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Visible-Light Photoredox Synthesis of Chiral α-Selenoamino Acids

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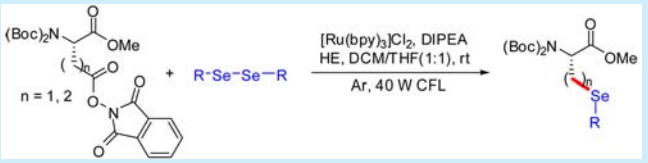
Supporting Information

ABSTRACT: *N*-Acetoxyphthalimide derivatives of two genetically coded proteinogenic amino acids, L-aspartic acid and glutamic acid, were used as visible light photoredox chiral sources and radical precursors, diorganyl diselenides were used as the radical acceptors, and the diverse chiral α-selenoamino acid derivatives were prepared in good yields at room temperature. Furthermore, decarboxylative coupling of *N*-protected dipeptide active ester with diphenyl diselenide provided the corresponding selenodipeptide. The simple protocol, mild reaction conditions, high efficiency, and chiral keeping of this method make it an important strategy for the synthesis of chiral molecules.



Amino acids are used as versatile building blocks in the pharmaceutical and agrochemical fields, and about 18% of the leading drugs and agrochemicals contain amino acid residues because of their chirality and reactive groups.[1] Unnatural amino acids, especially α-amino acids with unnatural substituents, have become star molecules, and they can mimic natural peptide structures and stabilize peptides against proteolytic attack. They are also used in the synthesis of complex molecules,[2] ligands, and catalysts.[3] Compared with the acquirement of natural α-amino acids through fermentation and extraction from cheap raw materials, the manufacture of unnatural amino acids is more complex and expensive, and they are usually produced by chemical synthesis of racemic mixtures and subsequent chemical or enzymatic separation. Recently, various useful synthetic methods have been developed,[4] including the asymmetric Strecker reaction,[5] the enantioselective hydrogenation of dehydroamino acid precursors,[6] and the asymmetric alkylation of glycine derivatives employing chiral auxiliaries[7] or chiral phase-transfer catalysts.[8] On the other hand, dietary selenium is an essential element in human nutrition and plays key roles in cancer prevention, immunology, aging, male infertility, and other physiological processes.[9] Organoselenium compounds have emerged as an exceptional class of biological and therapeutic molecules ranging from antiviral and anticancer agents to naturally occurring food supplements.[10] Selenoamino acids are used as important building blocks in the synthesis of selenoproteins.[11] Selenoproteins are thought to be responsible for most of the biomedical effects of dietary selenium, which is essential to mammals, and the reduction of incidence of cancers[12] and neurodegenerative diseases (such as Parkinson's and Alzheimer's diseases)[13] by dietary supplementation with selenomethionine via *Se*-(methyl)selenocysteine has been reported. Selenoamino acid derivatives (mainly arylselenocysteines) can serve as convenient precursors to dehydroamino acids,[14] which are useful electrophilic handles for the chemoselective preparation of peptide conjugates.[15] In addition, chiral selenides and diselenides-containing ligands have been employed as useful catalysts in various asymmetric transformations.[16] The previous methods for synthesis of chiral α-selenoamino acid derivatives mainly include reactions of halo and pesudohaloamino acid derivatives,[17] chiral 2-oxazolines,[18] or chiral aziridines[19] with selenium nucleophiles. However, most of these synthetic protocols above often suffer from lengthy synthetic steps and require the use of specialized reagents that are usually difficult to obtain. Recently, visible light photoredox catalysis has emerged as a powerful activation strategy in chemical transformations,[20] and some decarboxylative couplings have been developed.[21] To the best of our knowledge, there is no report on synthesis of chiral α-selenoamino acids using natural α-amino acids as the precursors under visible light photoredox catalysis thus far. Herein, we report visible-light photoredox synthesis of chiral α-selenoamino acids with the derivatives of two genetically coded proteinogenic amino acids, L-aspartic acid and glutamic acid, at room temperature, in which the carboxyls on the side chains of *N*-Bis(Boc)-Asp-OMe and *N*-Bis(Boc)-Glu-OMe are activated with *N*-hydroxyphthalimide to obtain the corresponding active esters *N*-Bis(Boc)-Asp(OPht)-OMe (**1a**) and *N*-Bis(Boc)-Glu(OPht)-OMe (**1b**) (Pht = phthalimide), and reactions of **1a** or **1b** with diorganyl diselenides (**2**) in the presence of Hantzsch ester (HE) afford chiral α-selenoamino acids (**3**) under visible-light photoredox catalysis.

Initially, visible-light photoredox coupling of *N*-Bis(Boc)-Asp(OPht)-OMe (**1a**) with diphenyl diselenide (**2a**) was selected as the model to optimize conditions including photocatalysts, solvents, atmosphere, and time. As shown in Table 1, the effect of solvent was investigated (entries 1−6) using 1 mol % of $[Ru(bpy)_2]Cl_2$ as the photocatalyst in the

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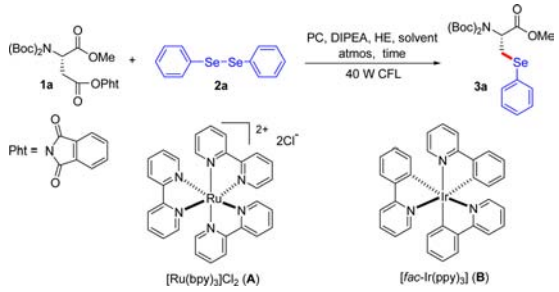
Table 1. Optimization of Conditions on Synthesis of Chiral α-Selenoamino Acid under Photoredox Catalysis[a]



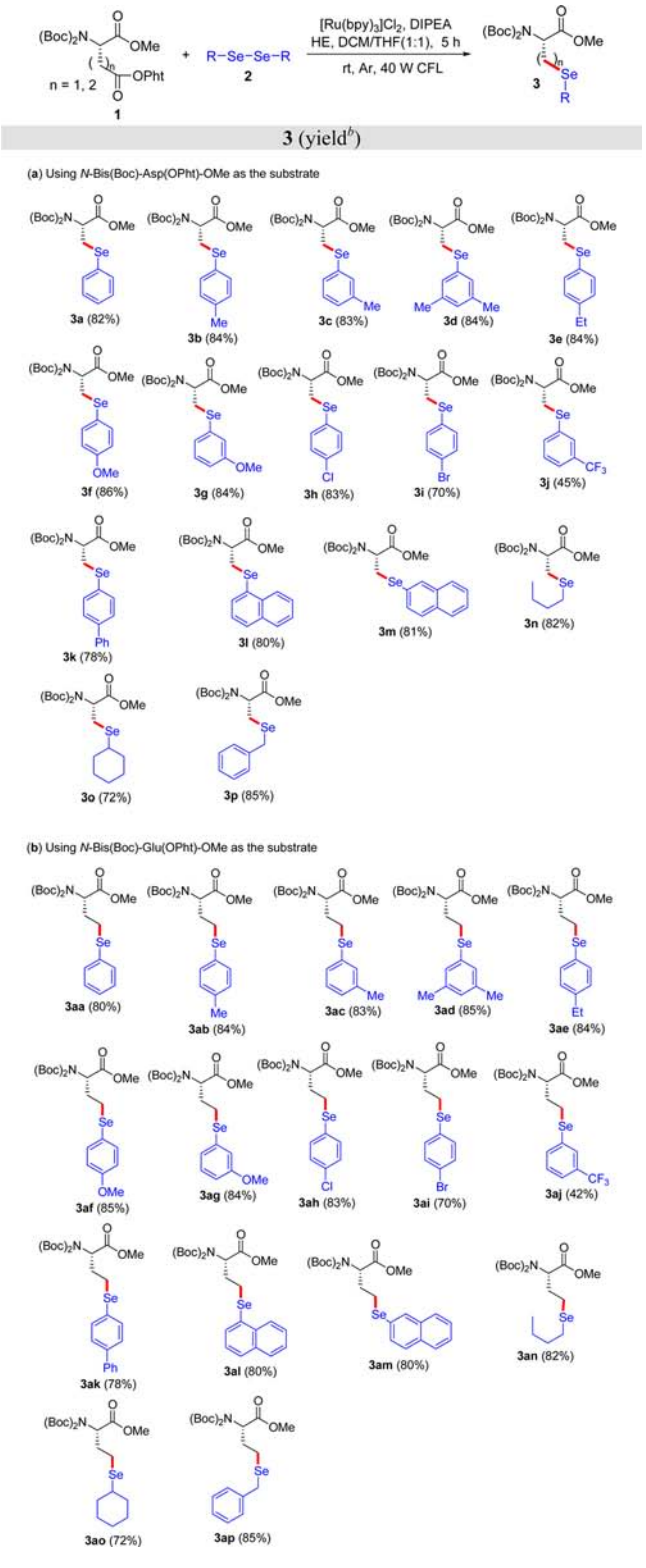
entry	PC	solvent	atmos	time (h)	yield[b] (%)
1	A	THF	Ar	5	79
2	A	DCM	Ar	5	80
3	A	DMF	Ar	5	70
4	A	DMSO	Ar	5	68
5	A	MeCN	Ar	5	54
6	A	THF/DCM (1:1)	Ar	5	82
7	A	THF/DCM (1:1)	Ar	4	76
8	A	THF/DCM (1:1)	Ar	24	82
9	B	THF/DCM (1:1)	Ar	5	32
10	-	THF/DCM (1:1)	Ar	5	0
11	A	THF/DCM (1:1)	Ar	5	0[c]
12	A	THF/DCM (1:1)	vacuum	5	82
13	A	THF/DCM (1:1)	air	5	52

[a]Reaction conditions: under Ar atmosphere and irradiation of visible light, *N*-Bis(Boc)-Asp(OPht)-OMe (**1a**) (0.15 mmol), diphenyl diselenide (**2a**) (0.15 mmol), photocatalyst (PC) (1.5 μmol), diisopropylethylamine (DIPEA) (0.375 mmol), Hantzsch ester (HE) (0.225 mmol), solvent (1.0 mL), temperature (rt, ~25 °C), time (4–24 h) in a sealed Schlenk tube. [b]Isolated yield. [c]No light. CFL = compact fluorescent light.

presence of diisopropylethylamine (DIPEA) and Hantzsch ester (HE) under argon atmosphere and irradiation of 40 W compact fluorescent light (CFL) at room temperature, and the results showed that a mixed solvent of THF and DCM (v/v = 1:1) was suitable (entry 6). The yield decreased when the reaction time was shortened (compare entries 6–8). We attempted 1 mol % of [*fac*-Ir(ppy)$_3$] as the photoredox catalyst, and only 32% yield was provided (entry 9). No reaction was observed in the absence of photocatalyst or light (entries 10 and 11). Reaction under vacuum gave the same yield as that under argon atmosphere (compare entries 6 and 12). Yield were reduced when the system was exposed to air (entry 13).

After obtaining the optimized photoredox conditions, we investigated the scope of this reaction by testing decarboxylative couplings of *N*-acetoxyphthalimide derivatives of L-aspartic acid and glutamic acid with diorganyl diselenides (**2**). As shown in Table 2a, reaction of *N*-Bis(Boc)-Asp(OPht)-OMe (**1a**) with various diorganyl diselenides (**2**) afforded good yields. For diorganyl diselenides (**2**), diaryl diselenides exhibited slightly higher reactivity than dialkyl diselenides, and diaryl diselenides containing donating-electron groups on the aryl rings provided higher yields than those containing electron-withdrawing groups. The visible-light photoredox decarboxylative couplings showed tolerance of some functional groups including amide, ester, ether, C–Cl and C–Br bonds, and CF_3. We investigated reactions of *N*-Bis(Boc)-Glu(OPht)-OMe (**1b**) with various diorganyl diselenides (**2**), and their reactivity and tolerance toward functional groups was similar to

Table 2. Synthesis of Chiral α-Selenoamino Acids[a]



[a]Reaction conditions: under Ar atmosphere and irradiation of visible light, *N*-Bis(Boc)-Asp(OPht)-OMe (**1a**) or *N*-Bis(Boc)-Glu(OPht)-OMe (**1b**) (0.15 mmol), diorganyl diselenide (**2**) (0.15 mmol), [Ru(bpy)$_3$]Cl$_2$ (1.5 umol), diisopropylethylamine (DIPEA) (0.375 mmol), Hantzsch ester (HE) (0.225 mmol), THF (0.5 mL), DCM (0.5 mL), temperature (rt, ~25 °C), time (5 h) in a sealed Schlenk tube. [b]Isolated yield.

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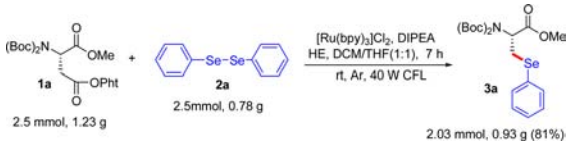
those using *N*-Bis(Boc)-Asp(OPht)-OMe (**1a**) as the substrate. It is worth noting that chirality of the obtained α-selenoamino acid derivatives is the same as that of L-aspartic acid and glutamic acid, so it is an easy task to make chiral molecules through this strategy.

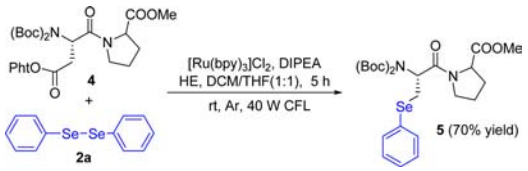
As shown in Scheme 1, we attempted the synthesis of **3a** on gram scale by using our method. To our delight, reaction of *N*-Bis(Boc)-Asp(OPht)-OMe (**1a**) with diphenyl diselenide (**2a**) under the standard conditions provided the target product (**3a**) in a high yield (81%). Therefore, the present method is very effective for synthesis of chiral α-selenoamino acids with biological and pharmaceutical activity.

Scheme 1. Gram-Scale Synthesis of 3a under Visible-Light Photoredox Catalysis



As shown in Scheme 2, reaction of dipeptide derivative *N*-Bis(Boc)-Asp(OPht)-ProOMe (**4**) with **2a** provided the target product (**5**) in 70% yield under the standard photoredox conditions. The result indicated that *N*-Bis(Boc)-protected peptide active esters also were effective radical precursors for the photoredox catalysis.

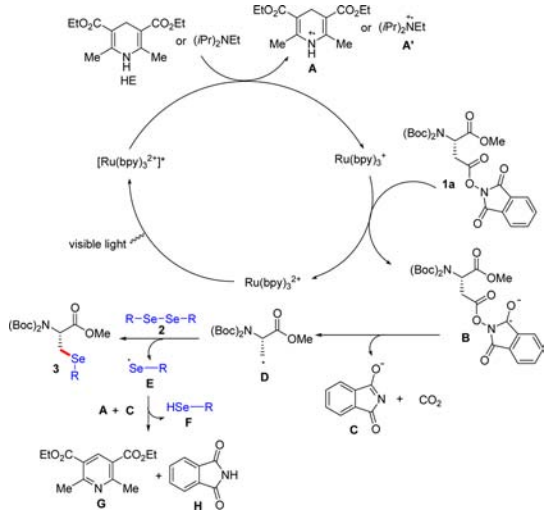
Scheme 2. Decarboxylative Coupling of Dipeptide Derivative *N*-Boc(Bis)-Asp(OPht)-ProOMe with Diphenyl Diselenide (2a) under Visible-Light Photoredox Catalysis



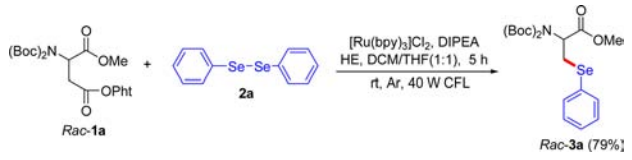
A plausible mechanism on the visible-light photoredox synthesis of chiral α-selenoamino acids is proposed in Scheme 3 according to the results above and the previous references.[20,21] Here, *N*-Bis(Boc)-Asp(OPht)-OMe (**1a**) is chosen as the example. Irradiation of $Ru(bpy)_3^{2+}$ with visible light gives the excited-state $[Ru(bpy)_3^{2+}]^*$, and the photoexcited catalyst was reduced by HE or DIPEA to give $Ru(bpy)_3^{+}$, in which HE or DIPEA transfers **A** or **A′**. Treatment of **1a** with $Ru(bpy)_3^{+}$ produces radical anion **B** regenerating catalyst $Ru(bpy)_3^{2+}$, and elimination of phthalimide anion (**C**) and carbon dioxide from **B** gives radical **D**. Reaction of **D** with diorganyl diselenide (**2**) leads to the target product (**3**) freeing seleno radical **E**, and treatment of **A**, **C** ,and **E** affords **F**, **G**, and **H**.

In order to confirm whether the visible-light photoredox decarboxylative coupling led to racemization of α-selenoamino acids, racemic *rac*-**1a** was first synthesized (see the Supporting Information for details). Next, reaction of *rac*-**1a** with **2a** under the standard photoredox conditions provided racemic methyl 2-(bis(*tert*-butoxycarbonyl)amino)-3-(phenylselanyl)propanoate (*rac*-**3a**) in 79% yield (Scheme 4). Subsequently, HPLC analysis of *rac*-**3a**, **3a**, and mixtures of *rac*-**3a** and **3a** with different ratios was performed with an ID-H chiral column using *n*-hexane/2-propanol (90:10) as the mobile phase (column pressure = 40 bar, flow rate = 1 mL/min). *rac*-**3a** afforded two peaks with almost same areas, and **3a** (note: it is (*R*)-**3a**) showed a single peak. We investigated the limits of detection by incremental doping of minor amounts of *rac*-**3a** into **3a**. Mixtures of *rac*-**3a** and **3a** with different ratios including molar ratios of *rac*-**3a**/**3a** 0.01:1, 0.005:1, and 0.001:1 were determined by HPLC, and the corresponding peaks with appropriate areas were afforded (see the Supporting Information for details). The results above exhibited that no racemization was observed for our photoredox synthesis of chiral α-selenoamino acids under the present determination conditions.

Scheme 3. Plausible Mechanism on Visible-Light Photoredox Synthesis of Chiral α-Selenoamino Acids



Scheme 4. Synthesis of *rac*-3a



In summary, we have developed a novel and efficient visible-light photoredox synthesis of chiral α-selenoamino acids with the assistance of photocatalyst $[Ru(bpy)_3]Cl_2$, in which *N*-acetoxyphthalimide derivatives of two genetically coded proteinogenic amino acids, L-aspartic acid and glutamic acid, were used as visible-light photoredox chiral sources and radical precusors, diorganyl diselenides were used as the radical acceptors, and the diverse chiral α-selenoamino acid derivatives were prepared in good yields at room temperature. Furthermore, decarboxylative coupling of *N*-protected dipeptide active ester with diphenyl diselenide provided the corresponding selenodipeptide. Importantly, the chirality of the precursors, L-aspartic acid and glutamic acid, was maintained because the decarboxylative couplings occurred at the β-carbon of L-aspartic acid or the γ-carbon of L-glutamic acid. The present study should afford a novel and useful strategy for synthesis of other unnatural chiral α-amino acids with biological and pharmaceutical activity, and we believe that the present method will find wide applications in organic synthesis.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00489.

General procedures, characterization data, and NMR spectra of obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

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