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Transition Metal-free Selenium-mediated Aryl Amines via Reduction of Nitroarenes

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A scalable and operationally simple on water seleno-mediated reduction of nitroarenes to the respective aryl amines with $NaBH_4$ is described. The reaction proceeds under transition metal-free conditions and is promoted by the formation of Na_2Se, which is the effective reducing agent involved in the mechanism. This mechanistic information enabled the development of a mild $NaBH_4$-free protocol for the selective reduction of nitro derivatives bearing labile moieties, including nitrocarbonyl compounds. The selenium-containing aqueous phase can be successfully reused up to four reduction cycles, thus further improving the efficiency of the protocol disclosed.

Introduction

Aryl amines are ubiquitous motifs in pharmaceuticals, dyes, agrochemicals, and polymers.[1,2] More than 60% of drugs and drug candidates contain the amine functionality.[3] Anilines constitute substructure of an array of pharmaceutical compounds (Scheme 1, part a), including fosamprenavir,[4] dapsone,[5] nomifensine,[6] procainamide,[7] paracetamol.[8] Undergoing a broad range of valuable transformations, aryl amines are also a privileged scaffold in organic synthesis and are employed as important intermediates for the preparation of a plethora of functionalised derivatives.[1,2,9]

Several methodologies for the synthesis of aryl amines have thus been developed. The reduction of nitroarenes provides direct and facile access to aryl amines and is arguably one of the most commonly employed strategies for their preparation.[10,11] The reduction of nitroaromatics into amines is considered the key intermediate stage in the synthesis of life-science products such as antioxidants, pharmaceuticals and agrochemicals.[12] For example, reductive conversion of nitro groups to amines accounts for almost 20% of all reduction reactions used in drug candidate synthesis.[3]

The Bechamp reaction – which relies on the reduction of nitroarenes using metals (Zn, Fe, Sn) in the presence of a Brønsted acid at elevated temperature – is traditionally employed to prepare aryl amines.[13,14] From the industrial point of view, aniline derivatives are generally synthesized by the hydrogenation of nitroarenes using noble metal-based thermal catalysts and H_2 pressurized gas as the reducing agent.

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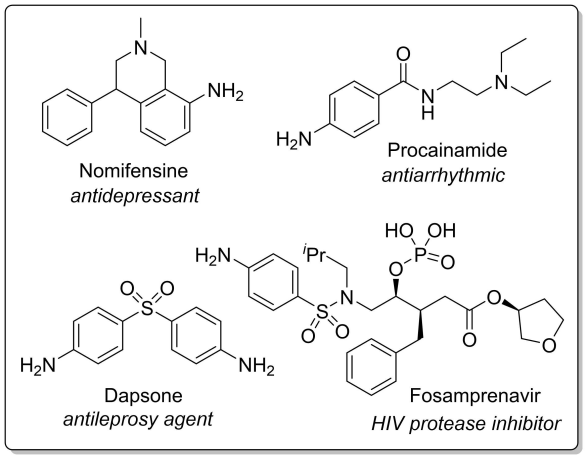
a) Pharmaceutical compounds containing aryl amines



b) Previous works

Se-catalysed reduction of nitroarenes

$$Ar{-}NO_2 + CO + H_2O \xrightarrow{Se^{(0)},\ Base} Ar{-}NH_2$$

$$Ar{-}NO_2 + NaBH_4 \xrightarrow[EtOH]{Se^{(0)}} Ar{-}NHOH$$

Se-catalysed oxidation of anilines to nitroarenes

$$Ar{-}NH_2 + H_2O_2 \xrightarrow[H_2O]{Se\text{-catalyst}} Ar{-}NO_2$$

c) This work

$$Ar{-}NO_2 \xrightarrow[H_2O,\ \Delta]{Se^{(0)}/NaBH_4/NaOH\ \textit{or}\ Na_2Se} Ar{-}NH_2$$

Scheme 1. Bioactive examples of aryl amines. Selenium-mediated redox functional group interconversions involving aryl amines.

However, the cost and the potential hazards of this process represent significant drawbacks. In addition, whereas the catalytic hydrogenation of simple nitroarenes poses few problems and can be effectively carried out on large scales, the presence of other reducible functional groups hampers its application to the synthesis of anilines bearing labile moieties. Thus, in some cases, the use of older, non-catalytic protocols still prevails despite the large amounts of waste produced through these processes.[15,16]

Since the Bechamp reaction was reported,[13] a number of methodologies for the reduction of nitroarenes to aryl amines have been developed. Different reducing agents, such as H_2, $NaBH_4$, silyl hydrides, hydrazine hydrate, $B_2(OH)_4$,[17] have been efficiently employed.[10,11] In situ hydrogen generation from acids or salts (i.e., from formic acid or formates[18] and hypophosphites[19] and from reaction of active metals with water) has also been exploited.[10,20] Additionally, non-classical organic reducing agents have been applied to develop alternative MPV (Meerwein–Ponndorf–Verley) type redox protocols.[10] However, although significant progresses have been made, most of these methodologies require harsh reaction conditions, employ transition metals, and also share drawbacks related to the use of hazardous reagents and/or solvents. In this scenario, the development of sustainable, efficient and selective approaches for the reduction of nitroarenes under safe and eco-friendly conditions is a great challenge. In this regard, photocatalysed[21–23] and biocatalysed[24,25] approaches have recently emerged.

Attractive methodologies for the conversion of nitroarenes to anilines under mild conditions harness the ability of sulfur- and selenium-containing reagents to behave as reducing agents under transition metal-free conditions. The use of negative divalent sulfur species (S^{2-}, HS^-, $[S_n]^{2-}$) for the reduction of nitroarenes dates back to 1842, when Zinin applied it to the synthesis of aniline.[26] However, albeit its potential, with the advent of catalytic procedures the Zinin reduction has received marginal attention.[27,28] A few protocols for the reduction of nitroarenes using elemental sulfur under basic conditions[29,30] or sodium dithionite[31] have been described.

A limited number of selenium-based methodologies, using H_2Se or Na_2Se as the effective reducing agent, have also been developed. In such procedures H_2Se and Na_2Se are often generated upon reaction of elemental selenium with CO or $NaBH_4$, respectively (Scheme 1, part b).[32–34]

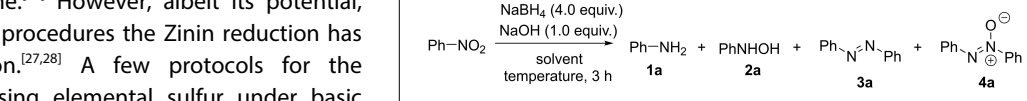
Indeed, while selenium-mediated oxidative functional group interconversions have been widely investigated and have become a well-established tool in organic synthesis,[35] the application of selenium reagents in reductive transformations have been far less explored. During our studies on the redox properties of selenium compounds,[36] we unveiled an efficient organoseleno-mediated protocol for the selective oxidative conversion of anilines to nitroarenes and azoxyarenes (Scheme 1, part b).[37] Spurred by the versatility and the multifaceted nature of selenium reagents, we considered to use reduced Se species (i.e., RSe^-, Se^{2-} anions) as reductants and envisaged the possibility to develop a selenium-catalysed approach for the reduction of nitroarenes to aryl amines. Herein, we report our successful development of seleno-mediated methodologies for the reduction of nitroarenes to anilines (Scheme 1, part c) and detail the role of selenium species in the reaction mechanism.

Results and Discussion

Selenium-catalysed reduction of nitroarenes with $NaBH_4$

We began our investigations studying the reduction of nitrobenzene to aniline. Considering that the reduction of elemental selenium with sodium borohydride readily occurs using polar protic solvents such as alcohols,[36b,38] an initial set of experiments was performed in ethanol, methanol, and water (Table 1, entries 1–3). In all cases, an excess of $NaBH_4$ (4.0 equiv.) was employed along with NaOH (1.0 equiv.) and elemental selenium (0.2 equiv.).[39] However, no traces of aniline **1a** were detected conducting the reaction at ambient temperature in ethanol and methanol (Table 1, entries 1 and 2). Indeed, a mixture of *N*-phenylhydroxylamine **2a**, azobenzene **3a**, and azoxybenzene **4a** in variable ratios was always formed. Traces of aniline **1a** were formed when H_2O was used as the solvent; notably, under these conditions *N*-phenylhydroxylamine **2a** proved to be the largely predominant reaction product (Table 1, entry 3). In all cases the starting material was completely consumed after 3 h of reaction (Table 1, entries 1–3), even though none of these conditions proved to be suitable for the effective reduction of nitrobenzene to aniline. Conversely, in absence of the base

Table 1.



Entry	Solvent	Temp.	Conv. [%][a]	Yield [%]			
				1a	**2a**	**3a**	**4a**
1	EtOH	RT	>96	–	40	22	38
2	MeOH	RT	>96	–	59	10	31
3	H_2O	RT	>96	5	90	–	5
4	EtOH	reflux	>96	–	15	65	20
5	H_2O	reflux	>96	92[b]	4	–	4
6	EtOH/THF	reflux	<5	–	–	–	–
7	EtOH/H_2O	reflux	>96	–	43	31	26
8	EtOH/H_2O	RT	>96	–	30	9	61
9[c]	H_2O	reflux	>96	64	15	11	10
10[d]	H_2O	reflux	>96	94	6	–	–
11[e]	H_2O	reflux	>96	60	15	6	19
12[f]	H_2O	reflux	>96	89	–	–	11
13[g]	H_2O	reflux	>96	86	6	–	8
14[h]	H_2O	reflux	26	94	–	6	–
15[i]	H_2O	reflux	>96	91	–	–	9

[a] Conversion was determined via ^{1}H NMR spectroscopy using internal standard. [b] 88% isolated yield. [c] 0.1 equiv. instead of 0.2 equiv. of Se^0 was used. [d] 0.4 equiv. instead of 0.2 equiv. of Se^0 was used. [e] 2.0 equiv. instead of 4.0 equiv. of $NaBH_4$ was used. [f] CsOH was used in place of NaOH. [g] KOH was used in place of NaOH. [h] 0.2 equiv. of NaOH was used; 64% of nitrobenzene remained unreacted. [i] 4.0 equiv. of NaOH was used.

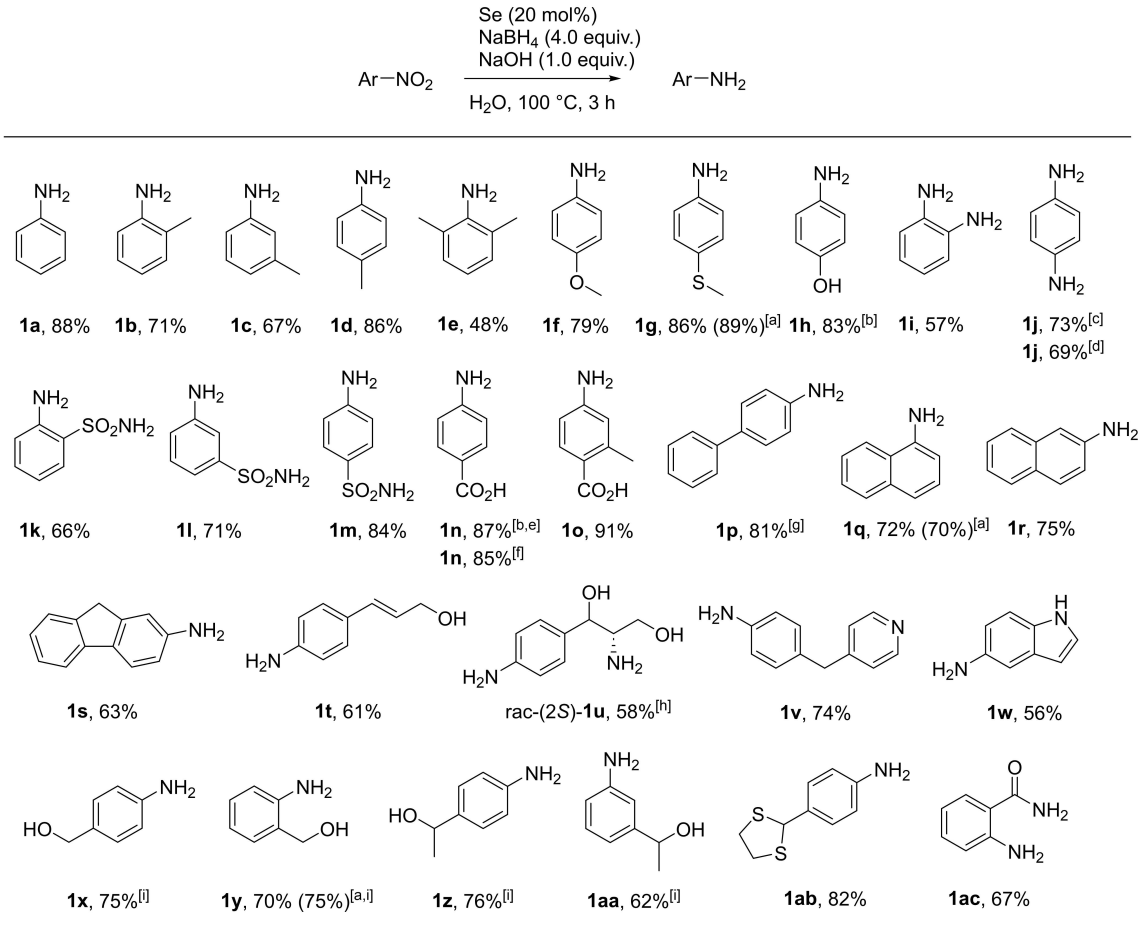
NaOH, the reduction of nitrobenzene was completely suppressed and the starting material was recovered unreacted.

We then evaluated the effect of the temperature and performed the above-described reaction under refluxing conditions (Table 1, entries 4 and 5). Although aniline **1a** was not formed in refluxing ethanol, the decreased amount of azoxybenzene **4a** in favour of the more reduced diazobenzene **3a** highlighted the key role of the temperature in determining the nature of the reaction products. Indeed, we were pleased to find that the reduction of nitrobenzene with Se/$NaBH_4$/NaOH in refluxing H_2O afforded aniline **1a** as the main reaction product (Table 1, entry 5). The formation of aniline was not achieved when mixed solvents (i.e. EtOH/THF, EtOH/H_2O) were used under different conditions (Table 1, entries 6–8).

We found that reducing the amount of selenium (from 0.2 equiv. to 0.1 eq, Table 1, entry 9) led to a significant erosion of selectivity, whilst its increasing (from 0.2 equiv. to 0.4 equiv., Table 1, entry 10) improved only slightly the reaction outcome. When the amount of $NaBH_4$ was decreased from 4.0 equiv. to 2.0 equiv. (Table 1, entry 11), the selectivity of the reaction resulted significantly diminished.

The effect of the nature of the inorganic base was also investigated and found not to significantly influence the reaction outcome; comparable results with respect to the use of NaOH were obtained either employing CsOH or KOH (Table 1, entries 12, 13). Finally, while decreasing the amount of the base to 0.2 equiv. proved to be detrimental for the formation of aniline **1a** (Table 1, entry 14), the use of a large excess of base (4.0 equiv.) did not further improve the selectivity of the reduction (Table 1, entry 15 vs entry 5 or 10).

With the optimised conditions in hands, we next set out to explore the scope and the limitations of this selenium-mediated reduction methodology (Scheme 2). A series of structurally diverse nitro derivatives was thus submitted to the optimised reduction protocol. The reaction was amenable to nitroarenes bearing electron-donating and electron-withdrawing substituents at different position of the aromatic ring. The three *ortho*-, *meta*-, and *para*- isomers of toluidine **1b**–**d** were smoothly achieved in good yields. Reduction of 2,6-dimethylnitrobenzene



Scheme 2. Reaction scope for the selenium-mediated reduction of nitoarenes with $NaBH_4$. Isolated yields are given. [a] Yields in parentheses refers to reactions performed on a 10 mmol scale. [b] 2.0 equiv. of NaOH were used. [c] The yield refers to the product obtained upon reduction of 4-nitroaniline. [d] The yield refers to the product obtained upon reduction of *N*-(4-nitrophenyl)acetamide. [e] The yield refers to the product obtained upon reduction of 4-nitrobenzoic acid. [f] The yield refers to the product obtained upon reduction of methyl 4-nitrobenzoate. [g] 4 equiv. of Se^0 were used. [h] Epimerization at C-1 was observed using the enantioenriched nitroarene precursor (see Supporting Information for details). [i] The yield refers to the product obtained upon reduction of the corresponding nitrocarbonyl compounds.

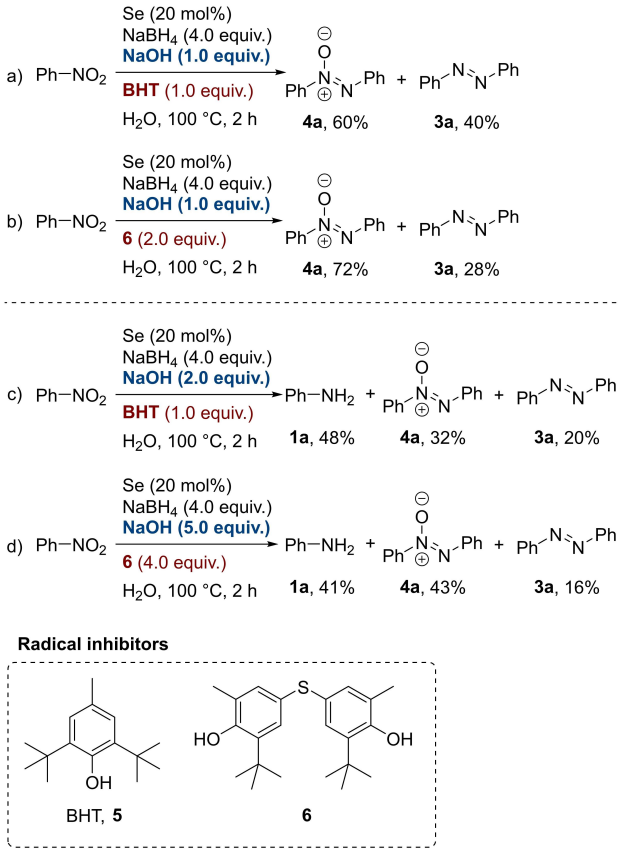
afforded 2,6-dimethylaniline **1e** in moderate yield, highlighting that the reaction is sensitive to the steric hindrance. 4-Anisidine **1f**, 4-thioanisidine **1g**, 4-aminophenol **1h**, 1,2-diaminobenzene **1i**, and 1,4-diaminobenzene **1j** were efficiently obtained from the corresponding nitroarenes bearing methoxy, methylthio, hydroxy, and amino electron-donating groups. Notably, owing to the acidity of phenols, which readily react with NaOH leading to its consumption, the reductive conversion of 4-nitrophenol to **1h** required the use of an excess of the base (2.0 equiv. of NaOH).

Nitroarenes bearing electron-withdrawing substituents were easily reduced to the corresponding substituted aryl amines (Scheme 2). Aminobenzenesulfonamides **1k–m** were therefore prepared in good yield. Similarly, 4-aminobenzoic acid **1n** and 2-methyl-4-aminobenzoic acid **1o** were successfully synthesised upon reduction of the corresponding nitrobenzoic acids. Notably, the aminoacid **1n** was also formed conducting the reduction reaction on ethyl-4-nitrobenzoate. Indeed, as expected, the hydrolysis of the ester functionality readily occurred under $NaBH_4$/NaOH/H_2O conditions. 4-Aminobiphenyl **1p** was also prepared upon reduction of the corresponding nitro derivative. However, a higher amount of Se^0 (0.4 equiv. instead of 0.2 equiv.) was necessary to obtain satisfactory yield of amine **1p**. This simple protocol was efficiently extended to the synthesis of polycyclic amines such as α- and β-naphthylamine **1q** and **1r**, and 2-aminofluorene **1s**. Interestingly, the reduction of 4-nitrocinnamyl alcohol selectively provided 4-aminocinnamyl alcohol **1t**, thus highlighting how the methodology well tolerates the presence of both alcohols and alkenes. The synthesis of the polyfunctionalised aminoalcohol **1u** via reduction of the parent nitroarene further demonstrates the functional group tolerance of the reaction with respect to free hydroxy and amino functionalities. However, epimerisation at the hydroxy-substituted C-1 carbon of **1u** was observed under these Se^0/$NaBH_4$/NaOH conditions. The reaction scope was also enlarged to include nitroderivatives bearing heteroaromatic moieties, enabling the synthesis of 4-(*p*-aminobenzyl)pyridine **1v** and 5-aminoindole **1w** in good yield (Scheme 2).

We next turned our attention to the reactivity of nitroarenes bearing carbonyl groups. Sodium borohydride is the reagent of choice to reduce aldehydes and ketones to the corresponding primary and secondary alcohols, respectively. Thus, as expected, the reduction of nitro aldehydes and ketones under the standard conditions provides access to the corresponding aminoalchols. Although the reduction of the nitro group was efficiently accomplished using this selenium-mediated protocol, the reduction of competing carbonyl functionalities could not be avoided. Nonetheless, this simple methodology enables the direct synthesis of aminobenzyl alcohols **1x,y** and amino-α-methylbenzyl alcohols **1z,aa** from the corresponding nitrobenzaldehyde and nitroacetophenone precursors. Furthermore, the protocol here unveiled well tolerates protected carbonyl groups, as showcased by the efficient synthesis of aniline derivative **1ab**, bearing the aldehyde functionality masked as 1,3-dithiolane. Amides were also well tolerated, thus enabling the application of the methodology to the selective reduction of nitrobenzamide to anthranilamide **1ac**, which is a valuable intermediate in the synthesis of biologically- and technologically-relevant compounds (Scheme 2). The reaction was found to be robust on a large scale, giving products **1g**, **1q**, and **1y** in 89%, 70%, and 75% yield, respectively on a 10 mmol scale (Scheme 2). Unfortunately, a number of nitroarenes bearing other labile moieties (i.e., boronic acids, nitriles, sulfones) were not selectively reduced under these reaction conditions. Additionally, a competitive nucleophilic aromatic substitution occurring with halo-substituted nitroarenes, hampers the application of this selenium-mediated approach to the synthesis of halo-substituted anilines. The substrate limitation of the Se^0/$NaBH_4$/NaOH methodology here developed is reported in the Scheme S1 (Supporting Information).

Investigation of the reaction mechanism

To glean insight into the mechanism of this unprecedented selenium-mediated reduction, we performed a series of experiments to confirm the nature of the key reactive intermediates and identify the effective reducing species involved in the reaction. An initial set of control experiments was conducted in order to understand whether the reaction could proceed through a radical pathway. Buthylhydroxytoluene **5** and the sulfide **6** were thus employed as radical inhibitors in two separate reactions under standard conditions (Scheme 3, reac-



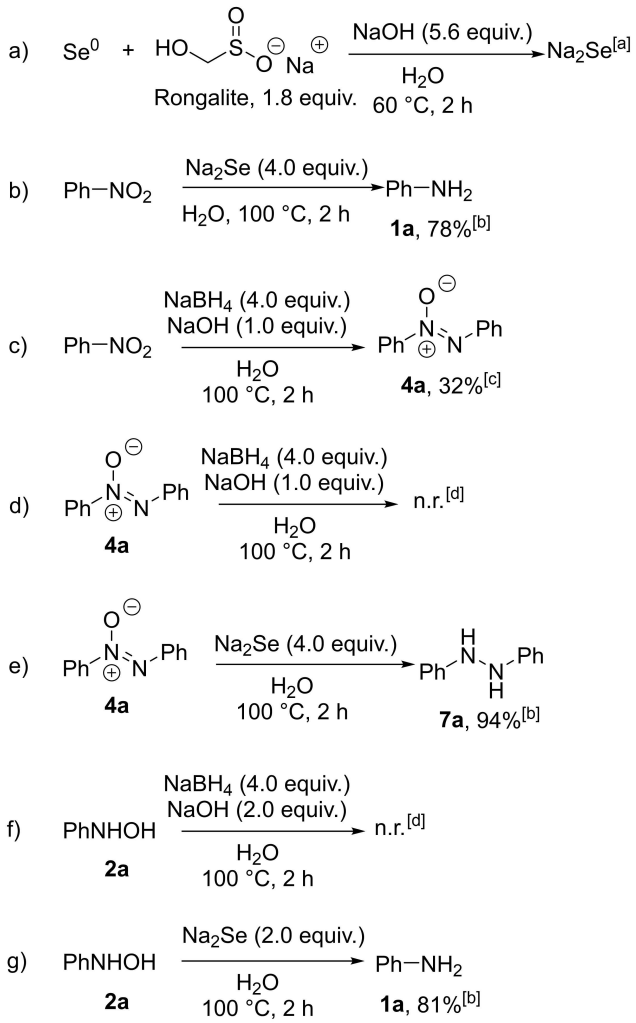
Scheme 3. Control Experiments with radical inhibitors.

tions a and b). Notably, in both cases the formation of aniline resulted completely suppressed, and a mixture of diazobenzene **3a** and azoxybenzene **4a** was achieved. However, these results do not provide a direct evidence of a radical mechanism. Indeed, an acid-base reaction between the phenolic proton(s) of BHT or **6** ($pK_a \approx 10.0$)[40] and NaOH leading to the consumption of the base – which was demonstrated to be critical for the formation of aniline – quickly occurs. The neutralisation of the base, rather than the radical inhibition, may account for the results obtained in the presence of phenol-derived systems **5** and **6**. To elucidate this point, two additional reactions (Scheme 3, reactions c and d) were performed using BHT and **6** (1.0 equiv. and 4.0 equiv., respectively) in the presence of an excess of NaOH (2.0 equiv. and 5.0 equiv., respectively). The formation of aniline **1a**, obtained under these conditions, led us to rule out a radical mechanism and further highlighted the key role of the base in the reduction methodology here unveiled.

The methodology here developed relies on the hypothesis that Na_2Se, in situ generated from elemental selenium and $NaBH_4$ in the presence of NaOH, is the active reducing species involved in the reaction mechanism. To test this hypothesis Na_2Se was freshly prepared upon reduction of Se^0 with rongalite (Scheme 4, reaction a)[41] and treated with nitrobenzene. The reaction, conducted in water in absence of any other additional reducing agent, afforded aniline **1a** in good yield and high selectivity (Scheme 4, reaction b). Additionally, treatment of nitrobenzene with $NaBH_4$/NaOH in H_2O at 100 °C in absence of selenium (Scheme 4, reaction c) provided only low yield of azoxybenzene **4a**, thus further corroborating the key role of selenium-containing reducing species in the reaction mechanism.

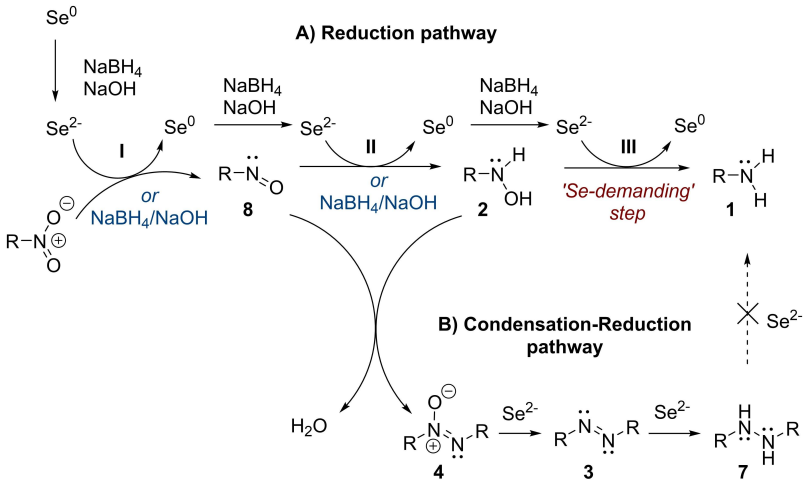
Azoxybenzene **4a** is obtained via condensation of *N*-phenylhydroxylamine **2a** with nitrosobenzene, two key intermediates commonly formed during the reduction of nitrobenzene to aniline.[16,42] During our studies on the optimisation of the reaction conditions we noticed that significant amounts of **4a** were often formed. We therefore investigated whether azoxybenzene could be a plausible reaction intermediate under our reduction conditions. However, neither the $NaBH_4$/NaOH system nor the Na_2Se were effective in promoting the reduction of **4a** to **1a**. (Scheme 4, reactions d and e). Notably, while azoxybenzene **4a** remained unreacted upon treatment with $NaBH_4$/NaOH, it smoothly reacted with Na_2Se in H_2O at 100 °C to give 1,2-diphenylhydrazine **7a** in excellent yield and selectivity. These results clearly ruled out a possible involvement of **4a** in the pathway leading to aniline. Finally, to evaluate whether *N*-phenylhydroxylamine **2a** could be a plausible intermediate, we attempted its reduction with both $NaBH_4$/NaOH and Na_2Se (Scheme 4, reactions f and g). Intriguingly, **2a** was efficiently reduced by Na_2Se to give aniline **1a** in good yield, whilst remaining completely unreacted upon treatment with the $NaBH_4$/NaOH system. Such results clearly support a direct reduction mechanism, albeit the condensation-reduction pathway is generally favoured under basic conditions.[16]

Based on our control experiments and literature reports[16,27,34,42] we propose the mechanism shown in Scheme 5. The reduction of the nitro derivative with Na_2Se – generated



Scheme 4. Control experiments. [a] Na_2Se was freshly prepared and readily used as it quickly decomposes at ambient temperature. See Supporting Information for details on the isolation of Na_2Se. [b] Isolated yield is reported. [c] Conversion is reported; 68% of nitrobenzene remained unreacted. [d] Only the unreacted substrate was recovered after the reaction.

in situ from elemental selenium under $NaBH_4$/NaOH conditions in water – provides the nitroso compound **8** and elemental selenium, which is easily reduced back to Na_2Se by the $NaBH_4$/NaOH reducing system (Scheme 5, step I). Control experiments (*vide infra*) indicated that, to a certain extent, the reduction of nitroarenes to **8** might also occur under selenium-free conditions, using the $NaBH_4$/NaOH system. However, the low conversion value observed for the reaction performed in absence of selenium (*vide supra*, Scheme 4, reaction c) suggested that the Se-free reduction plays only a marginal role in this step. Subsequently (Scheme 5, step II), the nitroso derivative **8** is reduced to the corresponding hydroxylamine **2** by either Na_2Se or $NaBH_4$.[43] The mechanism can then proceed through the two following alternative routes: i) a direct reduction pathway (Scheme 5A), involving the sequential reduction of nitrosobenzene **8** to hydroxylamine **2** and, finally to aniline **1**; ii) a condensation-reduction pathway (Scheme 5B),



Scheme 5. Proposed reaction mechanism.

involving the reaction of nitrosobenzene **8** with hydroxylamine **2** to afford the azoxybenzene **4**, which can be subsequently reduced to diazobenzene **3**, 1,2-diphenylhydrazine **7** and, finally, to aniline **1**. Our control experiments highlighted that **4a** does not undergo complete selenium-mediated reduction to give aniline **1a** (only 1,2-diphenylhydrazine **7a** was formed, see above), thus clearly indicating that the mechanism proceeds through a direct reduction pathway. Additionally, as the hydroxylamine **2a** proved to be completely unreactive under the selenium-free reductive conditions (Scheme 4, reaction f), the reduction of **2** to **1** (Scheme 5, step III) is reasonably the selenium-demanding step. In absence of selenium **2** is not reduced and undergoes condensation with **8** to yield the azoxy-derivative **4**. On the other hand, in the presence of Na_2Se, **2** is promptly reduced to **1**, thus limiting the formation of **4**. Indeed, our results highlighted that the step III cannot occur in absence of selenium. On the other hand, as the formation of azoxybenzene **4** – arising from condensation of **8** with **2** – is significantly reduced using Na_2Se, reasonably selenium also acts enhancing the constant rate of the step II. However, the formation of **4** under selenium-free conditions provides evidence that II is not a selenium-demanding step.

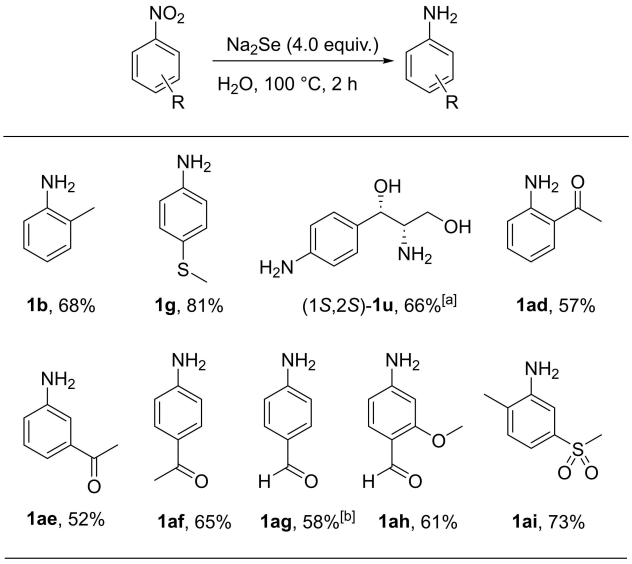
To elucidate the nature and the oxidation state of selenium species formed at the end of the reaction, the aqueous phase was analysed by ^{77}Se NMR spectroscopy. No signal related to water-soluble selenium species was detected. This result, coupled with an insoluble greyish powder always observed after the reaction, is supportive of the formation of Se^0.

Having elucidated the reaction mechanism and identified the selenium species formed after the reduction cycle, we sought to evaluate whether the aqueous phase could be recovered and reused as the selenium-containing medium to perform further reductions. In a model experiment, the aqueous phase recovered after the reduction of α-nitronaphthalene (10 mmol scale) was efficiently reused to prepare **1q** upon simple treatment with $NaBH_4$ and NaOH. No additional Se^0 was required and the aqueous phase could be employed for the reduction of α-nitronaphthalene to α-naphthylamine **1q** up to four cycles with no substantial yield decrease (see Supporting Information Figure S1).

Reduction of nitroarenes with Na_2Se

Having demonstrated that sodium selenide is the reducing agent effectively involved in the conversion of nitroarenes to anilines, we sought to develop an alternative sodium borohydride-free approach for the reduction of nitro derivatives and to evaluate its selectivity. Thus, a series of differently substituted nitroarenes were reacted with an excess of freshly prepared Na_2Se using water as the solvent (Scheme 6). Simple aryl amines **1b** and **1f** were achieved in comparable yield with respect to the selenium-mediated reduction with $NaBH_4$ (see Scheme 2).

Considering the mildness of Na_2Se as a reducing agent, we were attracted by the possibility to selectively reduce the nitro group in the presence of labile functionalities. Our attention was therefore focused on the reactivity of nitrocarbonyl compounds. Thus, 2-nitroacetophenone was treated with an excess of Na_2Se in H_2O and warmed at 100 °C for 1 h. Pleasingly, a selective reduction of the nitro functionality smoothly occurred, leading to 2-aminoacetophenone **1ad** (Scheme 6). 3-Aminoacetophenone **1ae** and 4-aminoacetophenone **1af** were also obtained in good yield via reduction of the corresponding nitro ketones with Na_2Se. To the best of our knowledge, in spite of their importance, examples of metal-free protocols for the selective reduction of nitrocarbonyl compounds to the corresponding aminocarbonyl derivatives are very rare.[20] Attracted by the selectivity and the versatility of our selenium-based approach, we explored the reactivity of the more challenging nitro aldehydes. Remarkably, 4-aminobenzaldehyde **1ag** was easily prepared simply warming 4-nitrobenzaldehyde with aqueous sodium selenide. Similarly, selective reduction of 4-nitro-2-methoxybenzaldehyde provided the amino aldehyde **1ah** in good yield. Finally, in order to further evaluate the



Scheme 6. Reduction of nitroarenes with Na_2Se. Isolated yields are given. [a] Synthesised from the corresponding enantioenriched functionalised nitroarene. [b] Partial decomposition was observed during purification on silica gel.

functional group tolerance of this methodology, the reaction was applied to additional nitro derivatives bearing labile functionalities, including sulfones, boronic acids, and nitriles. Interestingly, the reduction of the nitro group occurred with high selectivity in the presence of the potentially competing sulfone leading to the sulfonylaniline derivative **1ai**, which could not be prepared under $Se^0/NaBH_4/NaOH$ conditions (Scheme 6). On the other hand, nitroarenes bearing halogens, cyano or boronic acid moieties cannot be selectively reduced under these conditions. Particularly, halo-substituted nitroarenes undergo aromatic nucleophilic substitution with Na_2Se to afford a mixture of the corresponding amino-substituted diaryl selenides and diselenides. The substrate limitation of the reduction with Na_2Se is reported in the Schemes S2 and S3 (Supporting Information).

The possibility to recycle the aqueous phase to regenerate Na_2Se was also evaluated. Black/reddish selenium was recovered from the aqueous layer by filtration; in our hands, 87% of the used selenium could be recovered upon simple filtration of the aqueous layer. The recovered black/reddish selenium was then treated with rongalite and NaOH to afford white Na_2Se (*vide supra*), which could be successfully used to reduce nitrobenzene to aniline in good yield. The recovered selenium could also be efficiently used in the selenium-catalysed reduction of nitrobenzene using the $NaBH_4$/NaOH system as described above (Scheme 2).

Conclusions

In conclusion, we have unveiled an on water selenium-mediated approach for the reduction of nitroarenes to aryl amines using $NaBH_4$. The reaction scope encompasses a broad variety of differently substituted nitro derivatives. Careful mechanistic investigations highlighted that sodium selenide (Na_2Se) is reasonably the effective reducing agent involved in the process and provided evidence that the conversion of a *N*-arylhydroxylamine to the corresponding aniline is the key selenium-demanding step. These results also enabled the development of an alternative simple and mild methodology relying on the use of Na_2Se in water, in absence of any other additional reducing agent. This approach proved to be highly chemoselective for the reduction of nitro groups and was efficiently applied to the synthesis of aminoketones, aminoaldehydes, and aminosulfones.

Experimental Section

Reduction of nitroarenes to aryl amines with Se^0/NaBH4/NaOH

Elemental selenium (Se^0; 32 mg, 0.4 mmol, 0.2 equiv.) was suspended in H_2O (4 mL) and treated with $NaBH_4$ (304 mg, 8.0 mmol, 4.0 equiv.) and NaOH (80 mg, 2.0 mmol, 1.0 equiv.). The initial suspension was stirred at room temperature for 10 min, after which the suspension turned to a colourless-slightly yellow solution. Then, the nitroarene (2.0 mmol, 1.0 equiv.) was added and the mixture was stirred under reflux at 100 °C for 3 h. Afterwards, the aqueous reaction mixture was extracted with EtOAc (3×5 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash chromatography to yield the pure aryl amine **1**.

Preparation of Sodium selenide (Na_2Se)

Elemental selenium (Se^0, 0.40 mg, 5.06 mmol) was added to an aqueous solution (5 mL) of rongalite (sodium hydroxymethanesulfinate, 1.43 g, 9.25 mmol) and NaOH (1.13 g, 28.13 mmol) and the resulting mixture was stirred at 60 °C for 1 h. 2After this time, the formation of a white precipitate was observed. The mixture was cooled in an ice bath and the formed solid was quickly recovered by filtration under inert atmosphere (N_2). Partial decomposition of the white Na_2Se, with the concomitant formation of a brown-reddish solid, occurred upon storing Na_2Se. Thus, freshly prepared white Na_2Se was always used.

Reduction of nitroarenes to aryl amines with Na_2Se

Freshly prepared Na_2Se (500 mg, 4.0 mmol, 4.0 equiv.) was suspended in H_2O (8 mL) and the nitroarene (1.0 mmol, 1.0 equiv.) was added. The mixture was stirred under reflux at 100 °C for 2 h. Afterwards, the aqueous reaction mixture was extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by flash chromatography to yield the pure aryl amines **1**.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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