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Reductive opening of a cyclopropane ring in the Ni(II) coordination environment: a route to functionalized dehydroalanine and cysteine derivatives

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Abstract

Involvement of an α,α-cyclopropanated amino acid in the chiral Ni(II) coordination environment in the form of a Schiff-base is considered as a route to electrochemical broadening of the DA-cyclopropane concept in combination with chirality induction in the targeted products. A tendency to the reductive ring-opening and the follow-up reaction paths of thus formed radical-anions influenced by substituents in the cyclopropane ring are discussed. Optimization of the reaction conditions opens a route to the non-proteinogenic amino acid derivatives containing the α-β or β-γ double C=C bond in the side chain; the regioselectivity can be tuned by Lewis acids addition. One-pot combination of the reductive ring opening and subsequent addition of thiols allows obtaining the cysteine derivatives in practical yields and with high stereoselectivity at the removed β-stereocenter.

Electrochemistry provides a direct access to highly reactive species by means of harnessing electrons or electron holes as reagents [1,2]. This capacity can be efficiently exploited in organic synthesis for rational construction of complex multifunctional molecules [3–8].

Recently, we elaborated a versatile electrochemical approach to stereoselective functionalization of a side chain of amino acids involved in the Ni(II) chiral coordination environment [9–15]. A combination of redox-activity and chirality provided by the Ni-Schiff-base template, supported with the protection from redox-destruction of the amino acid skeleton, makes the suggested approach a convenient route to various types of non-proteinogenic amino acids [9,10,12,13]. Recently, several practical approaches to α,α-cyclopropanated amino acids in the form of Ni(II) Schiff-base complexes were suggested [16–19], including electrochemical ones [15]. Cyclopropane-containing amino acids are important component of various pharmaceuticals [20,21] and bio-additives [22]. Meanwhile, the cyclopropane fragment not only provides targeted pharmacophoric properties of the bio-active molecule [23] but also opens a route to its further functionalization, being a building block with wide variety of reactivity. A donor-acceptor cyclopropanes concept suggested in 1980-s [24] became extremely popular in the recent decade [25,26]. Donor-acceptor cyclopropanes constitute an easily available equivalent of all-carbon 1,3-zwitter-ions used in targeted synthesis of various alicyclic as well as carbo- or heterocyclic compounds [27–30]. The reactive synergy of the three-membered ring and the C-C bond polarization due to donor-acceptor substituents contributes to the rich chemistry of these compounds. However, strict requirements for the nature of substituents somewhat narrow the applicability of the method.

Electrochemical one-electron opening of a cyclopropane ring results in formation of ion-radical species instead of zwitter-ions, thus creating preconditions for different type of reactivity. Such processes are much less investigated.

The very first example of anodic cyclopropane ring opening was reported by Shono [31]. This publication sparked interest in this topic; a number of publications appeared but the reaction scope was mainly limited to rather simple compounds containing methyl and phenyl substituents [32–37].

When discussing examples of reductive cyclopropane ring opening, one should refer to early publications concerning the carbonyl- and nitro-substituted compounds [38–42]. The principal possibility of the process was demonstrated but the synthetic potential of the method was not sufficiently implemented.

Great success of the donor-acceptor cyclopropanes concept in organic synthesis stimulated a renaissance of interest to electrochemical ring opening. Quite recently, two publications from Kolb group appeared concerning anodic activation of donor-acceptor cyclopropanes followed by their functionalization with arenes [43] or yielding oxy-ketones or 1,2-dioxanes formation [44]; the latter process was inspired by previous report of Buriez [45]. Anodic fluorination of arylcyclopropane derivatives were reported recently [46,47], difluorination or oxyfluorination products were obtained [47]. Notably, anodic fluorination of cyclopropane derivatives bearing arylthio groups gives rise to a variety of possible reaction paths yielding monofluorinated sulfoxides as well as ring-open fluorinated products [46].

Thus, recent publications in the topic concern only anodic opening of a cyclopropane ring followed by further functionalization of the carbon skeleton, demonstrating great synthetic potential of the process.

Electrochemical cyclopropane opening followed by stereoselective functionalization has not been probed as yet. of a cyclopropane ring involved in a metal coordination environment has not been probed as yet. Herein, reductive three-membered ring opening in the chiral α,α-cyclopropanated amino acids involved in the Ni(II) Schiff-base coordination environment is reported. Follow-up transformations of thus formed radical anions will be discussed, including reactions with electrophiles, intramolecular cyclization and disproportionation process. Synthetic viability of the approach will be considered. One-pot multi-step synthetic protocol is suggested, based on addition of thiols to the mixture of isomeric alkenes formed in electroreductive opening of a cyclopropane ring in α,α-cyclopropanated amino acids yielding the cysteine derivatives in practical yields and with high stereoselectivity at the removed β-stereocenter. Thus, the present paper is further development of the extended research on electrochemically induced stereoselective transformations in the Ni(II) coordination environment yielding structurally and functionally novel types of tailor-made amino acids.

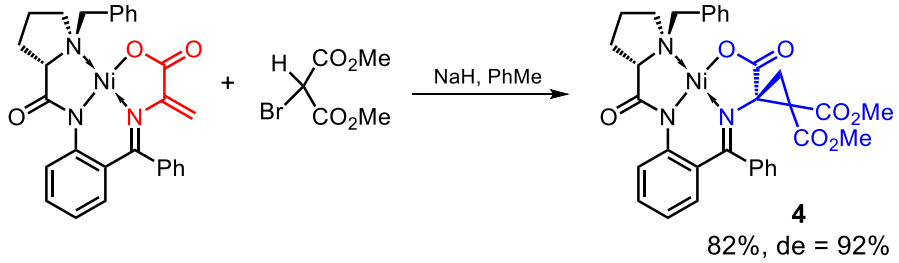
Results and discussion

Voltammetry study

As models, a series of Ni(II) Schiff base complexes containing α,α-cyclopropanated amino acids was synthesized (see Fig.1). Complexes **1-3** containing unsubstituted cyclopropane ring (**1**) or bearing Me (**2**) and COOMe (**3**) groups were obtained using previously reported protocols [15,19]. Complex (**4**) is new.

It was obtained by the reaction of electrophilic dehydroalanine complex with bromomalonate anion (Scheme 1). The reaction proceeds smoothly at room temperature giving rise to cyclopropane **4** in excellent diastereoselectivity (de = 92%) and high yield.

Scheme 1. *Synthesis of complex **4**.*



To choose the most promising candidates for electrochemical three-membered ring opening, the voltammetric study of was performed. The complexes containing unsubstituted cyclopropane ring (**1**) or bearing Me (**2**) substituents exhibit reversible one-electron reduction at similar potential values ($E_{1/2}$ = −1.42 V (**1**), −1.42 V (**2**) *vs.* Ag/AgCl, $KCl_{(sat.)}$). This indicates that the radical-anions formed are relatively stable, at least in the CV time scale. The complexes containing one (**3**) or two (**4**) COOMe-groups in the cyclopropane moiety making it more electron-deficient may be expected to be more prone to the ring opening, and the irreversibility of the cathodic redox process observed in the voltammograms (E_{pc} = −1.60 V *vs.* Ag/AgCl, $KCl_{(sat.)}$ for (**3**) and E_{pc} = −1.50 V for (**4**); Fig. 1) supported the suggestion. In the reverse anodic scan, a new oxidation peak (**A** in Fig.1; E_p^A = −0.06 V (**3**), 0.16 V (**4**) *vs.* Ag/AgCl, $KCl_{(sat.)}$) can be observed for both complexes **3** and **4** (though in the latter case it is more intensive); more likely, the peak corresponds to reoxidation of the anionic species formed after the ring opening. The reduction patterns for compounds **3** and **4** differ significantly. In the voltammogram corresponding to complex **4** containing two COOMe-groups, two consecutive reduction peaks can be observed. The more cathodic peak is reversible ($E_{1/2}$ = −1.87 V *vs.* Ag/AgCl, $KCl_{(sat.)}$). Analysis of semi-differential curves (see SI) indicates that the consumption of electrons at the first reduction peak is independent on the potential scan rate. In contrast, the more cathodic peak in semi-differential voltammogram gradually decreases with the scan rate increase. Thus, the second peak should be assigned to reduction of the product of the chemical step following the first reduction process.

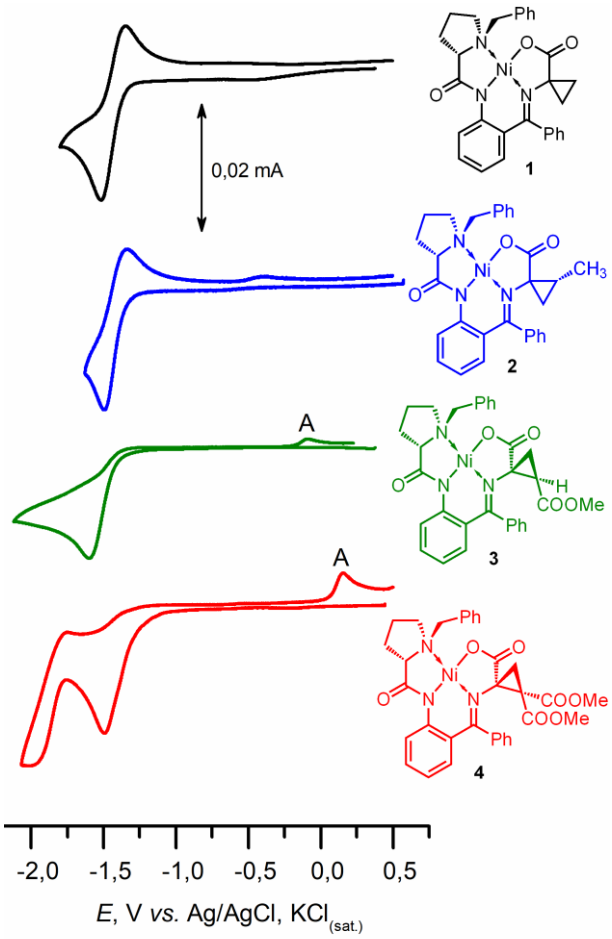


Fig. 1. Cyclic voltammograms obtained for complexes **1** (black), **2** (blue), **3** (green), **4** (red) (MeCN, 0.05 M Bu_4NBF_4, 100 mV/s, Pt).

Preparative electrolysis

Based on the voltammetry results, complexes **3** and **4** were chosen as the models for the preparative study. Electrolysis was performed in a two-compartment electrochemical cell in DMF using a glassy carbon plate as a working electrode and an iron rod as an auxiliary electrode. The process was carried out in the potentiostatic mode at the potential of 100 mV more cathodic than the peak potential value observed in the voltammogram; a charge corresponding to 1 mol equivalent of the starting complex was passed through the solution. The color of the solution was gradually changed from deep red to dark violet, typically for the anionic complexes. The solutions obtained were ESR-silent, indicating formation of the closed-shell species. The UV-Vis study showed an intensive absorption at 546 nm for **3** and at 519 nm for **4**. The significant bathochromic shift as compared to the deprotonated glycine complex (λ_{max} = 458 nm [9]) indicates an elongation of the conjugation chain and formation of the anionic complex which can be considered as a vinylog of the parent glycine derivative (Scheme 2).

Anionic species formed in the electrolysis of complex **3** can be protonated using acetic acid (pKa in DMSO = 12.3 [48]), in contrast to their counterparts formed from complex **4**. In the latter case, a stronger protonating agent is required, e.g., $PhNEt_2 \cdot HCl$ (pKa in DMSO = 2.45 for PhN^+HMe_2 [48]),. The pKa value of **6** determined in DMSO solution using UV-Vis method (see SI for the details) is 5.1, indicating high stability of the anion.

*Synthesis of the dehydroalanine derivatives **6***

The reaction products were isolated with column chromatography and analyzed using spectral methods. Both alkene and hydrogenated complexes are formed in the equimolar ratio, indicating disproportionation of the radical anions formed. The hydrogenated complexes **7** are of less synthetic value since they are more easily available than the corresponding substituted dehydroalanine derivatives. Additionally, the latter are of interest due to bioactivity [49,50]. To increase the yield of the alkene complexes, the addition of an external "H-abstractor" may be helpful, to suppress disproportionation. A possible candidate may be a reduced radical form of azobenzene. Indeed, the preparative electrolysis performed in the presence of the equimolar Ph_2N_2 additive changed the relative ratio of alkene to hydrogenated derivatives in favor of the former one (see Table 1).

Scheme 2. *Reductive three-membered ring-opening and follow-up chemical steps.*

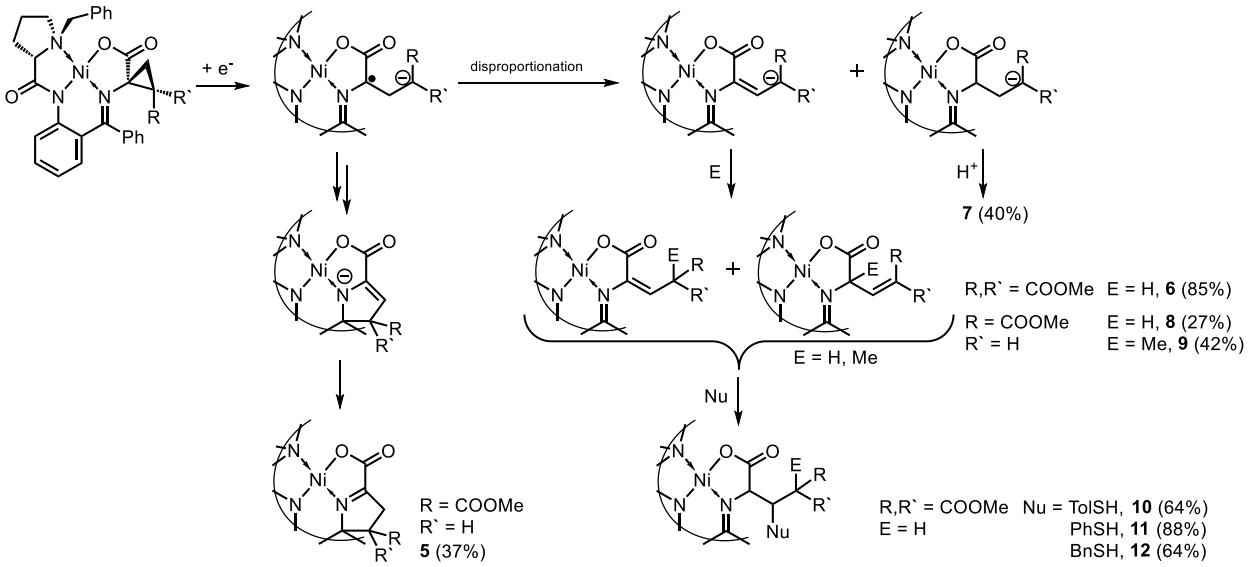


Table 1. The yields of the alkene complexes **6** and the hydrogenated derivative as dependent on the electrolysis conditions used for the ring opening in complex **4**.

Conditions	alkene complexes **6**, %	α-β alkene/β-γ alkene ratio	Hydrogenated derivative **7**, %
Bu_4NBF_4, −1.7 V	40	1.5 : 1	40
Bu_4NBF_4, Ph_2N_2 1eq, −1.5 V	85	1.5 : 1	10
Bu_4NBF_4, Ph_2N_2 1.5eq, −1.5 V	85	1.5 : 1	10
LiCl, −1.4 V	40	5 : 1	40
One-compartment cell with Zn or Mg anode	50	54 : 1	12

As follows from Table 1, the azobenzene additive allows increasing the yield of the alkene complexes up to 85% suppressing formation of the hydrogenated complexes. Spectral NMR analysis of the reaction mixture showed that two isomeric alkenes (containing the α-β or β-γ double

bond) are formed. In the isomers, two protons of the amino acid side chain create an AB system; in the α-β-isomer, both protons show correlations in the HMBC spectrum with the C atoms of the COOMe groups, whereas in the β-γ-isomer, only one H correlates with the COOMe and the other H atom correlates with the Schiff and carboxylic carbons (see Fig.2 and SI).

The experimental ratio of the isomeric alkenes (1.5:1) is close to the calculated value predicted from their relative thermodynamic stability (1.3:1, see SI). Using LiCl as a supporting electrolyte increases the ratio to 5:1. If the electrolysis is performed in the undivided cell equipped with Zn or Mg anode, the isomeric α-β and β-γ alkene complexes are formed in 54:1 ratio (though the total yield is decreased to 50%). One can suggest that coordination to the Lewis acid increases the regioselectivity of protonation in the allylic anions formed in the electrolysis.

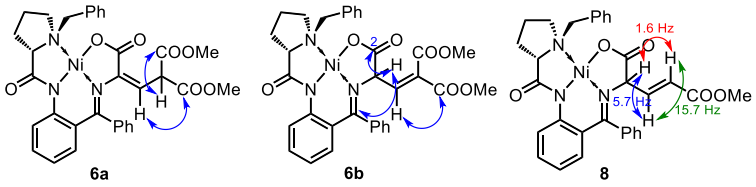


Fig. 2. Correlations in HMBC spectrum of **6a** and **6b** and spin coupling constants in ^{1}H NMR spectrum of **8**.

In case of complex **3**, the isolated yield of the alkene complex was low (20%); the Ph_2N_2 additive gives only insignificant increase (27%). Analysis of the spin coupling constants values (see SI for the details) testifies in favor of the β-γ-isomer selective formation. The dominant reaction product formed in the reductive opening of the cyclopropane ring in complex **3** was new derivative **5** containing the five-membered ring (see below and Scheme 2).

Intramolecular cyclization

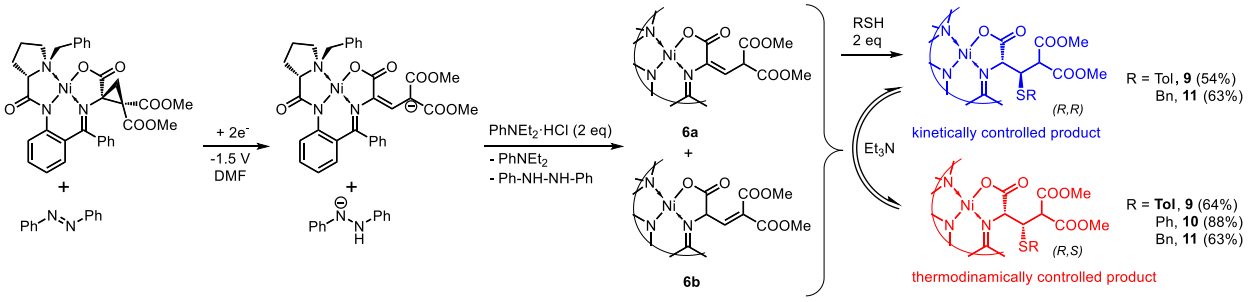
The anionic species formed in the ring opening in complex **3** undergo fast intramolecular cyclization via the nucleophilic attack at the imine fragment yielding new complex **5** which was isolated in the form of two diastereomers in a total yield of 37% indicating that this reaction route dominates. The compounds were characterized with the NMR (2D technique). Notably, insertion of the second COOR group in the starting cyclopropane complex **4** completely suppresses this reaction channel – intramolecular cyclization of the anions formed in the reductive cleavage of the three-membered ring was not observed. This may be attributed to the decreased nucleophilicity as well as to sterical reasons.

Reaction with electrophiles

Anions formed in the reductive ring opening in complex **4** are stable enough: they survive even in the presence of acetic acid and do not react with electrophiles (CH_3I, benzaldehyde). In contrast, addition of external electrophiles in the reaction mixture obtained in the electrolysis of **3** launches an additional reaction path, along with intramolecular cyclization described above. Thus, addition of CH_3I results in formation of the γ-methylated alkene complex **9** in the form of two diastereomers (5:1) in 42% yield.

The results obtained clearly indicate that follow-up functionalization of the anions formed after the ring opening with electrophiles (except H^+) has low synthetic value due to multiple competing reaction channels observed in case of **3** and decreased nucleophilicity of **4**. Consequently, it seems reasonable to focus on the one-pot nucleophilic functionalization of the double bond of the dehydroalanine derivatives formed after the reductive ring opening and subsequent protonation. Such approach opens a route to double functionalization of the amino acids side chain. Insertion of the sulfur-containing fragments is of special interest due to bioactivity of such compounds [51,52]; thus, elaboration of new synthetic protocols to these multifunctional molecules is a topical problem.

Scheme 3. *One-pot multi-step approach to the cysteine derivatives.*



Complex **4** was subjected to reductive ring opening at a potential of −1.5 V (Ag/AgCl, $KCl_{(sat.)}$) in the presence of equimolar amount of azobenzene as described above (two-compartment cell, DMF, Bu_4NBF_4, WE – glassy carbon, CE – an iron wire). After 2 F/mol amount of electricity passed and subsequent protonation with $PhNEt_2 \cdot HCl$, aryl- or benzyl sulfide was added. The reaction mixture was kept overnight and then the products were isolated using column chromatography and analyzed using spectral methods. The results obtained are given in Table 2 and Scheme 3.

Table 2. The yield and diastereomeric ratio of the cysteine derivatives obtained in a one-pot electrochemical reduction of complex **4** with subsequent thiol addition

	ArSH	eq ArSH	(*R*,*S*):(*R*,*R*) dr	Yield, %		Complex
1	TolSH	1	10:1	64%	-	**10**
2	TolSH	2	1:5	54%	-	**10**
3	TolSH	2	10:1	64%	+ 1 eq Et_3N	**10**
4	PhSH	2	12:1	88%	+ 1 eq Et_3N	**11**
5	BnSH	2	1:2.6	64%	-	**12**
6	BnSH	2	Pure (*R*,*S*)-isomer	42%	+ 1 eq Et_3N	**12**

The synthetic procedure was tested on three thiols, of both aromatic and aliphatic types. The first experiment with p-tolylsulfide gave the targeted cysteine derivative in practical 64% isolated yield, along with some amount of the alkene complex (see Scheme 3). In an attempt to increase the yield of the cysteine derivatives, the amount of the sulfide was doubled. Unexpectedly, this resulted in the inversion of the diastereomeric ratio (entry 2 in Table 2). To find a reason, the experiment was repeated in the presence of an additional base (1 mol equivalent of Et_3N); the result was identical to that previously obtained for the equimolar **4**: tolylsulfide mixture (compare entries 1 and 3 in Table 2). Thus, it seems reasonable to suggest that a base may induce epimerization of the product

yielding the most thermodynamically stable cysteine derivative[1]. The suggestion was proved by the control experiment. An equimolar mixture of the diastereomeric cysteine complexes **10** were dissolved in DMF containing Et_3N and TolSH (1:1) and left overnight at room temperature under argon. As a result, the (*R*,*S*):(*R*,*R*) diastereomeric ratio was changed from 1:1 to 13:1 in favor of the thermodynamically more stable (*R*,*S*)-diastereomer.

The experiment with thiophenol performed in the same reaction conditions (a two-fold excess of thiol and the Et_3N additive) gave the cysteine derivatives in 88% yield and with 12:1 diastereoselectivity; again, the (*R*,*S*)-diastereomer was the dominant (entry 4, Table 2), in line with the previous results with tolylsulfide.

In case of an aliphatic thiol (benzyl sulfide), the results were qualitatively similar. The diastereomeric ratio is inverted in favor of the kinetically controlled product when no Et_3N is added into the solution (entry 5, Table 2). In contrast, pure (*R*,*S*)-diastereomer was obtained when the solution containing 1 mol eq. of Et_3N was kept for 72 h under slight heating (40°C, entry 6); though in the expense of the yields decrease (a significant amount of the alkene (48% instead of 20% detected in exp.5 was also isolated from the reaction mixture).

Thus, the experiments indicated that the one-pot multi-step experimentally simple procedure allows achieving high stereoselectivity at the removed β-stereocenter, what is not an easy task. In all cases, the targeted cysteine derivatives were isolated in practical yields. It should be noted that there is no need to separate the isomeric alkene complexes formed after the cyclopropane ring opening, they can be involved in the follow-up reaction with nucleophiles in the form of a mixture. This simplifies the synthetic procedure; the multi-step process can be performed in electrochemical cell, with the potential switching off prior to addition of nucleophiles (thiols in our case).

Conclusion

Electroreductive opening of a cyclopropane ring in α,α-cyclopropanated amino acids in the form of Ni(II) Schiff-base complexes was studied. Preliminary voltammetry testing allowed to choose the most promising candidates for the preparative synthesis. The bulk electrolysis showed that substituents in the cyclopropane ring not only affect its tendency to the ring-opening, but also determine the follow-up reaction paths of thus formed radical-anions. Possible reaction paths include disproportionation reaction yielding a mixture of alkenes and corresponding hydrogenated derivatives, intramolecular cyclization and reaction with external electrophiles. Optimization of the reaction conditions opens a route to the amino acid derivatives containing the α-β or β-γ double C=C bond in the side chain; the regioselectivity can be tuned by Lewis acids addition. This type of non-proteinogenic amino acid derivatives is not easily available but strongly required due to their bioactivity.

One-pot nucleophilic *in situ* functionalization of the double bond of the dehydroalanine derivatives formed after the reductive ring opening and subsequent protonation opens a route to double functionalization of the amino acids side chain. Thus, addition of thiols to the mixture of alkenes formed in reductive opening of a cyclopropane ring in α,α-cyclopropanated amino acids allows

[1] Since the reaction is performed as a one-pot procedure, 1 eq of $PhNEt_2$ formed after protonation of the carbanion is already present in the reaction mixture. An excess of the thiol (which is sufficiently acidic) eliminates the base preventing epimerization of the product

obtaining the cysteine derivatives in practical yields and with high stereoselectivity at the removed β-stereocenter. The developed one-pot multi-step procedure highlights new perspectives provided by combination of electrochemically broaden DA-cyclopropane concept and chirality induction within a metal coordination sphere (which facilitates electrochemical ring opening and provides stereoinduction).

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