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Enantioselective organocatalytic syntheses of α -selenated α - and β -amino acid derivatives†

Victoria Haider,^{‡a} Paul Zebrowski,^{ID ‡a} Jessica Michalke,^b Uwe Monkowius,^{ID c} and Mario Waser,^{ID *a}

Selenium-containing amino acids are valuable targets but methods for the stereoselective α -selenation of simple amino acid precursors are rare. We herein report the enantioselective electrophilic α -selenation of azlactones (masked α -amino acid derivatives) and isoxazolidin-5-ones (masked β -amino acids) using Cinchona alkaloids as easily accessible organocatalysts. A variety of differently substituted derivatives was accessed with reasonable levels of enantioselectivities and further studies concerning the stability and suitability of these compounds for further manipulations have been carried out as well.

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Introduction

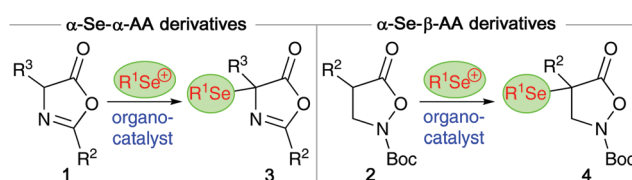
Non-natural α - and β -amino acids (AA) are compounds of high significance and value.^{1–3} Accordingly, the introduction of efficient and reliable strategies to access novel AA-derivatives in an enantioselective fashion has been a heavily investigated topic within the synthesis- and catalysis-oriented community.^{2–6} Hereby, the development of methods that allow for direct stereoselective functionalizations of simple (masked) α - or β -AA derivatives and precursors became an especially thoroughly explored field of research. More specifically, direct electrophilic α -functionalizations of suited (prochiral) AA-precursors emerged as versatile strategies to obtain valuable enantioenriched compounds straightforwardly. Besides asymmetric C–C bond formations, direct enantioselective C $_{\alpha}$ -heteroatom forming approaches to access diversely decorated chiral α -heterofunctionalized α - and β -AA-derivatives have been investigated in much detail.⁴ While (enantioselective) syntheses of α -halogenated, α -aminated, α -sulfanylated, and to some extent also α -oxygenated, α - and β -AA-derivatives have been regularly reported,⁴ conceptually similar asymmetric α -selenations of prochiral (masked) α - and β -AA precursors are, to the best of

our knowledge, so far still missing.⁷ Considering the high value of (chiral) organoselenium compounds for medical applications,^{8–10} as well as their use in (or for) stereoselective syntheses and catalysis approaches,¹¹ and the importance of Se-containing AA in particular,⁹ the lack in generally applicable methods to access novel α -selenated α -AA (α -Se- α -AA) or β -AA derivatives (α -Se- β -AA) comes as a surprise.

Over the last years, our group has had a fundamental interest in the development of organocatalytic protocols to access enantioenriched α -(hetero)-functionalized α - and β -AA derivatives.^{12,13} Inspired by the value of organoselenium compounds and considering the availability of established electrophilic Se-transfer reagents,¹⁴ we now became interested in developing organocatalytic protocols to control the asymmetric α -selenation of easily accessible azlactones **1** (as α -AA precursors)⁶ and isoxazolidin-5-ones **2** (as β -AA building blocks)^{15,16} (Scheme 1).¹⁷

Results and discussion

Based on our own recent experience in the field of asymmetric organocatalysis, we opted for the use of chiral quaternary



Scheme 1 Targeted organocatalytic electrophilic α -selenation of masked α - and β -AA derivatives **1** and **2**.

^aInstitute of Organic Chemistry, Johannes Kepler University Linz, Altenbergerstrasse 69, 4040 Linz, Austria. E-mail: mario.waser@jku.at

^bInstitute of Catalysis, Johannes Kepler University Linz, Altenbergerstrasse 69, 4040 Linz, Austria

^cSchool of Education, Chemistry, Johannes Kepler University Linz, Altenbergerstrasse 69, 4040 Linz, Austria

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‡ These authors contributed equally (in alphabetical order).



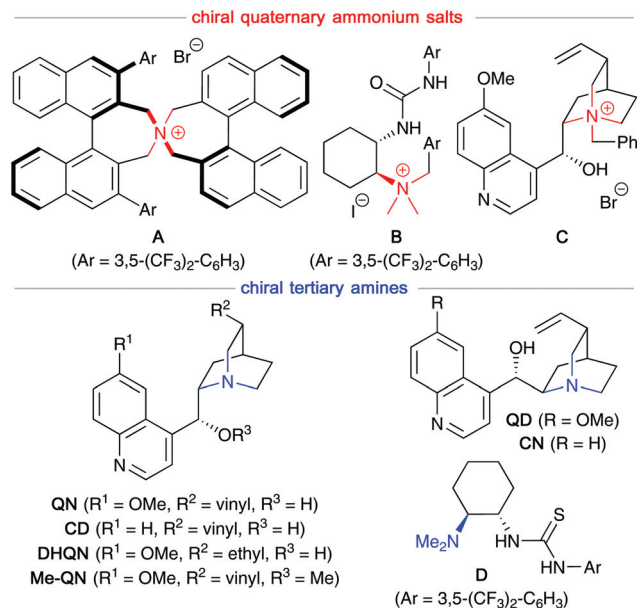


Fig. 1 Chiral organocatalysts tested herein.

ammonium salts (compounds A–C)¹⁸ and chiral organobases (*i.e.* Cinchona alkaloids¹⁹ and Takemoto's bifunctional thiourea-containing amine D;²⁰ Fig. 1) as catalysts for the herein investigated electrophilic α -selenation reactions.

α -Se- α -AA derivatives

We started our investigations by optimizing the α -selenation of the parent azlactone **1a** with the commercially available phthalimide-based PhSe-transfer agent **5a**^{14,21} (Table 1 gives an overview of the most significant results obtained in an exhaustive screening of different organocatalysts and conditions). First attempts with the established chiral ammonium salt catalysts A–C¹⁸ were found to be discouraging, as illustrated by the non-selective examples summarized in entries 1–3. A variety of other ammonium salt derivatives and conditions/bases were tested as well, but racemic **3a** was obtained in each case only. By switching to classical Cinchona alkaloids as chiral organobase catalysts next, results were more encouraging. First experiments utilizing the four naturally available alkaloids quinine (QN), quinidine (QD), cinchonine (CN), and cinchonidine (CD) gave promising results (entries 4–7), with QN and QD being more selective than their structural analogues CD and CN. Due to their pseudoenantiomeric relationship, the diastereomeric QN and QD gave access to both enantiomers of product **3a** in an enantio-enriched manner, albeit with a slightly higher enantioselectivity for the (–)-enantiomer (accessible by using QN; entry 4).

Comparing different solvents next (entries 4, 8, and 9), toluene was found to be superior to halogenated or ether-based solvents (other aromatic solvents did not allow for any improvement anymore). Modified quinine-derivatives were screened as well but, as exemplified for Me-QN, *O*-alkylation had a detrimental effect on the enantioselectivity (entry 10).

Table 1 Optimization of the organocatalytic asymmetric α -selenation of azlactone **1a**^a

| Entry | Cat. (mol%) | Base | Solvent | T [°C] | Yield ^b [%] | er ^c |
|-------|-------------|--------------------------------|---------------------------------|--------|------------------------|-------------------------------|
| 1 | A (10%) | K ₃ PO ₄ | Toluene | 25 | 85 | 52:48 |
| 2 | B (10%) | K ₃ PO ₄ | Toluene | 25 | 34 | 51:49 |
| 3 | C (10%) | K ₃ PO ₄ | Toluene | 25 | 78 | 53:47 |
| 4 | QN (10%) | — | Toluene | 25 | 82 | 82:18 |
| 5 | QD (10%) | — | Toluene | 25 | 96 | 28:72 |
| 6 | CN (10%) | — | Toluene | 25 | 84 | 38:62 |
| 7 | CD (10%) | — | Toluene | 25 | 95 | 60:40 |
| 8 | QN (10%) | — | CH ₂ Cl ₂ | 25 | 92 | 78:22 |
| 9 | QN (10%) | — | MTBE | 25 | 98 | 50:50 |
| 10 | Me-QN (10%) | — | Toluene | 25 | 90 | 68:32 |
| 11 | DHQN (10%) | — | Toluene | 25 | 90 | 85:15 |
| 12 | D (10%) | — | Toluene | 25 | 68 | 50:50 |
| 13 | DHQN (5%) | — | Toluene | 25 | 97 | 85:15 |
| 14 | DHQN (1%) | — | Toluene | 25 | 85 | 62:38 |
| 15 | DHQN (5%) | — | Toluene ^d | 25 | 97 | 87:13 |
| 16 | DHQN (5%) | — | Toluene ^d | 0 | 92(94) ^e | 89:11 (88:12) ^e |
| 17 | DHQN (5%) | — | Toluene ^d | –20 | 95 | 82:18 |

^a Unless otherwise stated, reactions were run for 1 h using 0.05 mmol **1a** and 0.055 mmol **5a** in the presence of the given catalyst in the indicated solvent (*c* = 0.05 M with respect to **1a**) under Ar and exclusion of light. ^b Isolated yields. ^c Determined by HPLC using a chiral stationary phase (given as (–)/(+)-enantiomeric ratio). ^d *c* = 0.0125 (based on **1a**). ^e 1 mmol scale.

Encouragingly however, dihydroquinine (DHQN) allowed for a slightly higher selectivity than QN (compare entries 11 and 4). Considering the beneficial effect of free OH-groups within the tested Cinchona alkaloids, we also used Takemoto's bifunctional thiourea-containing catalyst D,²⁰ which however did not allow for any enantioinduction (entry 12).

Having identified DHQN as the best-suited (easily accessible) chiral organobase catalyst for the asymmetric synthesis of the masked α -Se- α -AA **3a**, we carried out a final optimization with this alkaloid (entries 13–17). Lowering of the catalyst loading to 5 mol% was possible without negatively effecting the outcome (see entries 13 and 14) and a slightly higher dilution had a beneficial effect on the enantioselectivity (entry 15). With respect to the reaction temperature, 0 °C was found to be the optimum (entry 16), while lower temperatures had a detrimental effect on the selectivity again (entry 17). Gratifyingly, the reaction could also successfully be carried out under the optimized conditions on 1 mmol **1a** scale (entry 16), substantiating the robustness of the protocol.

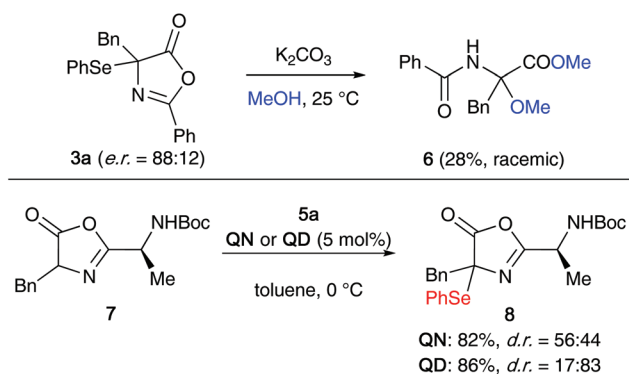
One important observation that we made during this optimization process was that product **3a** slowly decomposes when kept in solution, especially in the presence of light, by forming diphenyldiselenide. The stability is however significantly improved in the absence of light and the compound was found to be benchstable for several weeks when stored in



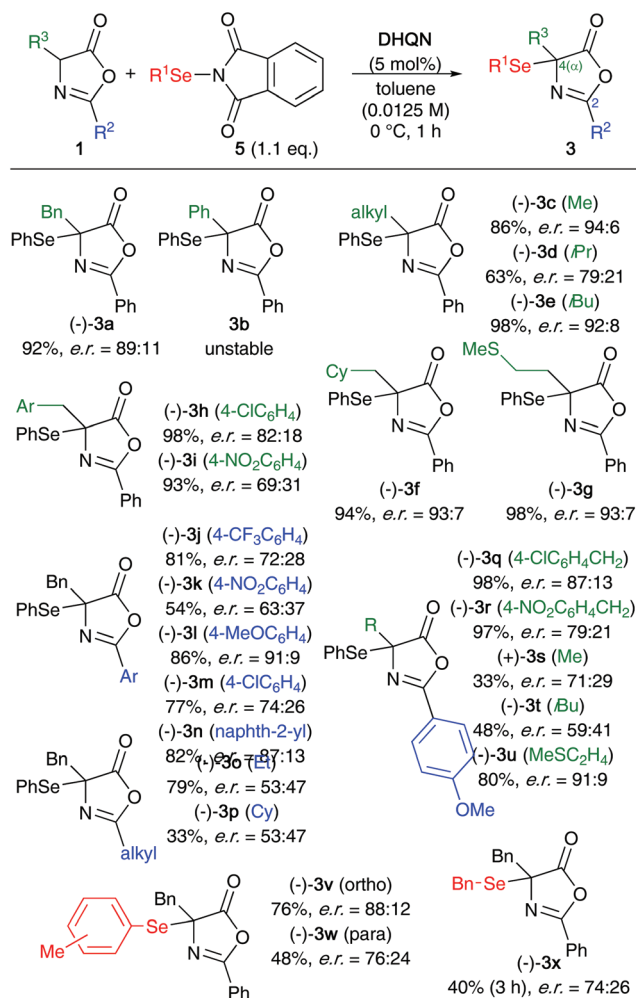
substance under argon in the dark. With this obvious sensitivity noted, we next tested the suitability of compound **3a** for further manipulations. Unfortunately however, we were not able to carry out the selective (nucleophilic) ring opening of this azlactone to analogous acyclic α -Se- α -AA derivatives, as compound **3a** undergoes relatively rapid decomposition and deselenation reactions upon treatment with acid or base. For example, as outlined in the upper part of Scheme 2, the treatment of enantioenriched **3a** with K_2CO_3 in MeOH lead to the formation of rac-**6** in low yield only (accompanied with unidentified side-products). Opting for other bases and solvents turned out to be even worse and besides several not further specified decomposition products again the formation of diphenyldiselenide was observed.

As it was not possible to access more advanced α -Se- α -AA derivatives from **3a**, we also explored the direct α -selenation of the dipeptide-based azlactone **7** (Scheme 2, lower reaction). Although it was possible to carry out this reaction with reasonable yields in the presence of either **QN** or **QD** (leading to opposite diastereoisomer preferences), product **8** was found to be very unstable and decomposed within a few hours when kept in solution.

Having identified suited conditions for the enantioselective α -selenation of **1a** (entry 16, Table 1) and with a better understanding of the sensitivity of the hereby accessed product **3a** at hand, we next investigated the application scope (Scheme 3) for a variety of differently substituted azlactones **1** (giving products **3a–u**) as well as utilizing alternative phthalimide-based Se-transfer reagents **5** (products **3v–x**). Unfortunately, the α -phenyl product **3b** was found to be very sensitive and although its formation was indicated by crude product 1H NMR analysis, it was not possible to isolate this derivative at all because of its fast decomposition. In sharp contrast, the α -alkylated targets **3c–g** were found to be more stable and could be obtained in satisfying isolated yields and with moderate to good enantioselectivities, depending on their substitution pattern (*i.e.* the presence of a bulky *i*-Pr group (**3d**) or a nitrobenzyl group (**3i**) had a negative effect on the enantioselectivity). Interesting effects were observed when varying the substituent in the 2-position of the azlactone skeleton (pro-



Scheme 2 Attempted ring opening of **3a** and direct α -selenation of the dipeptide-based azlactone **7**.



Scheme 3 Application scope for the enantioselective α -selenation of azlactones **1**.

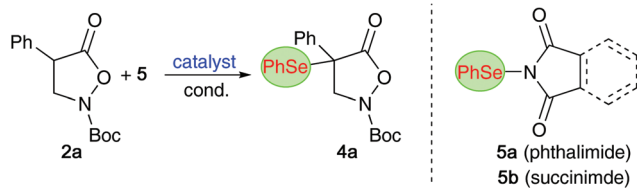
ducts **3j–p**). While the presence of an electronrich methoxybenzene group (**3l**) had a positive effect on the enantioselectivity, electronpoor aryl substituents, *i.e.* $-CF_3$ (**3j**) and $-NO_2$ (**3k**), lead to significantly reduced selectivities. Moreover, the presence of alkyl substituents in this position resulted in more or less racemic product formation only (**3o** and **3p**). Testing a few other 2-methoxybenzene containing substrates **1** with different residues in the α -position revealed a complex scenario of substituent effects. While the products **3q** and **3r** could be obtained with higher enantioselectivities than their 2-phenyl analogues **3h** and **3i**, the presence of an isobutyl group had a detrimental effect hereby (**3t** vs. **3e**).

A few alternative selenation reagents were prepared as well²² and tested herein (products **3v–x**), showing a rather pronounced dependency of the overall reaction progress and the enantioselectivity based on the nature of these reagents.

α -Se- β -AA derivatives

Having investigated the α -selenation of the masked α -AA compounds **1**, we next put our focus on the cyclic β -AA derivatives



Table 2 Optimization of the organocatalytic asymmetric α -selenation of isoxazolidin-5-one **2a**^a


| Entry | Cat. | 5 | Solvent | <i>t</i> [h] | <i>T</i> [°C] | Yield ^b [%] | er ^c |
|-------|---------------------|----|---------------------------------|--------------|---------------|------------------------|-------------------------------|
| 1 | A (5%) ^d | 5a | Toluene | 20 | 25 | 37 | 62:38 |
| 2 | B (5%) ^d | 5a | Toluene | 20 | 25 | 48 | 51:49 |
| 3 | C (5%) ^d | 5a | Toluene | 20 | 25 | 47 | 54:46 |
| 4 | D (5%) | 5a | Toluene | 2 | 25 | 81 | 51:49 |
| 5 | QN (10%) | 5a | Toluene | 2 | 25 | 68 | 75:25 |
| 6 | QD (10%) | 5a | Toluene | 2 | 25 | 65 | 32:68 |
| 7 | CD (10%) | 5a | Toluene | 2 | 25 | 65 | 73:27 |
| 8 | DHQN (10%) | 5a | Toluene | 2 | 25 | 73 | 76:24 |
| 9 | QN (5%) | 5a | Toluene | 2 | 25 | 43 | 69:31 |
| 10 | QN (10%) | 5a | CH ₂ Cl ₂ | 2 | 25 | 76 | 69:31 |
| 11 | QN (10%) | 5a | MTBE | 2 | 25 | 76 | 61:39 |
| 12 | QN (10%) | 5a | Toluene | 2 | 0 | 82 | 75:25 |
| 13 | QN (10%) | 5a | Toluene | 2 | -20 | 76 | 75:25 |
| 14 | QN (10%) | 5a | Toluene ^e | 2 | 25 | 78 | 76:24 |
| 15 | QN (10%) | 5b | Toluene | 2 | 25 | 74 | 81:19 |
| 16 | DHQN (10%) | 5b | Toluene ^e | 2 | 25 | 72 | 83:17 |
| 17 | DHQN (10%) | 5b | Toluene ^e | 14 | 0–25 | 69(72) ^f | 83:17 (83:17) ^f |

^a Unless otherwise stated, reactions were run using 0.05 mmol **2a** and 0.055 mmol **5** in the presence of the given catalyst in the indicated solvent (*c* = 0.05 M with respect to **2a**) under Ar and exclusion of light. ^b Isolated yields. ^c Determined by HPLC using a chiral stationary phase (given as (+)/(–)-enantiomeric ratio). ^d With 1.1 equiv. K₂CO₃. ^e *c* = 0.025 based on **2a**. ^f 0.8 mmol scale.

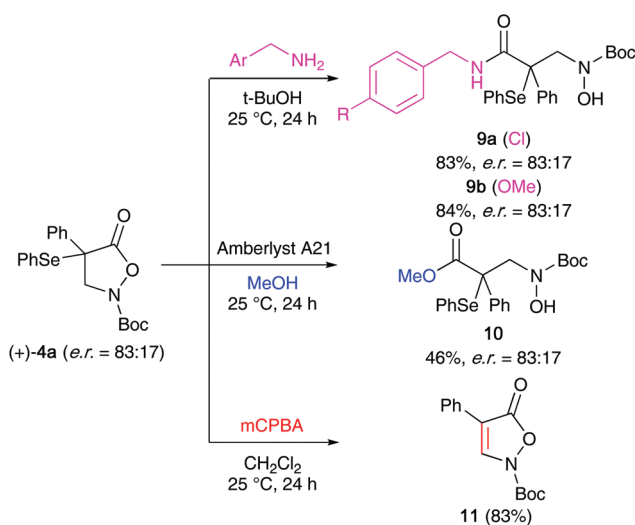
2 (Table 2). We started again by using chiral ammonium salt catalysts for the α -selenation of the parent substrate **2a** with the phthalimide-based reagent **5a** (entries 1–3). Surprisingly, although Maruoka's catalyst **A** was found to be very well-suited for asymmetric α -(hetero)functionalizations of compounds **2** in the past,^{12,13,16} only low levels of enantioselectivities could be achieved for the α -selenation of **2a** (entry 1 gives the best result obtained after screening a variety of different conditions). The alternative ammonium salts **B** and **C** as well as the bifunctional catalyst **D** were even less promising (entries 2–4) and we thus tested Cinchona alkaloids next. Interestingly, these chiral amines have so far only sparingly been used for asymmetric α -functionalizations of compounds **2**²³ and we were glad to see that they allowed for promising initial levels of enantioselectivities accompanied with reasonable yields under conditions similar to those used for azlactones **1**. Again, **QN** and **DHQN** performed slightly better than the other derivatives (entries 5–8) and the reaction was found to be carried out best in toluene in the presence of 10 mol% catalyst at temperatures between 0–25 °C (please see entries 9–14 for the optimization of conditions with **QN** as a catalyst). Interestingly, the enantioselectivity could be improved to some extent when using the succinimide-based reagent **5b** instead of **5a** (entry 15).²⁴

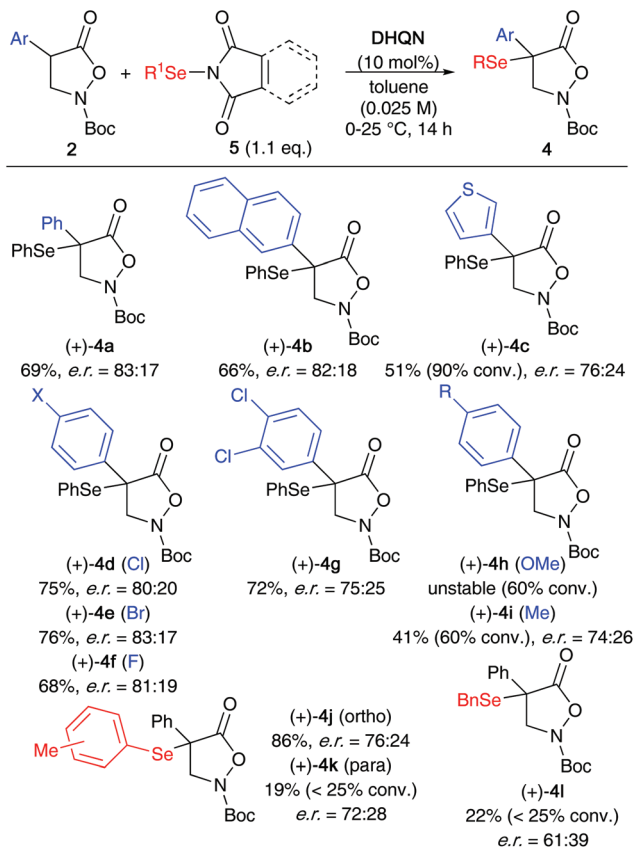
Finally, **DHQN** was used with **5b** under slightly diluted conditions, resulting in robust and scalable conditions allowing for moderate enantioselectivities (entry 17; in general, the reaction is complete within 2 h but can also be run overnight to ensure full conversion, *i.e.* for the larger scale experiment and for some other derivatives (*vide infra*)).

Interestingly, it was also possible to increase the enantiopurity of product **4a** up to er = 98:2 by slowly crystallizing racemic **4a** out of a solution of enantioenriched **4a** (er = 83:17) in Et₂O.²⁵

We next tested the suitability of compound **4a** for the transformations outlined in Scheme 4. Gratifyingly, the nucleophilic ring opening with benzylic amines (giving amides **9**) as well as with MeOH in the presence of Amberlyst A21 (accessing ester **10**) proceeded reasonably well without causing any erosion of er. The treatment of **4a** with mCPBA on the other hand led to a direct elimination reaction, most presumably *via* *syn*-elimination of the *in situ* formed selenoxide-species, which allows for the straightforward synthesis of alkene **11** hereby.

Finally, we also investigated the application scope for the **DHQN**-catalysed α -selenation of a variety of differently substituted α -arylated derivatives **2** (Scheme 5). It should be noted that we also tested the analogous α -benzylated substrate (Bn instead of Ar). Unfortunately however, and in accordance with our previous α -halogenation results,^{13b} this compound was found to be much less reactive than the α -aryl analogues, giving traces of targeted product only. Furthermore, we also observed a strong influence of the nature of the aryl substituent (Ar) on the outcome of the reaction in terms of yield, conversion, and enantioselectivity. The naphthalene-based **4b** as well as the halogenated products **4d–4g** could be obtained with complete conversion of the respective starting materials **2** and with moderate levels of enantioselectivities. In contrast, the thiophene-substituted **4c** as well as the MeO- and the Me-containing **4h** and **4i** were formed much slower and in these cases the enantioselectivities were also lower (**4h** could not be

**Scheme 4** Further manipulations of compound **4a**.



Scheme 5 Application scope for the enantioselective α -selenation of isoxazolidinones **2**.

isolated at all because of its low stability). Also, the use of alternative Se-transfer reagents (accessing products **4j–l**) was found to be difficult herein, illustrating that our protocol for the α -selenation of compounds **2** is unfortunately rather sensitive to substituent effects.

Conclusions

Using simple Cinchona alkaloids as chiral organobase catalysts allowed for the, to the best of our knowledge so far unprecedented, enantioselective electrophilic α -selenation of azlactones **1** (which were used as masked α -amino acid derivatives) and isoxazolidin-5-ones **2** (representing masked β -amino acids). Utilizing the herein developed methodology gave access to a variety of differently substituted α -Se-amino acid derivatives **3** and **4** with reasonable levels of enantioselectivities and in good yields. Unfortunately, it was not possible to obtain suited crystals of enantioenriched **3** and **4** that allowed for single crystal X-ray analysis and therefore the absolute configuration of the products accessed herein remains yet unknown.

Further studies concerning the stability and suitability of these compounds for further manipulations have been carried

out as well, demonstrating a certain sensitivity, especially in the presence of light and/or in solution.

Experimental details

Full experimental procedures as well as analytical details can be found in the online ESI.†

General procedure for the α -selenation of azlactones **1**

To a solution of **1** (1 equiv.) and DHQN (5 mol%) in toluene (0.0125 M with respect to **1**) under an atmosphere of argon was added the corresponding Se-transfer agent **5** (1.1 equiv.) at 0 °C and under exclusion of light. The reaction mixture was stirred for 1 h under these conditions. After filtration through a pad of Na₂SO₄ the crude product was subjected to silica gel column chromatography (eluent: heptanes:EtOAc gradient) giving products **3** in the report yields and enantiopurities (compare with Scheme 3).

Analytical details of product **3a**

Obtained as a white amorphous solid in 92% yield with er = 89 : 11. TLC (heptanes : EtOAc = 3.5 : 1): R_f = 0.49. $[\alpha]_D^{24}$ = –65.1 (*c* 1.00, CHCl₃). ¹H-NMR (300 MHz, CDCl₃, 298.0 K): δ /ppm = 7.57 (d, *J* = 9.0 Hz, 2H), 7.50 (d, *J* = 6.0 Hz, 2H), 7.39 (t, *J* = 9.0 Hz, 1H), 7.26 (t, *J* = 9.0 Hz, 2H), 7.19–7.14 (m, 4H), 7.12–7.02 (m, 4H), 3.54 (d, *J* = 12.0 Hz, 1H), 3.42 (d, *J* = 15.0 Hz, 1H). ¹³C-NMR (75 MHz, CDCl₃, 298.0 K): δ /ppm = 176.4, 160.7, 138.3, 134.6, 132.8, 130.2, 130.2, 129.2, 128.7, 128.5, 127.9, 127.6, 125.3, 73.9, 41.3. HRMS (ESI-QTOF, MeOH) *m/z*: [M + H]⁺ calculated for C₂₃H₁₇NO₂Se, 408.0498; found, 408.0500. HPLC: Chiralpak AD-H (*n*-hexane : i-PrOH = 20 : 1, flow rate 0.3 mL min^{–1}, 10 °C, λ = 220 nm), retention times $t_{R(\text{minor})}$ = 26.4 min, $t_{R(\text{major})}$ = 27.8 min.

General procedure for the α -selenation of isoxazolidinones **2**

A mixture of **2** (1 equiv.), DHQN (10 mol%) and dry toluene (0.025 M with respect to **2**) was stirred under Ar and cooled on an icebath. The selenation reagent **5** (1.1–1.2 equiv.) was added at once and the reaction flask was covered with aluminium foil. The reaction mixture was gradually warmed to room temperature and stirred for 14 h, whereupon it was concentrated under reduced pressure and directly subjected to column chromatography with gradient elution (silica gel, heptanes : EtOAc = 1 : 0 to 10 : 1) to obtain products **4** in the given yields and enantiopurities (compare with Scheme 5).

Analytical details of compound **4a**

Obtained in 72% yield with er = 83 : 17. TLC (EtOAc : heptanes = 10 : 1): R_f = 0.24 (UV). $[\alpha]_D^{23}$ = +90.2 (*c* 1.01, CHCl₃). ¹H-NMR (300 MHz, CDCl₃, 298.0 K): δ /ppm = 7.41–7.34 (m, 3H), 7.30–7.18 (m, 7H), 4.75 (d, *J* = 12.7 Hz, 1H), 4.34 (d, *J* = 12.7 Hz, 1H), 1.56 (s, 9H). ¹³C-NMR (75 MHz, CDCl₃, 298.0 K): δ /ppm = 172.1, 156.6, 138.3, 135.7, 130.6, 129.3, 128.8, 128.6, 127.5, 126.3, 84.7, 59.5, 49.3, 28.4. HRMS (ESI-QTOF, MeOH) *m/z*: [M + NH₄]⁺ calculated for C₂₀H₂₅N₂O₄Se⁺, 437.0974;



found, 437.0973. HPLC: Chiralpak AD-H (*n*-hexane : *i*-PrOH = 20 : 1, flow rate 1.0 mL min⁻¹, 20 °C, λ = 254 nm), retention times $t_{\text{R}}(\text{minor})$ = 9.7 min, $t_{\text{R}}(\text{major})$ = 11.0 min.

Author contributions

V. Haider and P. Zebrowski contributed equally to the experimental work as well as the preparation of the manuscript. J. Michalke carried out additional supporting experiments. U. Monkowius carried out single crystal X-ray diffraction analysis. M. Waser initiated and supervised the project and wrote the manuscript with input from all authors. All authors have given approval to the final version.

Conflicts of interest

There are no conflicts to declare.

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