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# Stereoselective arylthiolation of dehydroalanine in the Ni$^{II}$ coordination environment: the stereoinductor of choice

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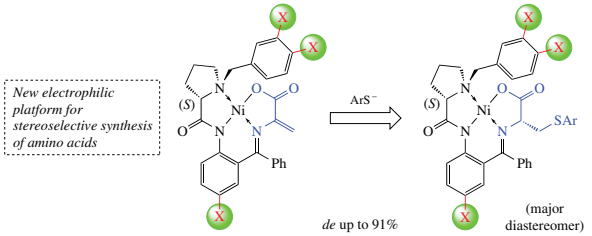
**Arylthiolation of new dehydroalanine Ni$^{II}$ Schiff-base complex containing (*S*)-2-[*N*-(*N*′-2,3-dichlorobenzylprolyl)-amino]-5-chlorobenzophenone auxiliary affords (*S,R*)-cysteine derivatives in high chemical yield (65–88%) and with excellent diastereoselectivity (*de* up to 91%), which significantly exceeds that for the commonly used analogue depriving of three chlorine atoms.**




*Keywords*: stereoselective synthesis, chiral template, Schiff bases, nickel complexes, arylthiolation, sulfides, cysteine derivatives, Michael addition.

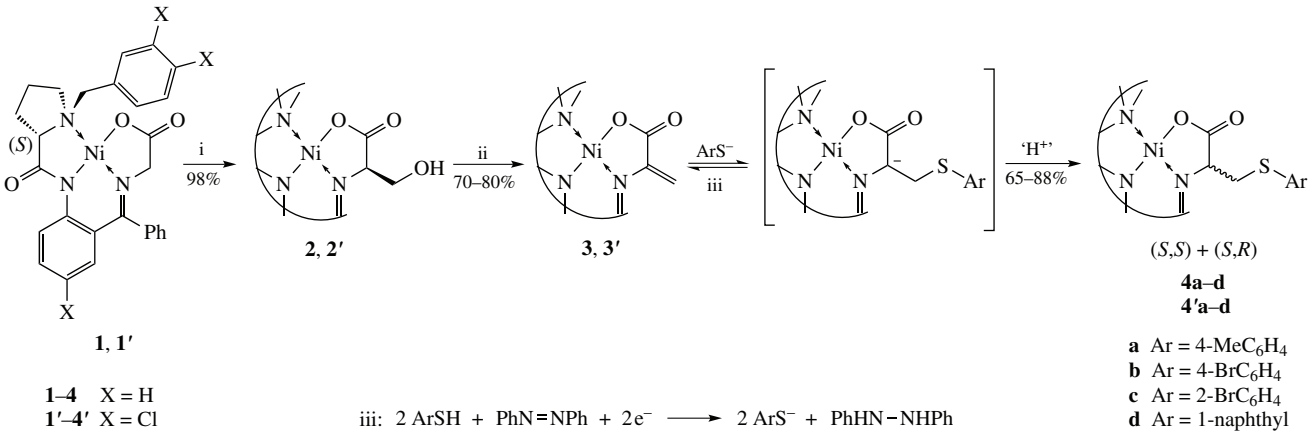
Sulfur-containing amino acids, *e.g.*, cysteine and its derivatives, are widely used in peptide synthesis[1,2] and in pharmaceutical industry.[7–11] This dictates a need for advanced approaches to structurally and functionally novel types of β-thiolated amino acids. Direct insertion of a sulfur-containing fragment into the β-position of amino acids is provided by nucleophilic addition of thiols to dehydroalanine derivatives serving as the Michael acceptors. To make the reaction stereoselective, the use of chiral auxiliaries is generally required. One of the efficient approaches is based on application of amino acid Ni$^{II}$ Schiff base complexes with chiral ligands creating an efficient asymmetric environment around the metal center as a platform for asymmetric synthesis of tailor-made α-amino acids.[12–17] In early works,[18–20] nucleophilic addition of thiols to chiral Schiff base derivative of dehydroalanine proceeded truly stereoselectively to afford the corresponding β-organylthiolated derivatives. To achieve high stereoselectivity, the reactions were commonly performed under the thermodynamic control. An excess of a strong base (DBU, DMF/$K_2CO_3$) facilitates epimerization of the adducts yielding thermodynamically more stable (*R*)-configured isomer (if the natural (*S*)-*N*-benzylproline was used as the chiral source). The mechanistically different route to the β-alkylthiolated amino acids involves the $S_N2$ alkylthiomethylation of chiral Ni$^{II}$ complexes of the alanine Schiff bases.[21] A comparison of proline and 3,5-dihydro-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine derived chiral ligands showed a clear superiority of the former in terms of yields and diastereoselectivity.

Completely different type of chiral dehydroalanine derivatives, namely, bicyclic metal-free compounds (obtained by lactonization of amino acid)[22,23] also behaved as excellent Michael acceptors for thiols, which was used to obtain sulfur-containing glycopeptides of biological relevance. This method turned out rather efficient, however the chiral auxiliary could not be recycled (contrary to the aforementioned Ni–Schiff base methodology).

In the publications mentioned above, the (*R*)-configured β-sulfanylated derivatives of dehydroalanine were obtained with high stereoselectivity. Notably, the (*R*)-isomers can be readily accessed from natural L-cysteine.[24,25] As for the scarcely documented analogous (*S*)-stereoisomers, they can be in principle obtained under the kinetic control conditions when the epimerization follow-up step is suppressed. These experimental conditions can be achieved when no base provoking epimerization of the initial product is present in the solution.[26] One of the ways to control the amount of a base in solution (thus controlling stereoselectivity level) is an application of the electrochemically generated base (the EGB-*in situ* methodology).[27,28] A base is generated *via* the reduction of the suitable precursor and performs deprotonation *in situ* under the voltammetric control,[28,29] which was successfully utilized for the $S_N2$ modification of some amino acid Schiff base nickel complexes.[28–31] However, the application of EGBs to control stereoselectivity of thiol addition to Michael acceptors in the Ni$^{II}$ coordination environment was not studied previously.

The stereochemical outcome of most such reactions, *e.g.*, comprising glycine and alanine-based Ni$^{II}$ Schiff base complexes, is generally dependent on the chiral auxiliary used.[32] Importantly, insertion of chlorine substituents into commonly used (*S*)-*o*-[*N*-(*N*′-benzylprolyl)amino]benzophenone[12,13] really improved stereoselectivity of the modification of glycine complexes.[33,34] In the meantime, dehydroalanine nickel complex equipped with chlorinated auxiliary has not been reported so far.

In the present paper, synthesis of new dehydroalanine Ni$^{II}$ Schiff base complex containing (*S*)-2-[*N*-(*N*′-2,3-dichlorobenzyl-




**Scheme 1** *Reagents and conditions:* i, MeOH, KOH, electrolysis (5 mA $cm^{-2}$), undivided cell; ii, $Ac_2O$, $Na_2CO_3$, MeCN, 60 °C; iii, ArSH, $Ph_2N_2$, $Bu_4NBF_4$, DMF, electrolysis (–1.4 V *vs.* Ag/AgCl, $KCl_{sat.}$), two-compartment cell.

prolyl)amino]-5-chlorobenzophenone auxiliary is reported (Scheme 1). The comparison between the new complex and its analogue depriving of three chlorine atoms in the Michael addition of arenethiols to the dehydroalanine double bond demonstrates dramatic superiority of the former in the stereoselectivity level. New β-arylthiolated amino acids (in the form of $Ni^{II}$ Schiff-base complexes) were obtained in high yield and with excellent stereoselectivity. Applicability of the EGB methodology for thiols deprotonation, as a possibility to switch from the kinetic control to thermodynamically controlled process by variation of the amount of the electrogenerated base was also tested.

Dehydroalanine complexes **3** and **3′** were synthesized *via* dehydration of the corresponding serine complexes **2** and **2′** (see Scheme 1). The latter ones, in turn, were obtained electrochemically[35] from glycine complexes **1** and **1′**, using new approach[35] which turned out to be very efficient and practical. Both new complexes, **2′** and **3′**, were isolated and fully characterized using HRMS and NMR (for details, see Online Supplementary Materials).

Both **3** and **3′** complexes being active Michael acceptors were subjected to the reaction with substituted thiophenols and thionaphtol. The corresponding S-arylated cysteine derivatives of type **4** were obtained in practical 65–88% yields for both chlorinated and non-chlorinated auxiliaries (see Scheme 1). The stereochemical result was dependent on the reaction conditions and the chiral template used. Under pure kinetic control (room temperature, no base added), the reaction was slow (~36 h) and gave both (*S*,*S*)- and (*S*,*R*)-β-arylthiolated complexes **4** in almost equimolar ratio. Addition of a base capable of deprotonating thiols fastens the reaction and significantly influences the stereochemical outcome. For the *in situ* deprotonation of ArSH, the EGB (azobenzene radical anions formed under controlled potential of –1.4 V *vs.* Ag/AgCl, $KCl_{sat.}$) was used. The concentration of the base could be tuned and controlled instrumentally; if necessary, the excess of the base was re-oxidized to preclude possible side reactions.

Though the processing was the same as previously described,[28] the voltammetric monitoring showed some differences. The intensive oxidation peak corresponding to the thiolate formed in the solution was observed indicating that deprotonation did really occur. However, the characteristic peak attributed to the oxidation of the anionic Ni complex which might be expected to appear after addition of the starting complex to the thiolate solution was not detected (Figure 1). Meanwhile, the targeted arylthiolated complex is formed (as indicated by the follow-up analysis of the reaction mixture). That meant that the source of protons was present in the reaction mixture. This result

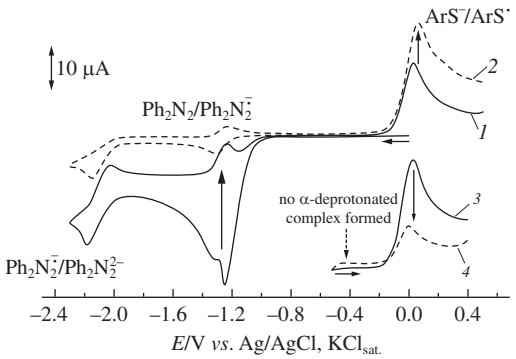



**Figure 1** Voltammetric monitoring of the reaction. CV curve (*1*) in the beginning and (*2*) in the end of the electrolysis. In the inset: CV curve of the thiolate solution (*3*) before and (*4*) after addition of complex **3**.

demonstrates that functioning of the azobenzene radical anions as a base towards CH and SH-acids is different. In the latter case, it acts similarly to the common chemical bases applied in the analogous reaction (see ref. 18).

The reaction was repeated with various amounts of thiol and the base (Table 1). If nucleophilic addition to **3** is performed in the presence of 0.6 mol equiv. of the azobenzene pre-base (the amount sufficient for complete deprotonation of thiols if the thiol and the dehydroalanine complex are taken in almost equimolar ratio, see Scheme 1), the reaction reaches its completion in *ca*. 1 h, and β-arylthiolated complexes **4a–d** are formed in *ca*. 70% yield. Additionally, some amount of the starting complex (*ca*. 20–30%) was also isolated. Among arylthiolated complexes, more stable (*S*,*R*)-isomer dominated but the diastereomeric ratio was low (see Table 1). However, this allowed us to isolate and characterize much less available (*S*,*S*)-diastereomers. This tendency was observed for all sulfur nucleophiles under investigation. The prevalence of the (*S*,*R*)-

**Table 1** Diastereomeric ratios for the arylthiolated complexes **4a–d** or **4′a–d** obtained in the reaction of **3** or **3′** with arenethiols in the presence of $Ph_2N_2$; chemical shift ($CDCl_3$) for the $H^8$ proton in diastereomers.

| Reaction parameters | (*S*,*R*)/(*S*,*S*) ratios and the $\delta_{H(8)}$ values | | | |
|---|---|---|---|---|
| | **4a** or **4′a** | **4b** or **4′b** | **4c** or **4′c** | **4d** or **4′d** |
| **3** + ArSH (1.1 molar equiv.) | 1.8 : 1 | 2.8 : 1 | 3.1 : 1 | 5.5 : 1 |
| **3** + ArSH (2.5 molar equiv.) | 3 : 1 | 4.5 : 1 | 5 : 1 | 8 : 1 |
| **3′** + ArSH (2.5 molar equiv.) | 1 : nd[a] | 1 : nd | 8 : 1 | 20 : 1 |
| $\delta_{H(8)}$ for *S*,*R*/*S*,*S*-**4a–d**/ppm | 8.23/8.52 | 8.20/8.49 | 8.26/8.53 | 8.29/8.55 |
| $\delta_{H(8)}$ for *S*,*R*/*S*,*S*-**4′a–d**/ppm | 8.16/nd | 8.13/nd | 8.15/8.47 | 8.19/nd |

[a] nd – the diastereomer was not determined in the reaction mixture.

diastereomer was slightly enhanced with the increase in the sterical bulkiness of the nucleophile since the *si*-attack is preferable than the *re*-attack. Thus obtained new series of the diastereomeric couples will serve as the objects for investigation of the stereodependent redox activity phenomenon which is currently in progress.

To enhance the yield of the arylthiolated derivatives, the molar amount of the thiolate was raised to 2.5 equiv., the amount of azobenzene was 1.2 equiv. In these cases, the starting complex was entirely consumed and the yield of products **4** reached 75–85%. The diastereomeric ratio was also increased (see Table 1). Again, the prevalence of the (*S*,*R*)-diastereomer was greater for the more bulky thionaphtol.

Notably, the changing of the chiral auxiliary turned out to be the most efficient route to achieve high diastereoselectivity level. Arylthiolation of new trichlorinated **3′** complex, contrary to its unsubstituted analogue **3**, demonstrated excellent stereoselectivity even in the presence of a low amount of thiolate (1.1 molar equiv.) yielding the (*S*,*R*)-isomers. For complexes **4′a**,**b**, no (*S*,*S*)-stereoisomer was detected; the obtained (*S*,*R*)/(*S*,*S*) diastereomeric ratio for **4′c** and **4′d** was 5.5 : 1 and 20 : 1, respectively. These results clearly demonstrate the advantages of the application of the chlorinated template providing higher stereoselectivity level as compared to the commonly used complex **3**.

The configuration of the α-amino acid stereocenter in compounds **1**–**4** was determined from the NMR data, *i.e.*, from the diagnostic chemical shift for the $H^8$ proton (see Table 1 and Figure S1 in Online Supplementary Materials). The chemical shift for the $H^8$ proton in the $Ni^{II}$ Schiff-base amino acid complexes with (*S*)-*o*-[*N*-(*N′*-benzylprolyl)amino]benzophenone is strongly dependent on the configuration of the α-amino acid carbon;[35] the reliability of the assignment was supported by numerous examples of the previously investigated complexes of this type. For the D-α-amino acid complexes, the chemical shift for this proton falls within the range of 8.45–8.60 ppm, whereas the corresponding interval is upfield-shifted (8.00–8.35 ppm) for the L-amino acid derivatives. This difference is attributed to the distortion of the Ni coordination environment (determining the mutual arrangement of the $H^8$ and the carbonyl group) due to the π-stacking interaction between the benzyl group in the proline fragment and the *o*-phenylene moiety which is commonly much stronger in the L-α-amino acid complexes. As follows from Table 1, the chemical shifts for the $H^8$ protons of the major diastereomers of complexes **1**–**4** are upfield-shifted and fall within the range of 8.20–8.30 ppm, whereas the corresponding values for the minor diastereomers match the interval of 8.45–8.55 ppm. Hence, the major and minor diastereomers have the (*S*,*R*)- and (*S*,*S*)-configurations, respectively, or, in other words, correspond to the L- and D-amino acid derivatives, respectively.

Pure (*S*,*S*)- and (*S*,*R*)-diastereomers of complexes **4a**–**c** were isolated and fully characterized by HRMS and NMR (see Online Supplementary Materials; attempted isolation of minor *S*,*S*-**4d** failed). As concerns the corresponding amino acids (which can be obtained *via* solvolysis of the complexes using HCl/MeOH[12]), the arylated derivatives of natural L-cysteine with the (*R*)-configuration of the α-amino acid stereo center are known,[36,37] in contrast to arylated D-cysteine derivatives containing 4-Me and 2-Br substituents which have not been described before, to the best of our knowledge.

To conclude, novel dehydroalanine $Ni^{II}$ Schiff-base complex containing (*S*)-2-[*N*-(*N′*-2,3-dichlorobenzylprolyl)amino]-5-chlorobenzophenone chiral auxiliary was synthesized from the corresponding new serine derivative. Notably, the stereoselectivity level (*de* up to 91%) provided by complex **3′** in arylthiolation of the dehydroalanine double bond yielding the (*S*,*R*)-cysteine derivatives significantly exceeds that for the commonly used non-chlorinated analogue **3**. New $Ni^{II}$ Schiff-base complexes based on β-arylthiolated amino acids of type **4** were obtained in high yields. These compounds are the direct precursors for the practically important arylated cysteine analogues. For generation of the nucleophilic species, deprotonation of the thiophenols was accomplished using the electrochemically generated base methodology, with azobenzene radical anions acting *in situ* under the voltammetric control. However, the results obtained in the deprotonation of the SH-acids showed no significant advantages over common chemical bases, contrary to the previously reported deprotonation of the CH-acids.[28,30,31]

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.05.018.

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