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Reduction of Selenoamides to Amines Using SmI_2–H_2O

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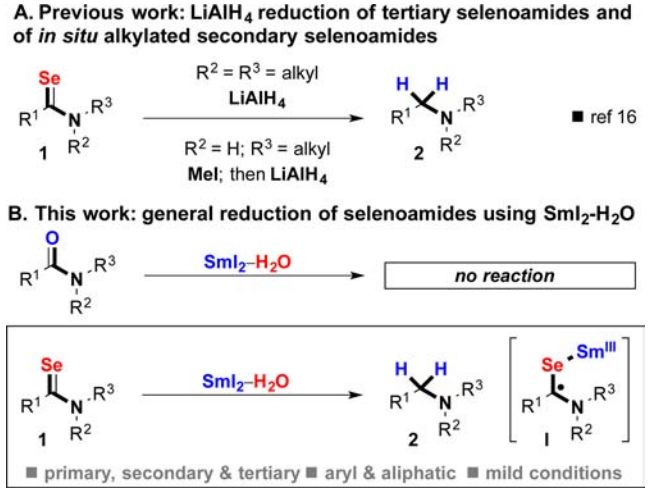
Supporting Information

ABSTRACT: Selenoamides are selectively reduced to amines by SmI_2 with H_2O. The process is general for primary, secondary, and tertiary aryl and alkyl selenoamide substrates and selectively delivers amine products. The reduction proceeds under mild conditions using SmI_2 activated by straightforward addition of H_2O, and does not require an additional Lewis base additive.

Samarium diiodide (SmI_2, Kagan's reagent) is one of the most widely used single electron transfer (SET) reagents.[1,2] The commercially available reagent has found particularly broad application in functional group reductions[3] and carbon–carbon bond-forming reactions.[4] Its ability to promote radical and anionic transformations, combined with the possibility of fine-tuning the reactivity of the reagent through the use of additives, typically allows high levels of chemo- and stereoselectivity to be achieved. Despite this versatility, for many years the reduction of carboxylic acid derivatives seemed to lie beyond the scope of SmI_2. Only recently, we reported the first reductions of unactivated carboxylic acid derivatives with SmI_2-based reagent systems under mild conditions, offering a safer and more selective alternative to pyrophoric alkali metals and metal hydrides.[5−11] The use of SmI_2 in combination with H_2O and amine additives is key to unlocking this reactivity and allows the reduction of carboxylic acids,[5] esters,[6−8] amides,[9] and nitriles[10] under a SET regime.[11] The ketyl-radical intermediates formed by SET to the carbonyl groups in esters and amides have been trapped in new radical cyclizations and cyclization cascades.[12]

Selenoamides are useful building blocks in synthesis[13] and medicinal chemistry[14] and are readily obtained using various methods including straightforward preparation from amides and nitriles.[15] However, their reduction is currently limited to tertiary selenoamides or to secondary selenoamides that are first activated by alkylation of selenium (Scheme 1A).[16] Thus, a reduction method is needed that is applicable to all selenoamides and allows the valuable functional handle to be manipulated without prior activation. Acyclic amides do not undergo productive reduction with SmI_2–H_2O but are reduced with SmI_2–H_2O–NR_3 to yield the corresponding *alcohols* rather than amines.[9] We proposed that easily accessible selenoamides would be reduced by SmI_2–H_2O, without the need for an amine additive and that the carbon selenium bonds would be cleaved preferentially to deliver *amine* products (Scheme 1B), thus completing a chemodivergent approach to the reduction of amides under mild conditions using Sm(II).

Scheme 1. (A) Limited Scope of Previous Selenoamide Reductions; (B) SmI_2-Mediated Reduction of Selenoamides



Herein we report a general reduction of selenoamides **1** to amines **2** using SmI_2–H_2O that proceeds under mild conditions via a SET mechanism.[17] Furthermore, we illustrate the potential to exploit the radical intermediates **I** formed by SET reduction of the selenocarbonyl group in intramolecular carbon–carbon bond formation (Scheme 1B).

To assess the feasibility of the transformation, we screened various reducing conditions using model substrate **1a** (Table 1). Reduction to the corresponding amine took place smoothly when using H_2O as the additive, and in contrast to the reduction of amides with SmI_2,[9] the addition of an amine additive was not necessary.

The use of 36 equiv of H_2O proved optimal (entry 1) as the use of larger amounts of the additive had a detrimental effect on the reaction outcome (entries 2 and 3). Reducing the amount

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Table 1. Optimization of Selenoamide Reduction Conditions[a]

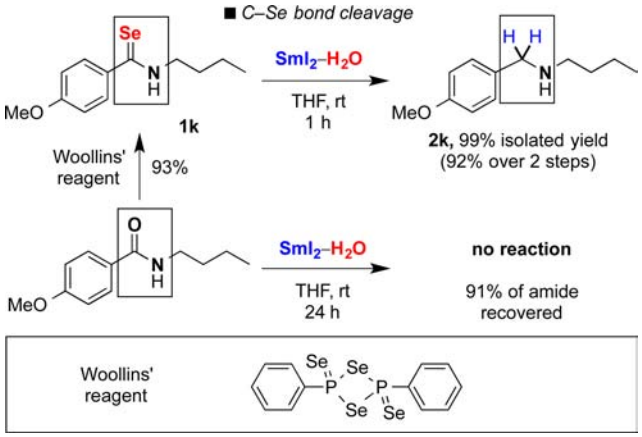
1a 2a

entry	SmI_2 (equiv)	H_2O (equiv)	yield (%)
1	6	36	94
2	6	200	93
3	6	800	72
4	4	36	70

[a]To selenoamide **1a** (0.1 mmol) in THF (1.0 mL) were added H_2O and SmI_2 (0.1 M in THF), sequentially.

of SmI_2 to 1 equiv (for a four-electron process) gave amine **2a** in a lower yield (entry 4). Thus, a slight excess of SmI_2 (entry 1) was used. As expected, when submitting *N*-butyl-4-methoxybenzamide to the optimized conditions, the starting material was recovered in 91% yield even after a prolonged reaction time (Scheme 2). Straightforward conversion of the

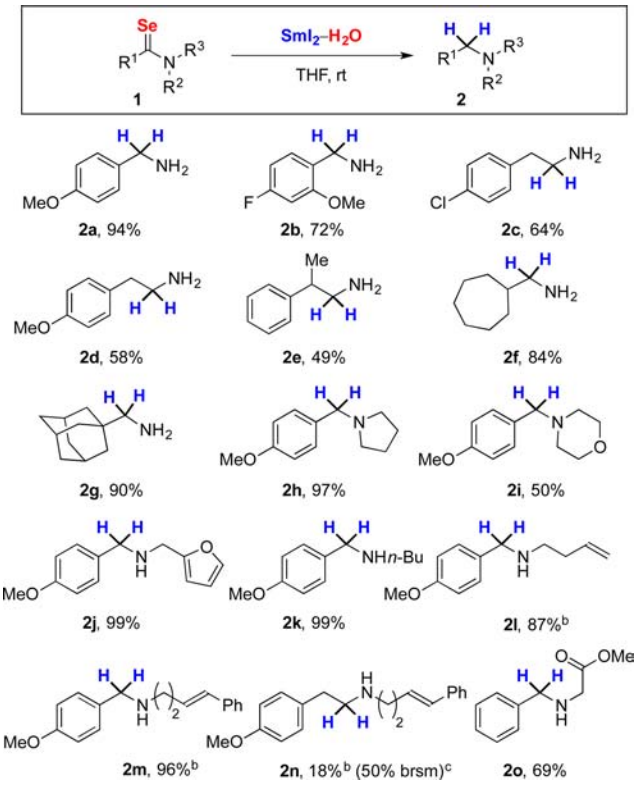
Scheme 2. Amide Reduction via the Corresponding Selenoamide



amide into the corresponding selenoamide **1k** using Woollins' reagent[15e] and subsequent treatment with SmI_2–H_2O gave the corresponding amine **2k** in an excellent overall yield of 92% (Scheme 2).

Next, we investigated the scope of the reaction using a range of starting materials including primary, secondary, and tertiary selenoamides and both aryl and aliphatic substrates (Scheme 3). First, we studied the reduction of various primary selenoamides **1a**–**g**. Aryl primary selenoamides **1a** and **1b** gave benzyl amines **2a** and **2b** in good yield. Similarly, primary benzyl selenoamides **1c**–**e** gave homobenzylic amines **2c**–**e** in moderate to good yield (49–64%), whereas reduction of hindered aliphatic selenoamides **1f** and **1g** gave the expected primary amines **2f** and **2g** in excellent yield (84% and 90% yield, respectively). Chloride (**2c**), fluoride (**2b**), methoxyl (**2a**, **2b**, **2d**, **2h**–**n**), alkenyl (**2l** and **2m**), and ester (**2o**) substituents were tolerated and, in particular, for substrates **2b** and **2c**, no reduction of the carbon–halogen bonds was observed. Tertiary selenoamides **1h** and **1i** were also reduced to amines **2h** and **2i**, respectively, and secondary aryl selenoamide **1j** was also smoothly reduced to benzylic amine **2j**. The preparation of **2h**–**j** illustrates the compatibility of the reduction with

Scheme 3. Reduction of Selenoamides with SmI_2–H_2O[a]

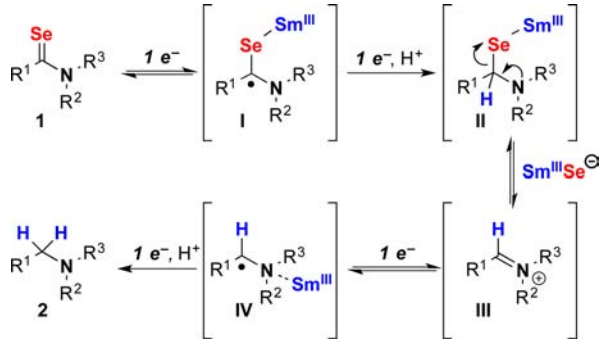


[a]To selenoamide **1** (0.1 mmol) in THF (1.0 mL) were added H_2O (36 equiv) and SmI_2 (0.1 M in THF, 6 equiv) sequentially. [b]SmI_2 solution was added slowly over 1 h. [c]Cyclization product **3n** was also isolated; see Scheme 5.

medicinally relevant heterocyclic motifs. Finally, secondary arylselenoamides **1k**–**m** and **1o** also proved to be good substrates; the corresponding secondary amines **2k**–**m** and **2o** were obtained in good to excellent yields (69–99%). As the more reducing SmI_2–H_2O–NEt_3 reagent system is required to reduce most lactones,[6] esters,[8] carboxylic acids,[5] amides,[9] and nitriles,[10] the presence of such functional groups is broadly compatible with selenoamide reduction using SmI_2–H_2O. Benzylselenoamide **1n**, possessing an alkenyl unit, gave amine **2n** in low isolated yield (50% based on recovered starting material), and a radical cyclization product was also isolated (*vide infra*).

A plausible reduction mechanism is shown in Scheme 4. After reversible SET to the carbon–selenium double bond, subsequent reduction and protonation of **I**, followed by selective

Scheme 4. Proposed Mechanism for the Reduction of Selenoamides with SmI_2–H_2O



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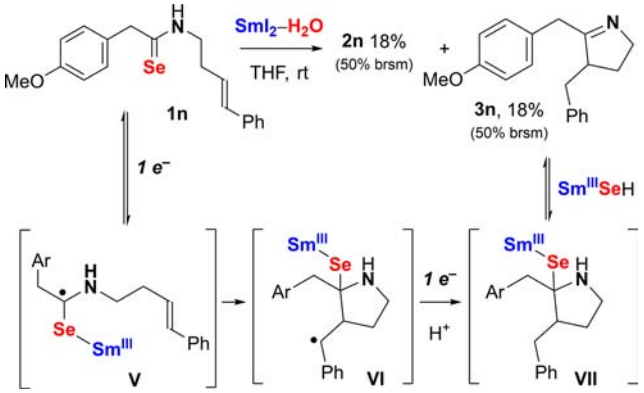
elimination of samarium selenide from **II**, forms iminium **III**. Further reduction and protonation gives amine products **2**.

For the reduction of **1n** with SmI_2–H_2O, cyclic imine **3n** was isolated in addition to amine **2n** (Scheme 5). In contrast, the

Scheme 5. Cyclization of Selenoamide 1n Using SmI_2–H_2O



reduction of **1m** did not give products of cyclization (amine **2m** was the only isolated product). This is likely due to the facile reduction of the benzyl radical intermediate to the corresponding anion which outcompetes cyclization in this case. Formation of **3n** illustrates the potential to utilize radicals **V** formed by SET to selenoamides in intramolecular carbon–carbon bond forming reactions. It is also important to note that the ability to reduce amides, activated by conversion to the corresponding selenoamides, using SmI_2–H_2O should allow radical intermediates to be intercepted that would otherwise be readily reduced under the more reducing SmI_2–H_2O–NR_3 conditions.

In conclusion, we have developed the first general and selective reduction of selenoamides to amines, including tertiary, secondary, and primary aliphatic and aryl substrates. The SET process employs commercially available SmI_2, activated by straightforward addition of H_2O, and does not require an additional Lewis base additive. Amides are not reduced under these conditions; thus, transformation of amides into the corresponding selenoamides followed by SET reduction with SmI_2–H_2O represents a new strategy for amide reduction. The potential to exploit the radical intermediates in cyclizations to form heterocyclic imines has also been illustrated by the first radical cyclization of a selenoamide.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03325.

General experimental procedures, characterization details, and ^1H and ^{13}C NMR spectra of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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