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Synthesis of Chiral Selenazolines from *N*-Acyloxazolidinones via a Selenative Rearrangement of Chiral Cyclic Skeletons

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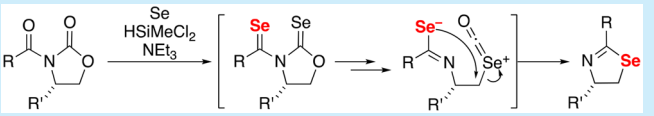
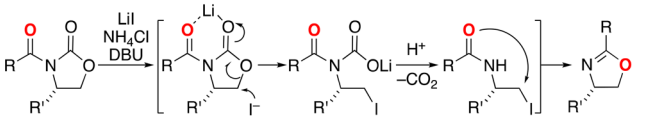
Supporting Information

ABSTRACT: A synthetic route to chiral selenazolines from readily available *N*-acyloxazolidinones via a selenative rearrangement of a chiral cyclic skeleton is reported. The reaction proceeds in the presence of elemental selenium, a hydrochlorosilane, and an amine. Although the stability of the obtained selenazoline products is relatively low, a wide range of selenazolines was successfully prepared.



Oxazolines and thiazolines are widely found in a variety of compounds such as natural products,[1] biologically active compounds,[2] and chiral ligands,[3] where they play important roles in their functionality. Consequently, the synthesis of such compounds has attracted significant attention for more than a century.[4] In contrast, the corresponding selenium isologues, i.e., selenazolines, which also play specific roles in vivo,[5] have seldomly been studied, owing to the synthetic difficulties associated with their formation and the instability of the selenated starting materials and products.[6] Recently, we have developed a new route to selenium-containing compounds from carbonyl species via the formal reductive activation of stable elemental selenium with a hydrochlorosilane as the terminal reductant.[7] During the course of our studies, we conducted the reaction with *N*-acyloxazolidinones and, unexpectedly, obtained selenazoline products (Figure 1, bottom). A similar transformation of *N*-acyloxazolidinones with lithium iodide and an amine had previously been reported for the synthesis of chiral oxazolines (Figure 1, top), but reports on the application to the synthesis of chiral selenazolines as well as thiazolines do not exist.[8] Herein, we report a new route to chiral selenazolines via the reaction between chiral *N*-acyloxazolidinones, elemental selenium, hydrochlorosilanes, and amines. The reaction did not involve racemization on their chiral center.

Previous report: Synthesis of oxazolines via the decarboxylative chiral rearrangement of *N*-acyl-2-oxazolidinones



This work: Synthesis of selenazolines via a selenative formally decarboxylative chiral rearrangement of *N*-acyl-2-oxazolidinones

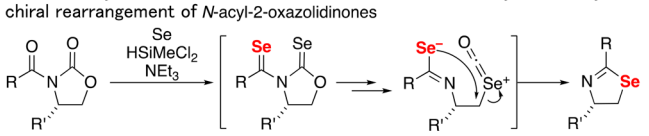
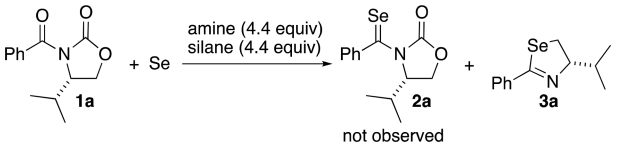


Figure 1. Previously reported synthetic routes to oxazolines and the synthesis of selenazolines in this work.

In order to gain insight into the chemoselectivity of such selenation reactions between amide carbonyl and cyclic carbamoyl carbonyl moieties, we conducted a reaction between *N*-benzoyloxazolidinone (**1a**), trichlorosilane, and dibenzylamine at 115 °C for 15 h, which generated the corresponding selenazoline **3a** as the major product in moderate yield, although the crude reaction mixture contained a series of unidentified decomposition byproducts (Table 1, entry 1). In the reaction mixture, simple selenated compounds such as **2a** were not detected. Subsequently, we tested various amines in order to optimize the reaction conditions. Amines are essential for this reaction, given that **3a** was not obtained in their absence (entry 2). Nucleophilic amines were not effective, and the use of *N*,*N*-dimethyl-4-aminopyridine (DMAP) or 1,4-

Table 1. Optimization of the Reaction Conditions[a]



entry	amine	silane	temp (°C)	solvent	yield[c] (%)
1	$HNBn_2$	$HSiCl_3$	115	toluene	49
2		$HSiCl_3$	115	toluene	trace
3	DMAP	$HSiCl_3$	115	toluene	trace
4	DABCO	$HSiCl_3$	115	toluene	25
5	NEt_3	$HSiCl_3$	115	toluene	45
6	NEt_3	$HSiCl_3$	140	mesitylene	44
7	NEt_3	$HSiMeCl_2$	140	mesitylene	52
8[b]	NEt_3	$HSiMeCl_2$	160	mesitylene	56

[a]Unless noted otherwise, reactions were conducted for 15 h in a screw-capped test tube. [b]Reaction time: 3 h. [c]Isolated yields.

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diazabicyclo[2.2.2]octane (DABCO) did not afford the desired selenazoline in satisfactory yield (entries 3 and 4). On the other hand, the use of triethylamine furnished the selenazoline in moderate yield, which is comparable to that from the reaction with dibenzylamine (entry 5). In the interest of an easier separation of the products and amines, a more volatile triethylamine was selected for the further optimization of the reaction conditions. Although more complex mixtures were obtained at higher temperatures, the product yield was not affected (entry 6). The use of the less reactive methyldichlorosilane resulted in the suppression of the side reactions and increased the yield of **3a** (entry 7). Meanwhile, we detected a time-dependent spontaneous decomposition of the selenated intermediates and selenazoline product under those reaction conditions, probably due to their highly labile nature. We thus conducted the reaction at 160 °C in order to shorten the reaction time and increase the yield to 56% in only 3 h (entry 8). Notably, this reaction mixture was cleaner than those obtained from longer reaction times, although we did detect trace amounts of several compounds that retain the oxazolidinone skeleton. In addition, a racemization was not observed at the chiral center of the aminoalcohol moiety of the oxazolidinone under these reaction conditions in the reaction with enantiopure substrates (*R*)- and (*S*)-**1a**.[9] Addition of LiI, which is a key additive for previous oxazoline synthesis,[8] did not affect the reaction efficiency at all.

With these reaction conditions in hand, we subsequently investigated the substrate scope (Figure 2). Substrates with functionalized phenyl groups or electron-rich heterocycles on the acyl moiety were well tolerated under these conditions

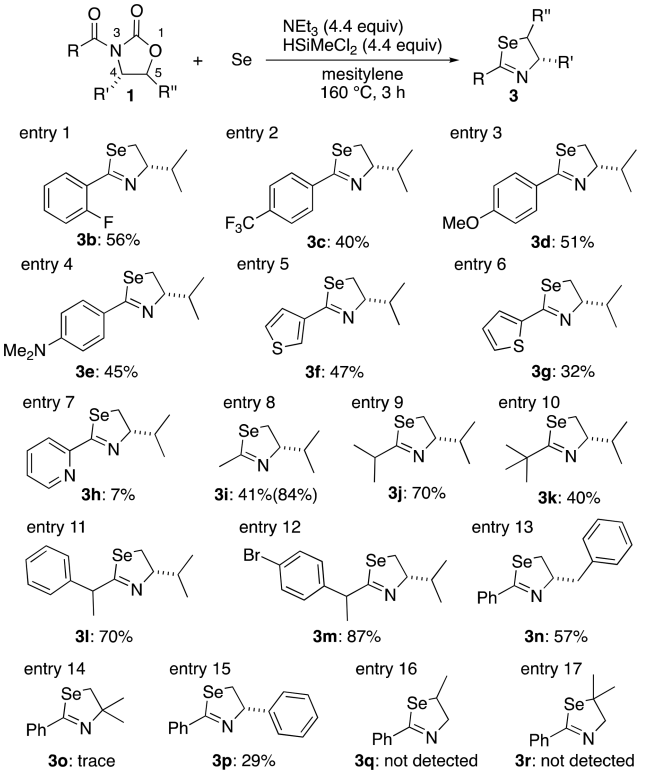
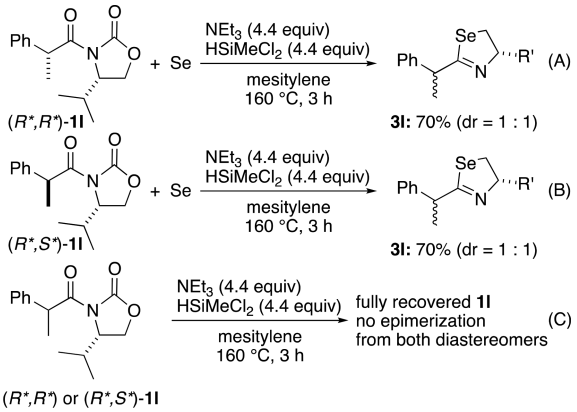


Figure 2. Investigation of substrate scope of the reaction. Reactions were conducted in a screw-capped test tube. All yields refer to isolated yields. Yields in parentheses were determined by ^{1}H NMR using $(CH_2Cl)_2$ as the internal standard.

(entries 1−6), although the yield significantly decreased when a 2-pyridyl group was introduced at that position (entry 7). Alkyl substituents also withstood the reaction conditions to furnish the corresponding products (**3i**−**m**; entries 8−12), although the isolated yield of highly volatile **3i** was relatively low. In addition, the stability of the corresponding 2-*tert*-butylselenazoline **3k** was comparatively low and significant decomposition was observed even upon storage under argon after isolation (entry 10). On the other hand, the yields of 2-(1-arylethyl)selenazolidinones **3l** and **3m** were good, probably due to their comparatively high stability (entries 11 and 12). Nevertheless, complete epimerization at the α-position of the amide carbonyl moiety on the substrate was observed; the reaction of the isolated diastereomers furnished the corresponding products in the same 1:1 diastereomer mixture (Scheme 1A and 1B). In contrast, no epimerization of

Scheme 1. Reactions of the Individual Diastereomers of 1l



(*R**,*R**)- and (*R**,*S**)-**1l** occurred under the standard conditions in the absence of elemental selenium (Scheme 1C). This result clearly suggests that such an epimerization occurs after the selenation. Generally, the selenocarbonyl moiety has the higher acidity of the α-position compared to that of the conventional "oxo"carbonyl group on account of the difficulties associated with the hybridization of the atomic orbitals on the selenium atom. Regarding the substituents on the amino alcohol moiety in the oxazolidinone, a benzyl-substituted aliphatic group at the 4-position afforded the corresponding product in a yield comparable to that of **1a** (entry 13). On the other hand, 4,4-disubsituted **1o** did not afford **3o** (entry 14), and an aromatic substituent at the 4-position decreased the yield of **3p** (entry 15). Finally, substituents at the 5-position critically influence the efficiency of the reaction, and the corresponding selenazolines were not detected (entries 16 and 17). In short, the stability trend of the selenazolines is mainly due to the bulkiness of the substituent on the 2-position, and tertiary substituents and aryl groups bearing a relatively bulky substituent at the *ortho*-position[10] significantly give a negative impact for the stability as well as yields of the products.

To compare the reaction behavior between the present selenation and the analogous thionation, we conducted the same experiment using elemental sulfur (Scheme 2). The reaction afforded the corresponding thiazoline in moderate yield, although significant amounts of *N*-thioacyloxazolidinone **2a**′ and eliminated oxazolidinthione **4a**′ were also generated. We also performed reactions using Woollins' or Lawesson's

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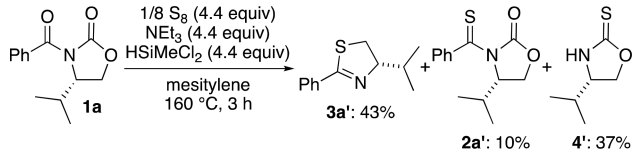
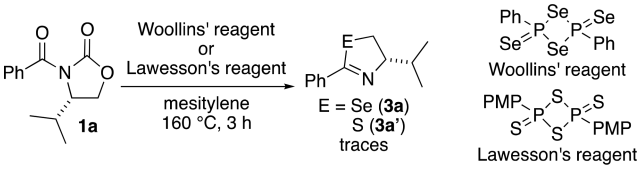
Scheme 2. Reaction between 1a, NEt_3, $HSiMeCl_2$, and Elemental Sulfur



reagents instead of selenium and sulfur, but **3a** and **3a′** were obtained in only trace amounts (Scheme 3).

PMP = *p*-$MeOC_6H$

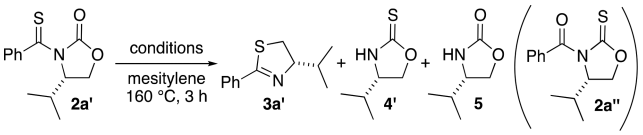
Scheme 3. Reaction with Woollins' and Lawesson's Reagents



PMP = *p*-$MeOC_6H$

To gain insight into the reaction pathway, we subsequently conducted several control experiments and related reactions. Considering their similarities, thioacyl substrate **2a′** was used for the control experiments, given that **2a** could not be isolated. Initially, attempts to initiate the reaction by simple heating failed, and **2a′** was recovered quantitatively (Table 2,

Table 2. Control Experiments for the Corresponding Thiazoline Synthesis

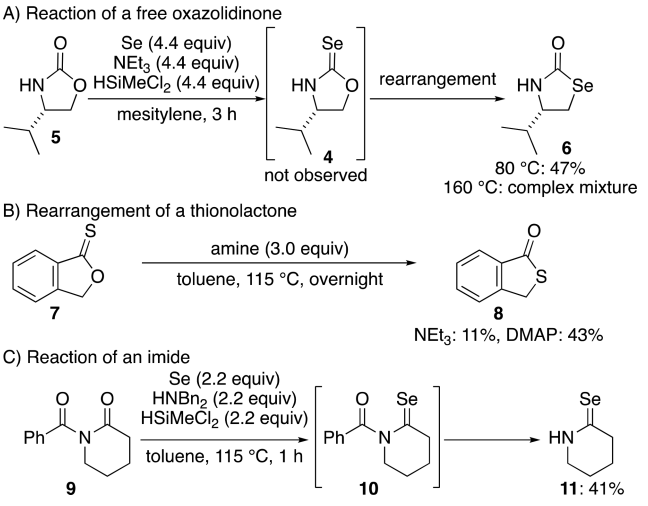


entry	additives[a]	3a′ (%)	4′ (%)	5 (%)	2a′ (%)
1					>95
2	$HSiMeCl_2$				>95
3	NEt_3	12		15	60
4	$HSiMeCl_2$, NEt_3	10		22	56
5	S_8, $HSiMeCl_2$, NEt_3	35	32		10
6[b]	S_8, $HSiMeCl_2$, NEt_3	35	39		

[a]4.4 equiv for **2a′**. [b]**2a′′** was used as the substrate instead of **2a′**.

entry 1). While addition of $HSiMeCl_2$ did not affect the distribution of the products (entry 2), NEt_3 promoted the reaction, although **3a′** was obtained in low yield (entry 3). Again, addition of $HSiMeCl_2$ under these reaction conditions did not influence the product distribution (entry 4), whereas further addition of elemental sulfur (under otherwise identical conditions) significantly improved the yield of **3a** to a value comparable to that of **1a** (entry 5). A similar result was obtained from the reaction of **2a′′** under identical conditions (entry 6). These results suggest that the formation of the thiazoline proceeds via the 2-fold thionation of **1a**. Furthermore, a reaction of free oxazolidinone **5** was carried out under the standard selenation conditions at 80 °C, which did not afford the corresponding oxazolidiselone **4** but selenazolidinone **6** in moderate yield (Scheme 4A), which

Scheme 4. Further Control Experiments and Related Reactions



decomposed at 160 °C. Oxazolidiselone **4** was previously synthesized by Silks and co-workers,[11] but in that case, the compounds were treated below room temperature. These results indicate that the ready selenation of the oxazolidinone moiety is followed by a rearrangement under harsh conditions that may be assisted by attack of amines added or in situ generated nucleophilic species to make ease of ring opening as well. Moreover, **6** is unstable under these high-temperature reaction conditions and readily decomposes even if it is generated during the present selenazoline reaction. A similar rearrangement was observed for thionolactone **7**, even though the reaction needed a nucleophilic amine such as DMAP, probably due to the low reactivity of the C−O bond in the thionocarboxy ester moiety (Scheme 4B). The different product distributions obtained from the selenazoline- and thiazoline-forming reactions under the respective reaction conditions (vide supra) probably reflect the reactivity of the intermediates, where the selenated intermediates are much more reactive toward the rearrangement from **4** to **6** by C−O bond cleavage (Scheme 2) and the low-energy barrier of successive recyclizations from **2** to **3** (Table 1, entry 7). Moreover, the reaction of *N*-benzoyl-*δ*-lactam (**9**) furnished selenated and debenzolylated *δ*-selenolactam (**11**) in moderate yield (Scheme 4C). Usually, the selenation and thionation of lactam moieties proceed faster than at chainlike amide moieties.[7a] Moreover, the pK_a value of selenoamides is significantly lower than that of the corresponding "oxo"amides (vide supra), which also renders the selenolactam moiety a good leaving group. This result suggests that the elimination of the oxazolidiselone moiety occurs readily to give **4** after the initial selenation at the carbamoyl carbonyl group, followed by successive rapid rearrangement and/or direct decomposition reactions.

Based on these results, we would like to propose a plausible reaction pathway (Scheme 5). Initially, the selenation[12] should occur randomly at the amide or carbamoyl moiety to give **I** or **I′**; a further selenation should furnish diselenated intermediate **II**. Moreover, once generated, **I′** would readily decompose under these conditions via formation of **6**, and both reactions may exist in competition. The moderate yield obtained in most cases should thus probably originate from the selectivity of those initial selenation processes. The contribution regarding

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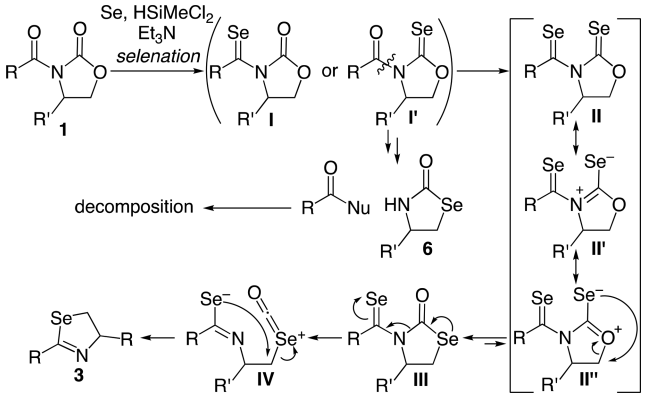
Scheme 5. Probable Reaction Pathway



the orbital hybridization on the selenium atom from resonance forms **II′** and **II″** should be higher than that of **II**, and in particular, the rearrangement to **III** should readily occur from **II″**, probably assisted by the amine or in situ generated nucleophilic species on the ring-opening process.[13] The carbamoyl C−N bond should thus be weakened by the effect of the orbital hybridization described above, leading to a formal decarboxylation (elimination of O=C=Se species) to give intermediate **IV**, though the highly nucleophilic selenium atom may remain on the intermediate at this stage. Successive intramolecular S_N2-type cyclizations should then afford the corresponding selenazoline **3**. On the other hand, as shown in Scheme 3, the reaction does not proceed when phosphorus-based chalcogenation reagents are used, which suggests that the silane and the amine also play an important role in several steps of the reaction pathway, particularly as a Lewis acid and/or nucleophilic catalyst on the rearrangement and formal decarboxylation step.

In conclusion, we have developed a new route to chiral selenazolines that proceeds via a selenative rearrangement of chiral *N*-acyloxazolidinones. The steric information on the position α to nitrogen was totally retained under the reaction conditions, which was confirmed by a racemization test with an enantiopure substrate. Although the product yields are still modest, mainly owing to their instability, a wide variety of chiral selenazolines could be prepared by this method. Further applications of these chiral selenazolines, particularly in the preparation of the chiral metal complexes[10] and in asymmetric catalysis, are currently in progress in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02520.

Attempts of synthesis of several bidentate and pincer-type ligands and complexes, brief estimations of stabilities of **II** and **III** by DFT calculations, experimental details, and copies of ^{1}H and ^{13}C NMR of novel compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(9) For details, see Figure S1 in the Supporting Information.

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(10) For the further preliminary examples of other compounds toward chiral ligand as well as preparing metal complexes, see Schemes S1−4, and descriptions in the Supporting Information. Those compounds are not fully characterized owing to productivity and stability so far.
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(13) In addition, **III** is more stable by ca. 16 kcal/mol than the corresponding **II** as estimated by density functional theory (DFT) calculations at the B3LYP//6-31G(d, p) level (Figure S2); thus, the equilibrium of the rearrangement is highly biased to **III**. Gaussian 09 (rev.D.01) was used for the DFT calculations; full details of the citation of the Gaussian package are in the Supporting Information.

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