for the oxidation of a number of organic compounds, including alkenes,[5,7,8] alkynes,[5] alcohols,[5,7-9] aldehydes, and ketones,[5] have been developed. Several selenium-catalysed versions of the Baeyer-Villiger oxidation,[10] as well as selenium-mediated α-oxyfunctionalization of alkenes[11] and ring contraction of cycloalkanones,[12,13] have also been reported. Additionally, a range of valuable selenium(IV) oxide-mediated protocols for the allylic oxidation of alkenes, cycloalkenes and alkynes, as well as for the trans-dihydroxylation of olefins have emerged as powerful transformations.[6]

The synthetic potential of such selenium-mediated routes is showcased by their use in the total synthesis of a number of natural products. For example, the $SeO_2$-mediated oxidation of the α-methylene group of a cyclohexanone derivative to the corresponding α-keto group is one of the steps involved in the total synthesis of 6-*epi*-(−)-hamigeran B.[14] The organoselenium-catalysed oxidation of indolines to indoles has been applied to the final step of the total synthesis of ergot alkaloyds, such as (±)-lysergol.[15] The well-

known $SeO_2$/TBHP-promoted allylic oxidation was successfully employed for the preparation of a key intermediate in the total synthesis of (−)-okilactomycin (Figure 1).[16]



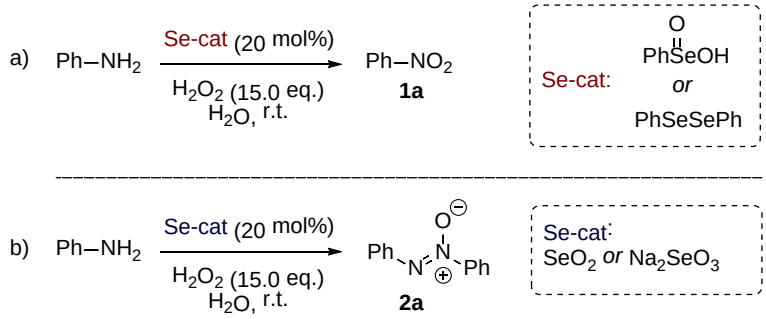

6-*epi*-(-)-Hamigeran B (±)-Lysergol (+)-Okilactomycin

Figure 1. Structures of selected natural products whose total synthesis involves selenium-mediated oxidation steps.

Besides the above-described transformations, the selenium-mediated thiol-disulfide oxidative interconversion has also received considerable attention because of its importance in biology. Indeed, the oxidation of glutathione (GSH) to the corresponding disulfide (GSSG) using peroxides (*i.e.*, $H_2O_2$), which in turn is reduced to safe species (*i.e.*, $H_2O$), plays a key role in the detoxification of cells from reactive oxygen species (ROS).[17-20] This simple but essential reaction is catalysed by glutathione peroxidases (GPxs), which are selenoenzymes and feature a selenocysteine residue in their catalytic pocket. Considering the potential importance of this transformation, a steadily growing number of selenium-containing small molecules capable to catalyse the oxidation of thiols to disulfides have been reported over the past decades.[21-33]
Oxidative transformations of alkenes and amines are broadly employed in the synthesis of biologically important small molecules. However, while the selenium-mediated epoxydation and dihydroxylation of alkenes have been widely explored, the oxidation of amines has received far less attention. Indeed, while a very few methodologies for the conversion of anilines to nitrosoarenes[34] or azoxyarenes[35] have been described, a selenium-based route for the oxidation of anilines to nitroarenes has been only recently developed by our group.[36] Nitro derivatives occupy an important position in organic synthesis[37] and are employed as versatile building blocks for the preparation of pharmaceutical,[38,39] dye,[40,41] materials,[42] and perfumes.[43] In some cases, the synthesis of nitroarenes *via* oxidation of anilines represents an attractive alternative to the variety of available nitration methodologies.[44-47]
During our studies in the chemistry of chalcogens, we became interested in the development of selenium-catalysed methodologies for the oxidation of sulfur- and nitrogen-containing functional groups.[26,28,29,31,36,48] Very recently, we focused our attention on anilines and envisaged the possibility to develop a sustainable route for their conversion to nitroarenes by exploiting the redox chemistry of organoselenium compounds.[36]

During our initial optimisation studies, a series of selenium-containing compounds at different oxidation state were evaluated as catalysts in the oxidation of aniline with hydrogen peroxide. Dialkyl- and diaryl-selenides and diselenides, as well as benzeneseleninic acid were employed. The study was also enlarged to include inorganic selenium species, such as selenium dioxide ($SeO_2$), sodium seleninate ($Na_2SeO_3$), and potassium selenonate ($K_2SeO_4$). This screening led us to find that both diphenyl diselenide (PhSeSePh) and benzeneseleninic acid (PhSeOOH) were effective in promoting the oxidation of aniline to nitrobenzene **1a** with high selectivity (Scheme 1, *reaction a*). Notably, the selectivity of the reaction could be controlled by simply switching the nature of the catalyst; indeed, azoxyarenes **2a** were formed upon using selenium(IV) oxide or sodium seleninate (Scheme 1, *reaction b*). Besides selenium-based catalysts, other chalcogen-

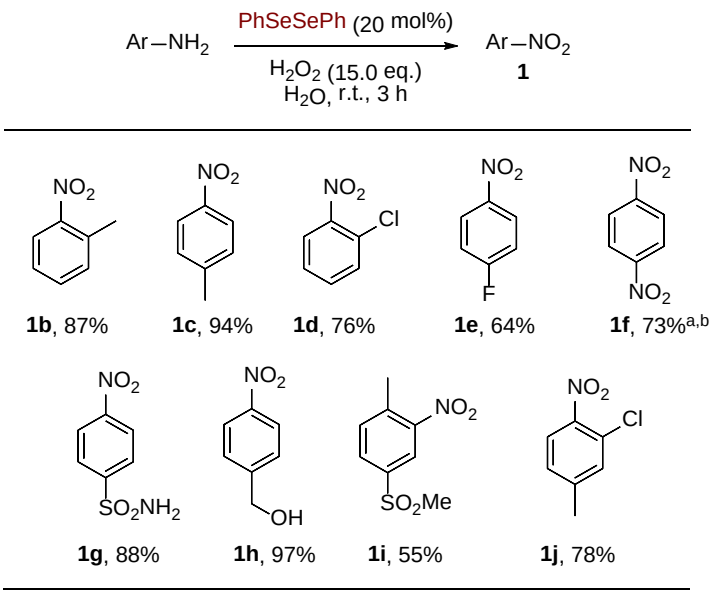
containing compounds – including disulfides, tellurides and ditellurides – were evaluated and found to be ineffective in promoting the oxidation herein described.




Scheme 1. selenium-promoted synthesis of nitroarenes and azoxyarenes.

As reported in the Scheme 1, the use of $H_2O$ as the solvent and the possibility to efficiently conduct the reaction at ambient temperature, represent additional attractive features of these selenium-promoted oxidation routes.

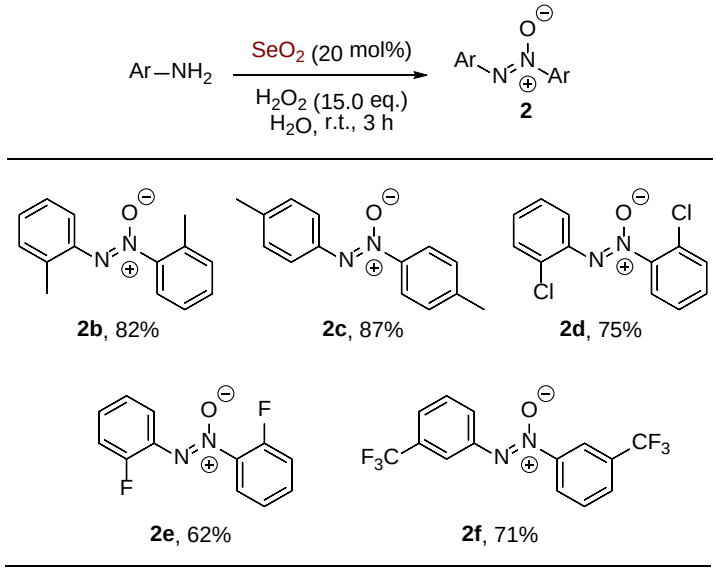
The substrate scope of both these processes was wide and a range of nitroarenes **1** and azoxyarenes **2** were easily prepared in high yields under the optimised reaction conditions. Anilines bearing both electron-donating and electron-withdrawing substituents were amenable to these Se-mediated methodologies and were efficiently converted into the corresponding substituted nitro- and azoxy- derivatives **1** and **2**. (Schemes 2 and 3). Further functionalisable halo-substituted derivatives were also achieved.



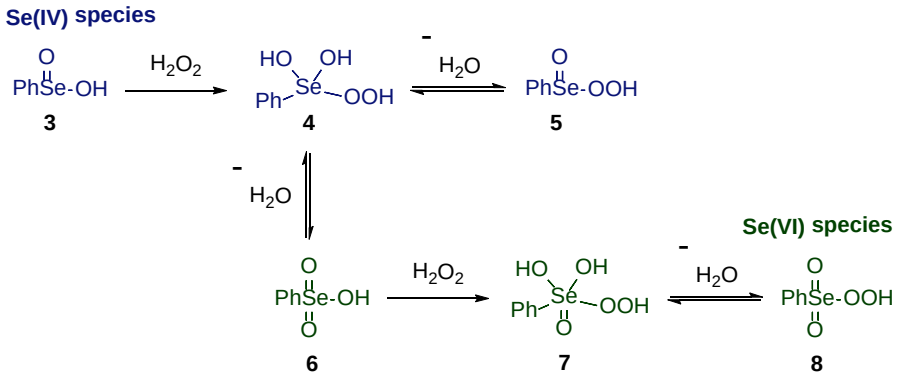

Scheme 2. Se-mediated oxidation of anilines to the corresponding nitroarenes (selected examples). Isolated yields are given. [a]Obtained from 4-nitroaniline. [b]The reaction mixture was warmed at 60 °C.

The reaction mechanism of selenium-mediated oxidation reactions generally proceeds through Se(IV) species (*i.e.*, benzeneseleninic acid and peroxybenzeneseleninic acid). However, the involvement of Se(VI) species (*i.e.*, benzeneselenonic acid and peroxybenzeneselenonic acid) in the epoxidation of alkenes has

been recently demonstrated.[49] Some Se(IV) and Se(VI) species involved in selenium-promoted oxidation reactions, along with their interconversion equilibria, are reported in the Scheme 4.




Scheme 3. Se-mediated oxidation of anilines to the corresponding azoxyarenes (selected examples). Isolated yields are given.

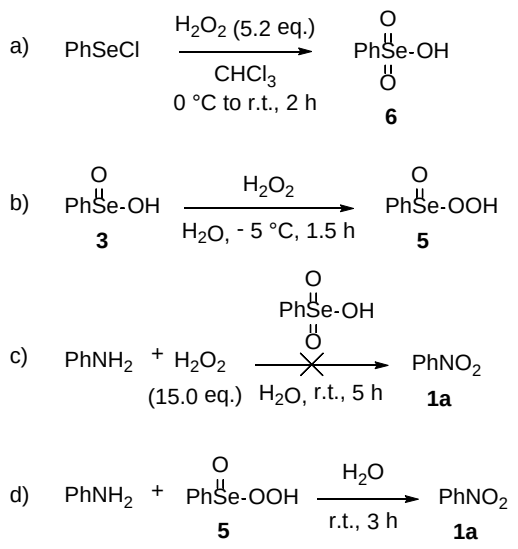



Scheme 4. Some Se(IV) and Se(VI) species involved in selenium-promoted oxidation processes.

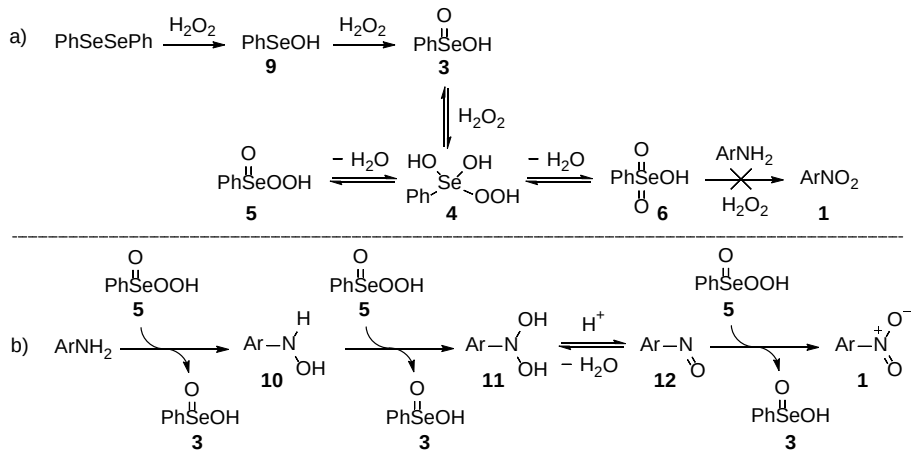
Our studies suggested that while Se(IV) species play a key role in the mechanism of the *on water* selenium-mediated oxidation of anilines to nitroarenes, Se(VI) species do not behave as effective oxidants in this transformation. Indeed, benzeneselenonic acid **6** – easily prepared upon treatment of benzeneselenyl chloride with hydrogen peroxide[50] (Scheme 5, *reaction a*) – does not promote the oxidation of aniline to nitrobenzene using hydrogen peroxide (Scheme 5, *reaction c*). On the other hand, peroxybenzeneseleninic acid **5** – obtained according to the literature[51] *via* oxidation of benzeneseleninic acid with $H_2O_2$ (Scheme 5, *reaction b*) – quickly oxidises aniline to provide nitrobenzene (Scheme 5, *reaction d*), thus demonstrating the key role of Se(IV) oxidants in this reaction mechanism.

Spurred by these observations, we proposed the mechanism reported in the Scheme 6. Oxidation of diphenyl diselenide with hydrogen peroxide provides benzeneselenenic acid **9**, which is further oxidised to give benzeneseleninic acid **3**.[52] Oxidation of **3** with hydrogen peroxide affords the peroxyselenurane **4**,

which can undergo dehydration to afford peroxybenzeneseleninic acid **5** or benzeneselenonic acid **6**. The latter has been demonstrated ineffective in promoting the conversion of aniline to nitrobenzene using hydrogen peroxide as the oxidant and water as the solvent (Scheme 6, *part a*). Conversely, **5** proved to effectively oxidise aniline to nitrobenzene; therefore, the proposed mechanism relies on the reactivity of peroxybenzeneseleninic acid **5** as the oxidant (Scheme 6, *part b*). Reaction of **5** with anilines reasonably provides the hydroxylamine **10**, which is further oxidised by **5** to afford the dihydroxylamine derivative **11**. In both these reactions, benzeneseleninic acid **3** is also formed. The active oxidant **5** is regenerated upon oxidation of **3** with hydrogen peroxide. The dihydroxylamine **11** probably undergoes an acid-promoted water elimination to provide the corresponding nitroso derivative **12**. Both benzeneseleninic acid and benzeneselenonic acid can promote the conversion of **11** to **12**. A final oxidation step is required to oxidise the nitrosoarene **12** to the nitroarene **1**.




Scheme 5. Synthesis of benzeneselenonic acid **6** and peroxybenzeneseleninic acid **5** and their reactivity in the oxidation of aniline.




Scheme 6. Selenium species formed upon oxidation of diphenyl diselenide (*Part a*). Proposed mechanism for the oxidation of anilines to nitroarenes and selenium species involved (*Part b*).

Notably, these results highlight that the mechanism operating for the selenium-mediated oxidation of anilines to nitroarenes proceeds through different species with respect to that involved in the mechanism of the epoxidation of alkenes. Particularly, while Se(VI) species (*i.e.*, selenonic acid, selenonium benzeneselenonate) have been showed to behave as catalysts in the epoxidation of olefins,[49] we recently demonstrated that such compounds do not play a catalytic role in the *on water* oxidation of anilines to nitroarenes with $H_2O_2$,[36] which plausibly relies on Se(IV) species (*i.e.*, benzeneseleninic acid). The active oxidant involved in the oxidation of anilines is reasonably peroxybenzeneseleninic acid **5** (or the peroxyselenurane derivative **4**). The above-described findings suggest that the active oxidants and the catalytic pathway of selenium-promoted oxidative interconversions might depend on the nature of the substrate and on the reaction conditions, thus opening new avenues for the development of selective oxidation protocols.

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