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Title: Operationally Convenient and Scalable Asymmetric synthesis of (2S)- and (2R)-□-(Methyl)cysteine Derivatives via Alkylation of Chiral Alanine Schiff Base Ni(II) Complexes

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Operationally Convenient and Scalable Asymmetric synthesis of (2*S*)- and (2*R*)-α-(Methyl)cysteine Derivatives via Alkylation of Chiral Alanine Schiff Base Ni(II) Complexes

Junya Yamamoto,[a] Aki Kawashima,[a] Akie Kawamura,[a] Hidenori Abe,[a] Hiroki Moriwaki,*[a] Norio Shibata,[b] and Vadim A. Soloshonok *[c,d]

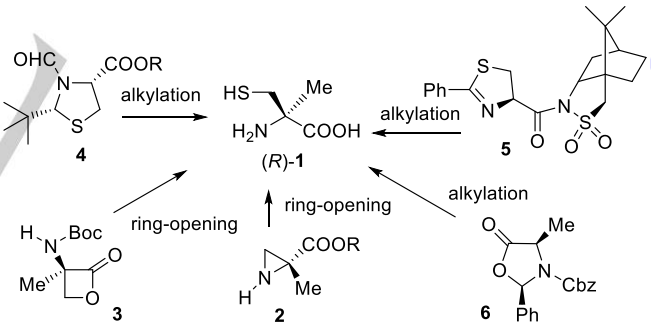
Dedicated to the memory of Professor Teodor Silviu Balaban, a generous, thoughtful friend and a talented scientist.

Abstract: This research demonstrates that the methylation of *N*-benzyl cysteine Schiff bases derived Ni(II) complexes leads to the formation of the corresponding dehydroalanine containing products and cannot be used for preparation of the target α-(methyl)cysteine. In sharp contrast, the alternative strategy involving the thiomethylation of the Ni(II) complexes of alanine Schiff bases, is viable and practically attractive approach affording the desired α-(methyl)cysteine containing derivatives. This work also reveals a significant, and rather unexpected, difference in the stereochemical performance of proline and 3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine derived chiral ligands, showing a clear superiority of the former in terms of chemical yields and diastereoselectivity of the α-(methyl)cysteine products formation.

Introduction

The design of peptides and peptidomimetic ligands with rationally controlled number of conformations holds a well-established pharmaceutical potential and currently is an exciting area of multidisciplinary research activity.[1] In particular, installation of tailor-made[2] sterically constrained α-amino acids into key positions of peptide chains bring about noticeable conformational restrictions of the corresponding ϕ, ψ and χ angles in the folded three-dimensional structure.[3] In this regard, synthesis and applications of α,α-disubstituted amino acids have received truly tremendous consideration.[4] Among them, α-(methyl)cysteine is a quite rare, naturally occurring example of quaternary amino acids isolated from blue-green algae.[5] Specifically, several natural products, containing α-(methyl)cysteine fragment, such as mirabzoles,[6] tantazoles[7] and thiangazoles[8] were found to possess promising antitumor and anti-HIV-1 activities, providing considerable impetus for the development of asymmetric synthesis and in-depth biological study of α-(methyl)cysteine and its derivatives.

The most successful strategy for preparation of α-(methyl)cysteine **1** (Scheme 1) in enantiomerically enriched form is based on the ring opening of aziridine **2**[9] or β-lactone **3**[10] with appropriate thiolate nucleophiles. While the reactions occur with rather good yield and stereocontrol, the disadvantage of this approach is lengthy multistep synthesis of starting cyclic derivatives **2** and **3**. An alternative synthesis of α-(methyl)cysteine **1** was performed by chlorination of (*S*)-α-(methyl)serine followed by thaizoline formation and hydrolysis under acidic conditions. However, the yield of chlorination was not satisfactory, although enantioselective aldol reaction of alanine with formaldehyde using enzyme afforded (*S*)-α-(methyl)serine in very high yield.[10c]



Scheme 1. Literature methods for asymmetric synthesis of α-(methyl)cysteine **1**.

Interestingly, the more straightforward approach to α-(methyl)cysteine **1** via quaternization of the amino acid **1** precursors, turned out to be not so successful. Thus, some well-known general method, such as asymmetric alkylation of Seebach chiral thiazolidines[11] did not give the target product, highlighting a synthetic challenge associated with the liable nature of a sulfhydryl group.[12] Further research in this area resulted in the preparation of α-(methyl)cysteine **1** via α-methylation of the chiral cysteine derivatives **4**[13] and **5**[14] as well as by thiomethylation of alanine derived precursor **6**.[15] One of the features these methods have in common, is the necessity to use low temperature (-78 °C) and very strong bases (*n*-BuLi) to generate the corresponding enolates. However, these highly nucleophilic conditions are not fully

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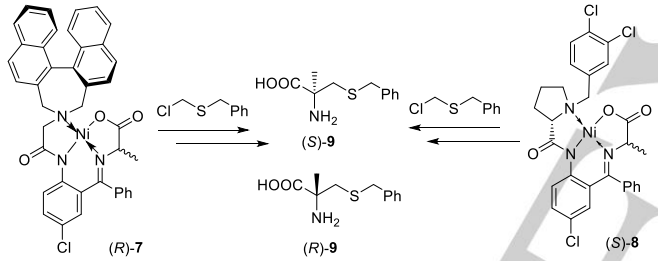
compatible with the labile nature of a sulfhydryl group and afforded the target alkylation products in rather moderate (~50%) chemical yields. Among other literature approaches reported for preparation of α-(methyl)cysteine **1**, is the resolution of the corresponding racemic derivatives using bio-catalysis[16] and HPLC on chiral stationary phases.[17]

One may agree that the current state of the methodology available for preparation of α-(methyl)cysteine **1** in enantiomerically pure form evidently calls for the development of more practical solutions to access the pharmaceutical potential of amino acid **1** and its derivatives.

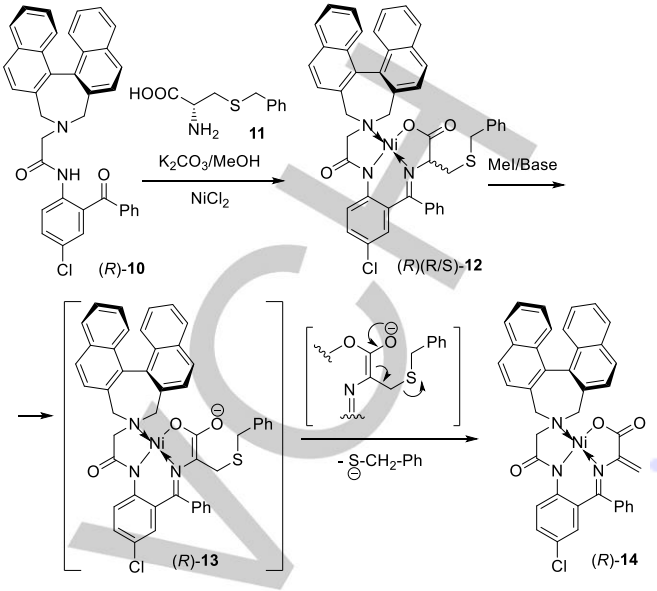
Considering our continuous interest in the development of new approaches for synthesis of various tailor-made amino acids[18] and, in particular, conformationally constrained derivatives[19] we decided to explore the application of chemistry of Ni(II) complexes of chiral glycine and alanine Schiff bases **7a**,**b** (Scheme 2)[20,21] for preparation of amino acid **1**. Here we report that thiomethylation of alanine Schiff base derived Ni(II)-complexes can be conducted under rather mild conditions and with synthetically sounding chemical yields and diastereoselectivity. The developed method can be readily scaled up, offering a convenient excess to enantiomerically pure (*S*)- and (*R*)-α-(methyl)cysteine **1** and its derivatives.



Scheme 2. This work: asymmetric synthesis of (*S*)- and (*R*)-α-(methyl)cysteine derivative **9** in enantiomerically pure form via homologation of chiral Ni(II) complexes (*R*)-**7** and (*S*)-**8**.

Results and Discussion

Recently, we introduced new axially chiral ligands **10** (Scheme 3) and reported some preliminary results on their application for asymmetric preparation of α-amino acids via deracemization, (*R*)-to-(*S*) interconversion of unprotected amino acids, and alkylation of the corresponding glycine Ni(II)-complex derivatives.[22] Ligands **10** have an advanced practical potential, as due to the presence of axial chirality, these compounds are non-racemizable and can be recycled virtually indefinitely. Consequently, we were excited to explore their application for preparation of the target α-(methyl)cysteine derivatives.



Scheme 3. Reaction of chiral ligand (*R*)-**10** with *S*-benzyl-L-cysteine **11** to afford diastereomeric Ni(II)-complexes **12** and attempts of the methylation.

As shown in Scheme 3, ligand (*R*)-**10** was reacted in methanol (45 °C) with *S*-benzyl-L-cysteine **11** (2 eq.), in the presence of $NiCl_2$ (2 eq.) and K_2CO_3 (6 eq.)[23] to form in situ the corresponding Schiff base, followed by the coordination by Ni(II), to afford final products (*R*)(*R*/*S*)-**12**. The reaction was accompanied by the formation of some byproducts and compounds **12** were isolated with 55% yield as a mixture of two diastereomers in about 94/6 ratio. Since the next alkylation step proceeds via the formation of enolate **13**,[24] the diastereomers were not separated and mixture (*R*)(*R*/*S*)-**12** was directly used to study the methylation reaction. After short screening of the reaction conditions, it became evident that the treatment of (*R*)(*R*/*S*)-**12** with a strong base results in a relatively clean formation of dehydroalanine complex (*R*)-**14**. ^{1}H-NMR spectrum of compound (*R*)-**14** has characteristic signals of the CH_2=C protons at 4.15 and 5.65 ppm and its formation can be explained by the preferential stabilization of enolate **13** via elimination of the corresponding benzylthiolate.[25] Using NaH as a base, dehydroalanine complex (*R*)-**14** was prepared with excellent 90% yield. While these results were negative in terms of preparation of the target α-(methyl)cysteine, the discovery of rather unstable nature of cysteine containing complexes **12** has certain methodological significance for practical synthesis of dehydroalanine complex (*R*)-**14**. Thus, by analogy with other types of dehydroalanine Schiff base Ni(II)-complexes,[25, 26] compound (*R*)-**14** can be of exciting synthetic potential as a reagent for general asymmetric synthesis of α-amino acids via nucleophilic additions to the electrophilic C=CH_2 moiety.

With these results in hand, we decided to change our strategy for the methylation of cysteine derived complexes to the thiomethylation of the corresponding alanine derivatives. This new approach is presented in Scheme 4.

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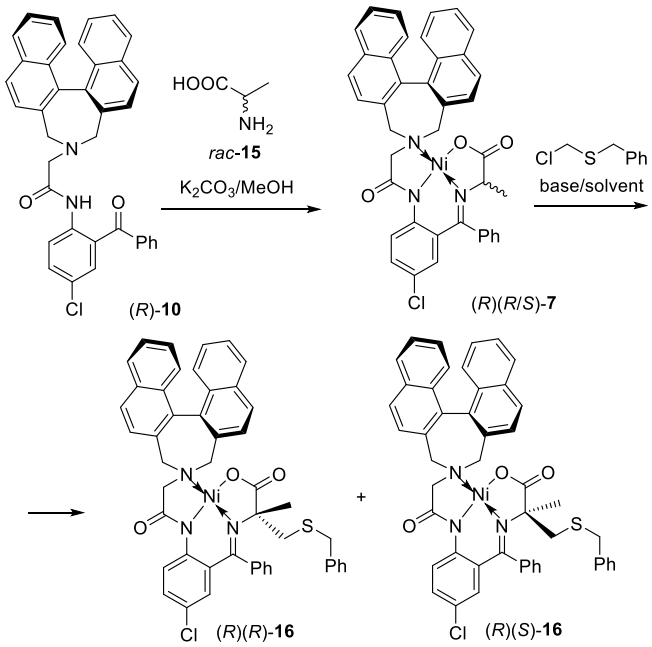
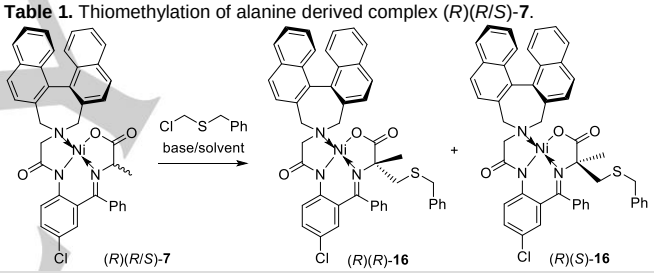


Scheme 4. Reaction of chiral ligand (*R*)-**10** with racemic alanine **15** to afford diastereomeric Ni(II)-complexes **7** and its benzylthiomethylation giving rise to (*R*)(*R*)- and (*R*)(*S*)-**16**.

The required for this approach, alanine derived complex (*R*)(*R*/*S*)-**7** was prepared by the reaction of ligand (*R*)-**10** with racemic alanine **15** in the presence of base (K_2CO_3) and Ni(II) ions.[22] In this case the reaction proceeded with excellent (>95%) yield furnishing a mixture of diastereomers with a significant (>90/10) excess of the corresponding α-(*S*) stereoisomer.[22] Alanine containing complex (*R*)(*R*/*S*)-**7** is a very stable compound allowing to study its thiomethylation under various reaction conditions. Some key representative results[27] are summarized in Table 1.

As one can see form the data presented in Table 1, application of NaH as a base and THF as a solvent (entry 1), was quite successful for preparation of the desired thiomethylation products (*R*)(*R*)-**16** and (*R*)(*S*)-**16**. Under these conditions, the optimal results were obtained at about 76% conversion of the starting alanine complex **7**. The reaction was relatively sluggish and accompanied by formation of byproducts[28], noticeably increasing at the higher conversion rates. Diastereomers (*R*)(*R*)-**16** and (*R*)(*S*)-**16** were obtained in a ratio of 84.3/15.7 and separated by column chromatography. Analytically pure samples of (*R*)(*R*)-**16** and (*R*)(*S*)-**16** were isolated with 31% and 7% yield, respectively. Though under these conditions we were able to prepare the target products, moderate stereochemical outcome prompted us to consider the alternative conditions, such as usually used for synthesis of quaternary amino acids via Ni(II)-complexes chemistry.[29] Thus, application of NaOH in DMF, resulted in a faster reaction rate (entry 2), but the target benzylthiomethylation also proceeded with noticeable amount of byproducts formation, forcing us to stop the process at about 43% of the starting alanine complex **7** consumption. Assuming that the byproducts might originate from, unstable under these conditions, *S*-(benzyl)thiomethyl chloride, we conducted the reaction in presence of KI to provide for the in situ Cl/I exchange. This idea turned out to be fruitful, allowing to reach at least 63% conversion of the starting complex **7** with minimum contamination of the reaction mixture with the unwanted byproducts (entry 3). Importantly, under these modified conditions, the diastereoselectivity of the thiomethylation was improved to 89.3/10.7 (entry 3 vs. 2). Chromatographic purification of the resultant mixture afforded diastereomerically pure (*R*)(*R*)-**16** and (*R*)(*S*)-**16** with 49% and 7%, respectively. Numerous attempts to use other bases/solvents gave mostly subpar to NaOH/DMF results. For example, application of KO-*t*-Bu as a base in DMF resulted in higher reaction rates but gave the lower yield and diastereoselectivity (entry 4). Considering the results obtained, one may conclude that, while the application of axially chiral ligand **10**/alanine derived complex **7** allowed the preparation of desired products **16** containing α-(methyl)cysteine, the observed stereochemical outcome leaves a room for improvement.

Table 1. Thiomethylation of alanine derived complex (*R*)(*R*/*S*)-**7**.



	Base (eq.)	Solv (v/w)	RX [a] (eq.)	Temp (°C)	Time (h)	Conversion Yield (%)	dr [b]
1	NaH (3)	THF (20)	3.0	r.t.	4.5	76 [d]	84.3:15.7
2	NaOH (5)	DMF (3)	2.5	0	1	43	86.7:13.3
3	KONa (5)	DMF (3)	2.5 [c]	0	1	63 [e]	89.3:10.7
4	KO*t*Bu (3)	THF (5)	2.5 [c]	r.t.	0.3	33	84.0:16.0

[a] RX = Cl-CH_2-S-CH_2Ph. [b] Determined on the crude reaction mixtures by HPLC analysis. [c] KI (2.75 eq.) was added to the reaction mixtures. [d] Diastereomerically pure to (*R*)(*R*)-**16** (31%) and (*R*)(*S*)-**16** (7%) were obtained by column chromatography. [e] Diastereomerically pure to (*R*)(*R*)-**16** (49%) and (*R*)(*S*)-**16** (7%) were obtained by column chromatography.

Over the past decade, our group has introduced various new types of chiral ligands useful for general asymmetric synthesis of α-amino acids via Ni(II) chemistry.[30] In particular,

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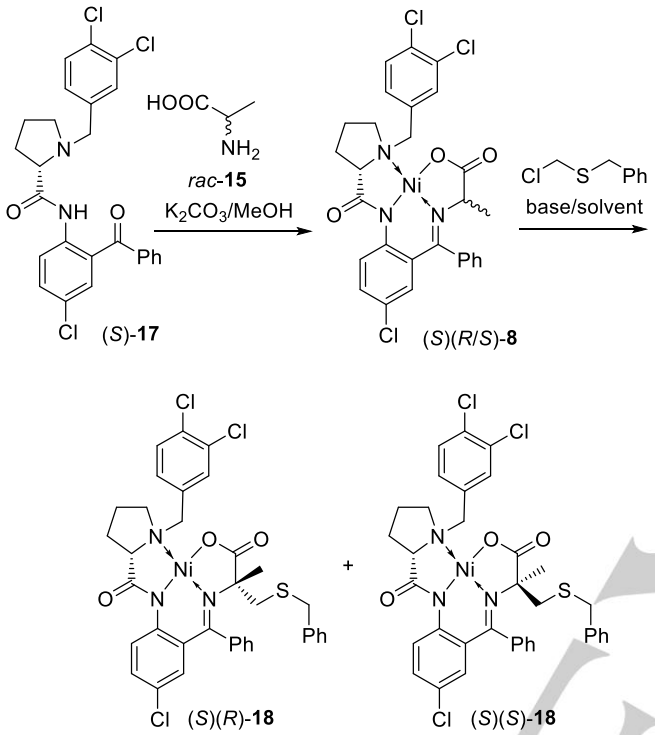
proline derived ligands **17** (Scheme 5) showed excellent levels of stereocontrol in the deracemization and (*R*)-to-(*S*) interconversion of unprotected α- and β-amino acids. However, the application of ligands **17** for preparation of quaternary α-amino acids still remains unexplored.

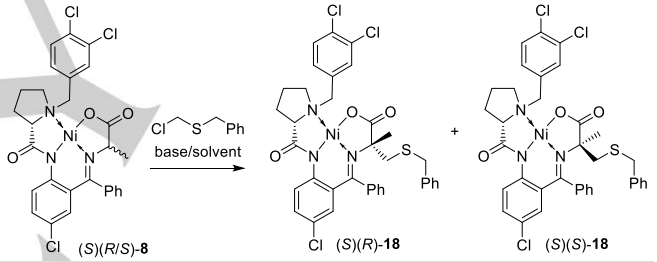


Scheme 5. Reaction of chiral ligand (*S*)-**17** with racemic alanine **15** to afford diastereomeric Ni(II)-complexes **8** and its benzylthiomethylation giving rise to (*S*)(*R*)- and (*S*)(*S*)-**18**.

Synthesis of alanine derived complex (*S*)(*R*/*S*)-**8** was performed according to previously described procedure, by the in situ formation of the corresponding Schiff base between of ligand (*S*)-**17** with racemic alanine **15**, followed by the complexation with Ni(II) ions in the presence of base (K_2CO_3).[31a,b] The reaction occurred with excellent (>95%) chemical yield giving rise to diastereomeric mixture **8**, noticeably enriched (~99/1) in the corresponding α-(*S*) product.[22] Thiomethylation of alanine complex (*S*)(*R*/*S*)-**8** was investigated under various conditions; most important and successful results[32] are listed in Table 2.

Thiomethylation of alanine complex (*S*)(*R*/*S*)-**8**, conducted in DMF using NaOH as a base, was rather successful. Thus, products (*S*)(*R*)-**18** and (*S*)(*S*)-**18** were isolated with 58% yield (entry 1) by passing the reaction mixture through short silica gel column to cut off the remaining starting **8** as well as byproducts. Noticeably, the diastereomeric ratio was about 90/10, with the preference for (*S*)(*R*) configured **18**. Increasing the amount of NaOH and reaction temperature, resulted in a faster rate of the thiomethylation and markedly improved chemical yield (entry 2), up to 77%. On the other hand, the diastereomeric ratio of (*S*)(*R*)-**18** and (*S*)(*S*)-**18** was slightly decreased to about 89/11. Further attempts to improve this outcome by dilution of the reaction mixture, to provide for better mixing, did not give the desired results (entry 3). Changing the solvent from DMF to THF resulted in a significant decrease of the reaction rate and reduced chemical yield (entry 4 and 5). Application of stronger bases, for example KOH (entry 6) caused an increase in the byproducts formation and lower yields of products (*S*)(*R*)-**18** and (*S*)(*S*)-**18**. Thus, the results presented in entry 2 were considered as optimal providing the diastereomers (*S*)(*R*)-**18** and (*S*)(*S*)-**18** with respected stereochemical outcome. Our next goal was to find a simple method for diastereomeric purification of the major product (*S*)(*R*)-**18**. Taking advantage of high crystallinity of the compounds under study, we meticulously performed a series of crystallization experiments.[33] Eventually, we found that the solvent systems consisting of CH_2Cl_2/di-isopropyl ether (1/1) and CH_2Cl_2/AcOEt (1/4) allowed for expedient purification of (*S*)(*R*)-**18** via recrystallization to at least 98.9:1.1 diastereomeric purity.

Table 2. Thiomethylation of alanine derived complex (*S*)(*R*/*S*)-**8**.



	Base (eq.)	Solv (v/w)	RX [a] (eq.)	Temp (°C)	Time (h)	Yield (%) [b]	dr [c]
1	NaOH (5)	DMF (2.5)	2.5	0-5	1.5	58	90.4:9.6
2	NaOH (10)	DMF (2)	4	15-17	0.75	77	88.9:11.1
3	NaOH (10)	DMF (4)	4	15-17	0.5	56	89.2:10.8
4	NaOH (5)	THF (5)	2.5	15-17	12	43	85.5:14.5
5	NaOH (5)	THF (20)	2.5	20-25	17	53	86.4:13.6
6	KOH (5)	DMF (2.5)	2.5	15-17	1	36	89.1:10.9

[a] RX = Cl-CH_2-S-CH_2Ph. [b] Isolated yield of both diastereomers [c] Determined on the crude reaction mixtures by HPLC analysis.

Being satisfied with these results, we next proceeded to the final objective of this study, isolation of α-(methyl)cysteine **9** and its *N*-Boc derivative **19** (Scheme 6). To this aim, we studied

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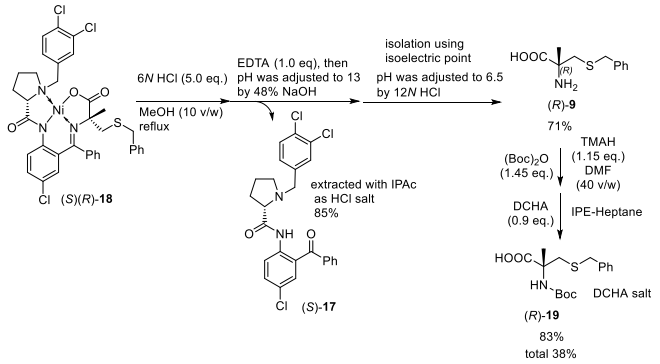
the disassembly of major diastereomer (*S*)(*R*)-**18**, as presented in Scheme 6.



Scheme 6. Disassembly of major diastereomer (*S*)(*R*)-**18**, recovery of chiral ligand **17** and isolation of α-(methyl)cysteine **9** and its *N*-Boc derivative **19**.

Disassembly of complex (*S*)(*R*)-**18** was conducted under standard acidic conditions[34] by treatment of MeOH solution of **18** with 6*N* HCl. After disappearance of the distinct red color of the Ni(II) complex, EDTA was added, followed by the treatment with NaOH to bring the pH to about 13. The chiral ligand was recycled by the extraction with isopropyl acetate, affording (*S*)-**17** with 85% yield. The remaining aqueous phase was treated with HCl to bring the pH to about 6.5. Free amino acid (*R*)-**9** was isolated by precipitation at the isoelectric point with 71% yield. Finally, *N*-Boc derivative DCHA (dicyclohexlyamine) salt was prepared with 83% yield using literature procedure using (Boc)2O in the presence of tetramethylammonium hydroxide (TMAN).[35] Accordig to the extensive data on Ni(II) complexes disassemblely, the acidic reaction conditions do not compromize the diastereo- and/or enantiomeric purity of the isolated amino acids.[21] Therefore, one may assume that the enantiomeric composition of products **9** and **19** is the same as that of the starting diastereomer **18** (98.9:1.1 ~ 97.8% ee).

Conclusions

In this work we examined two different methodological approaches, as well as application of two different types of Ni(II) complexes, to access the target structure of α-(methyl)cysteine derivatives. The data obtained clearly demonstrate that the methylation of cysteine derived Ni(II) complexes cannot be realized due to the inherent instability of the enolate intermediates, leading to the formation of the corresponding dehydroalanine containing products. On the other hand, the thiomethylation of the corresponding Ni(II) complexes of alanine Schiff bases, was found to work well affording the target α-(methyl)cysteine containing derivatives. We also demonstrate that new type of proline derived chiral ligands and the corresponding Ni(II) complexes show clearly superior stereochemical outcome of the thiomethylation procedure allowing for reliable preparation of free as well as *N*-Boc protected *N*-benzyl-α-(methyl)cysteine.

Experimental Section

General methods

All reagents and solvents were used as received. Reactions were magnetically stirred and monitored by thin layer chromatography on Merck silica gel 60-F_{254} coated 0.25 mm plates, detected by UV and ninhydrin. Flash chromatography was performed with the indicated solvents on silica gel (particle size 0.064-0.210 mm). Yields reported are for isolated, spectroscopically pure compounds. HPLC was performed on a SHIMADZU LC-2010CHT chromatograph with a CLASS-VP™ analysis data system using the Inertsil™ ODS-3 column (particle size 3 µm, 150 x 4.6 mm i.d.) operated at 1.0 mL/min, 30 ºC and monitored at wavelength of 254 nm with a linear gradient of 10 mM aqueous ammonium formate containing 0.1% formic acid (eluent A) and acetonitrile (eluent B) from A: B = 40:60 to 20:80 (0 to 25 min) and 20:80 (25 min to 45 min), unless otherwise stated. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian GEMINI 200 spectrometer. Chemical shifts are given in ppm (δ), referenced to tetramethylsilane (TMS) for ^{1}H-NMR and the ^{13}C-resonances of $CDCl_3$ (δ = 77.0 ppm) or DMSO-d_6 (δ = 39.5 ppm) for ^{13}C-NMR as internal standards. The letters s, d, t, q, m, and br stand for singlet, doublet, triplet, quartet, multiplet, and broad, respectively. High-resolution mass spectra (HRMS) were recorded with a Waters Synapt G2 HDMS in the ESI mode. Optical rotations were recorded on a DIP-370 polarimeter (Jasco Inc.). Melting points were recorded on a Mettler Toledo MP70 Melting Point System and are not corrected. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. All physicochemical data reported for the Ni(II) complexes are due to the single diastereomers after purification by chromatography or crystallization.

The absolute configuration of complexes **16** and **18** was determined based on their chiroptical properties as described in detail in previous publications.[21,22]

General procedure of the synthesis for Ni(II) complex

Nickel(II)-(*S*)-*N*-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)pyrrolidine-2-Carboxamide/(*S*)-2-aminopropanoic acid Schiff Base Complex 8 : To a solution of (*S*)-**17** (20.0 g, 38.15 mmol) in methanol (400 mL) were added nickel(II) chloride (5.44 g, 83.93 mmol), L-alanine (3.74 g, 83.93 mmol) and potassium carbonate (21.1 g, 305.20 mmol) successively. The resulting mixture was refluxed for 17 h, and then was quenched by pouring icy 5% aqueous acetic acid (800 mL) to give a precipitate. The precipitate was filtrated, washed with water and dried in vacuo at 45 °C overnight to afford the crude Ni(II) complex (22.2 g, 95%, a red crystal) as a mixture of (*S*)(*S*)-**8** and (*S*)(*R*)-**8**, whose diastereomeric ratio was determined to be 98.9:1.1 (97.8% *de*) by HPLC analysis in which the major (*S*)(*S*)-**8** was eluted at a reaction time (t_R) of 8.0 min

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while the minor (*S*)(*R*)-**8** at 10.4 min under the conditions described in General methods.
mp 260.2 ºC (dec.) (MeOH). $[\alpha]_D^{25}$ = +3035 (*c* = 0.100, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.58 (d, *J* = 7.0 Hz, 3H, Me), 2.00-2.14 (m, 1H, pyrrolidine part for Pro CH_2), 2.21-2.34 (m, 1H, pyrrolidine part for Pro CH_2), 2.54-2.72 (m, 2H, pyrrolidine part for Pro CH_2), 3.23 (d, *J* = 12.8 Hz, 1H, one of the benzyl CH_2N), 3.39 (dd, *J* = 5.9, 11.0 Hz, 1H, pyrrolidine part for Pro CH_2), 3.53-3.77 (m, 2H, α-H of Pro part and pyrrolidine part for Pro CH_2), 3.90 (q, *J* = 7.0 Hz, 1H, α-H of Ala part), 4.32 (d, *J* = 12.8 Hz, 1H, one of the benzyl CH_2N), 6.58 (d, *J* = 3.0 Hz, 1H, ArH), 6.90 (d, *J* = 6.7 Hz, 1H, ArH), 7.11 (dd, *J* = 2.6, 9.2 Hz, 1H, ArH), 7.25-7.30 (m, 1H, ArH), 7.38 (d, *J* = 8.1 Hz, 1H, ArH), 7.43-7.60 (m, 3H, ArH), 7.81 (dd, *J* = 2.2, 8.1 Hz, 1H, ArH), 8.03 (d, *J* = 9.2 Hz, 1H, ArH), 8.85 (d, *J* = 1.8 Hz, 1H, ArH). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 21.8 (Me of Ala part), 24.1 (pyrrolidine part for Pro CH_2), 30.8 (pyrrolidine part for Pro CH_2), 58.4 (pyrrolidine part for Pro CH_2), 62.8 (CH_2 of benzyl), 66.8 (α-H of Ala part), 71.2 (α-H of Pro part), 124.3 (ArC), 125.7 (ArC), 127.2 (ArC), 127.4 (ArC), 129.2 (ArC), 129.3 (ArC), 130.0 (ArC), 130.1 (ArC), 131.0 (ArC), 132.0 (ArC), 132.2 (ArC), 132.5 (ArC), 133.3 (ArC), 133.51 (ArC), 133.53 (ArC), 134.8 (ArC), 140.3 (ArC), 169.8, 179.9, 180.0 (CN and 2 x CO). IR (KBr) 1254, 1466, 1625, 1688, 2859, 2978, 3446 cm^{-1}. MS (ESI) *m/z* found 614 $[M + H]^+$, 636 $[M + Na]^+$. HRMS calcd for $C_{28}H_{25}Cl_3N_3NiO_3$ $[M + H]^+$: 614.0315, found 614.0310, calcd for $C_{28}H_{24}Cl_3N_3NaNiO_3$ $[M + Na]^+$: 636.0134, found 636.0133.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-2-[3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepin-4-yl]acetamide/(*RS*)-2-aminopropanoic acid Schiff Base Complex 7 : By using (*R*)-**10** (200 mg, 0.35 mmol), nickel(II) acetate tetrahydrate (176 mg, 0.71 mmol), DL-alanine (63 mg, 0.71 mmol) and potassium carbonate (293 mg, 2.12 mmol) according to General Procedure, the Ni(II) complex (208 mg, 85%, a red crystal) as a mixture of (*R*)(*S*)-**7** and (*R*)(*R*)-**7**, whose diastereomeric ratio was determined to be 99.99:nd (>99.99% *de*) by HPLC analysis in which the major (*R*)(*S*)-**7** was eluted at a retention time (t_R) of 21.3 min while the minor (*R*)(*R*)-**7** at 22.2 min under the conditions described in General methods.
mp 227.3 ºC (dec.) (acetone). $[\alpha]_D^{25}$ = +2356 (*c* = 0.100, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$, the data reported below for the corresponding (*R*)(*S*)-**7**): δ 1.51 (d, *J* = 7.1 Hz, 3H, Me), 2.71 (d, *J* = 12.1 Hz, 1H, one of azepine CH_2N), 3.08 (d, *J* = 15.6 Hz, 1H, one of azepine CH_2N), 3.68 and 3.76 (ABq, *J* = 13.9 Hz, 1H each, acetanilide $NCOCH_2$), 3.81 (q, *J* = 7.0 Hz, 1H, α-H of Ala part), 4.56 (d, *J* = 15.7 Hz, 1H, one of azepine CH_2N), 4.84 (d, *J* = 12.1 Hz, 1H, one of azepine CH_2N), 6.64 (d, *J* = 2.5 Hz, 1H, ArH), 6.94 (*br*d, *J* = 6.0 Hz, 1H, ArH), 6.96-7.30 (m, 4H, ArH), 7.36-7.56 (m, 8H, ArH), 7.95-8.02 (m, 3H, ArH), 8.16 (d, *J* = 8.3 Hz, 1H, ArH), 8.43 (d, *J* = 9.1 Hz, 1H, ArH), 8.78 (d, *J* = 8.3 Hz, 1H, ArH). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 21.4 (Me of Ala part), 58.7 ($NCOCH_2$), 61.9 (CH_2 of azepine), 66.3 (CH_2 of azepine), 66.8 (α-CH of Ala part), 125.1 (ArC), 126.1 (ArC), 126.37 (ArC), 126.41 (ArC), 126.5 (ArC), 126.9 (ArC), 127.3 (ArC), 127.4 (ArC), 127.5 (ArC), 127.6 (ArC), 127.8 (ArC), 128.1 (ArC), 128.4 (ArC), 128.6 (ArC), 128.7 (ArC), 129.15 (ArC), 129.17 (ArC), 129.2 (ArC), 129.4 (ArC), 130.2 (ArC), 131.0 (ArC), 131.2 (ArC), 131.5 (ArC), 132.4 (ArC), 132.6 (ArC), 132.66 (ArC), 132.68 (ArC), 134.0 (ArC), 135.5 (ArC), 136.0 (ArC), 140.8 (ArC), 170.1, 174.6, 179.7 (CN and 2 x CO). IR (KBr) 1167, 1256, 1319, 1466, 1588, 1649, 1685, 2957, 3044, 3432 cm^{-1}. MS (ESI) *m/z* found 694 $[M + H]^+$, 716 $[M + Na]^+$. HRMS calcd for $C_{40}H_{31}ClN_3NiO_3$ $[M + H]^+$: 694.1407, found 694.1411, calcd for $C_{40}H_{30}ClN_3NaNiO_3$ $[M + Na]^+$: 716.1227, found 716.1239.

General procedure of the alkylation for Ni(II) complex

Alkylation of (*S*)(*S*)-8 with benzyl chloromethyl sulfide : To a suspension of the Ni(II) complex of alanine (*S*)(*S*)-**8** (500 mg, 0.81 mmol, 1.0 eq.) in DMF (2.5 mL, 5 v/w) were added sodium hydroxide (powdered, 162 mg, 4.06 mmol, 5.0 eq.) and benzyl chloromethyl sulfide (350 mg, 2.03 mmol, 2.5 eq.) at 0 °C under an argon atmosphere. The mixture was stirred for 1.5 h at 0 °C, and then was quenched by pouring icy 5% aqueous acetic acid (40 mL) to give a precipitate. The precipitate was filtrated and washed with water and heptane and dried in vacuo at rt. The crude alkylated Ni(II) complex was purified by recrystallization (CH_2Cl_2/IPE/heptane = 2/2/8 (v/w)) to afford (*S*)(*R*)-**18** major as a red orange solid (470 mg, 58%). Recrystallized (*S*)(*R*)-**18** diastereomeric ratio was determined to be 98.83:1.17 (97.66% *de*) by HPLC analysis in which the major (*S*)(*R*)-**18** was eluted at a reaction time (t_R) of 18.0 min while the minor (*S*)(*S*)-**18** at 18.6 min under the conditions described in General methods.
(*S*)(*R*)-**18** (major): mp 244.9 ºC (dec.) (CH_2Cl_2/IPE/heptane). $[\alpha]_D^{25}$ = +2004 (*c* = 0.102, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.23 (s, 3H, α-Me), 1.97-2.11 (m, 2H, pyrrolidine part for Pro CH_2), 2.46 (d, *J* = 12.8 Hz, 1H, CCH_2S), 2.77 (d, *J* = 12.8 Hz, 1H, CCH_2S), 2.43-2.81 (m, 2H, pyrrolidine part for Pro CH_2), 3.35 (d, *J* = 12.8 Hz, 1H, CH_2Ar), 3.82 and 3.93 (ABq, *J* = 13.6 Hz, each 1H, CCH_2Ph), 3.28-3.94 (m, 3H, pyrrolidine part for Pro CH_2 and α-H), 4.44 (d, *J* = 12.8 Hz, 1H, CH_2Ar), 6.54 (d, *J* = 2.6 Hz, 1H, ArH), 6.78 (d, *J* = 2.6 Hz, 1H, ArH), 7.04-7.12 (m, 2H, ArH), 7.22-7.53 (m, 8H, ArH), 7.72 (dd, *J* = 2.2, 8.1 Hz, 1H, ArH) 7.97 (d, *J* = 9.2 Hz, 1H, ArH), 8.90 (d, *J* = 2.2 Hz, 1H, ArH). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 23.0 (α-Me), 29.3 (pyrrolidine part for Pro CH_2), 30.7 (pyrrolidine part for Pro CH_2), 37.8 (CCH_2S), 40.7 (SCH_2Ph), 58.5 (pyrrolidine part for Pro CH_2), 63.3 (pro α-C), 71.4 (CH_2Ph), 77.2 (quaternaly α-C), 124.5 (ArC), 125.4 (ArC), 126.8 (ArC), 127.0 (ArC), 127.2 (ArC), 128.3 (ArC), 128.5 (ArC), 129.0 (ArC), 129.3 (ArC), 129.7 (ArC), 129.97 (ArC), 130.01 (ArC), 130.9 (ArC), 131.7 (ArC), 132.2 (ArC), 133.1 (ArC), 133.4 (ArC), 133.8 (ArC), 135.0 (ArC), 135.2 (ArC), 137.8 (ArC), 140.1 (ArC), 172.5, 180.1, 181.3 (CN and 2 x CO). IR (KBr) 1243, 1353, 1462, 1644, 1659, 3023, 3056, 3447 cm^{-1}. MS (ESI) *m/z* found 772 $[M + Na]^+$. HRMS calcd for $C_{36}H_{32}Cl_3N_3NaNiO_3S$ $[M + Na]^+$: 772.0481, found 772.0456.

(*S*)(*S*)-**18** (minor): mp 213.5ºC (dec.) (toluene/IPE); $[\alpha]_D^{25}$ = +2100 (*c* = 0.107, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.51 (s, 3H, α-Me), 2.00-2.21 (m, 2H, pyrrolidine part for Pro CH_2), 2.40 (d, *J* = 12.8 Hz, 1H, CCH_2S), 2.47-2.59 (m, 2H, pyrrolidine part for Pro CH_2), 2.80 (d, *J* = 12.8 Hz, 1H, CCH_2S), 3.27 (d, *J* = 12.5 Hz, 1H, CH_2Ar), 3.32-3.40 (m, 2H, pyrrolidine part for Pro CH_2),

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3.65-3.85 (m, 1H, pyrrolidine part for Pro CH_2), 3.70 and 3.82 (ABq, *J* = 13.2 Hz, each 1H, SCH_2Ph), 4.45 (d, *J* = 12.5 Hz, 1H, CH_2Ar), 6.55 (d, *J* = 2.7 Hz, 1H, ArH), 6.89 (d, *J* = 7.7 Hz, 1H, ArH), 7.08 (dd, *J* = 2.6, 9.2 Hz, 1H, ArH), 7.12-7.54 (m, 10H, ArH), 7.82 (d, *J* = 9.2 Hz, 1H, ArH), 8.43-8.47 (m, 2H, ArH). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 23.8 (CCH_2S), 27.0 (pyrrolidine part for Pro CH_2), 30.7 (pyrrolidine part for Pro CH_2), 37.8 (CCH_2S), 42.4 (SCH_2Ph), 58.8 (pyrrolidine part for Pro CH_2), 63.4 (pro α-C), 70.7 (CH_2Ph), 77.3 (quaternaly α-C), 124.7 (ArC), 125.5 (ArC), 127.1 (ArC), 127.7 (ArC), 128.2 (ArC), 128.3 (ArC), 128.5 (ArC), 129.0 (ArC), 129.4 (ArC), 129.9 (ArC), 131.0 (ArC), 131.1 (ArC), 131.6 (ArC), 132.1 (ArC), 133.0 (ArC), 133.4 (ArC), 133.5 (ArC), 134.89 (ArC), 134.90 (ArC), 138.1 (ArC), 139.6 (ArC), 172.8, 180.2, 181.8 (CN and 2 x CO). IR (KBr) 1246, 1348, 1461, 1641, 1667, 2972, 3443 cm^{-1}. MS (ESI) *m/z* found 750 $[M + H]^+$, 772 $[M + Na]^+$. HRMS calcd for $C_{36}H_{33}Cl_3N_3NiO_3S$ $[M + H]^+$: 750.0662, found 750.0661, calcd for $C_{36}H_{32}Cl_3N_3NaNiO_3S$ $[M + Na]^+$: 772.0481, found 772.0480.

Nickel(II)-(*R*)-*N*-(2-benzoyl-4-chlorophenyl)-2-[3,5-dihydro-4*H*-dinaphth[2,1-*c*:1',2'-*e*]azepin-4-yl]acetamide/*S*-benzyl-L-cysteine Schiff Base Complex 12 : By using (*R*)-**10** (5.00 g, 7.34 mmol), nickel(II) chloride (1.14 g, 8.81 mmol), *S*-benzyl-L-cysteine (1.86 g, 8.81 mmol) and potassium carbonate (5.07 g, 36.70 mmol) according to General Procedure, the Ni(II) complex (*R*)(*R*)-**12** (3.60 g, 60%, a brown crystal).
mp 202.4 °C (dec.) (IPE/toluene). $[\alpha]_D^{25}$ = +1766 (*c* = 0.103, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.38 (dd, *J* = 13.7, 4.6 Hz, 1H, CCH_2S), 2.63 (d, *J* = 12.1 Hz, 1H, one of azepine CH_2N), 2.84 (dd, *J* = 13.7, 2.5 Hz, 1H, CCH_2S), 3.01 (d, *J* = 15.2 Hz, 1H, one of azepine CH_2N), 3.70 (s, 2H, acetanilide $NCOCH_2$), 3.96 and 4.07 (ABq, *J* = 13.3 Hz, each 1H, SCH_2Ph), 4.03-4.10 (m, 1H, α-H of Cys part), 4.61 (d, *J* = 15.2 Hz, 1H, one of azepine CH_2N), 4.78 (d, *J* = 12.1 Hz, 1H, one of azepine CH_2N), 6.52 (d, *J* = 7.5 Hz, 1H, ArH), 6.56 (d, *J* = 2.5 Hz, 1H, ArH), 7.00 (d, *J* = 7.5 Hz, 1H, ArH), 7.15-7.54 (m, 17H, ArH), 7.97 (d, *J* = 8.5 Hz, 1H, ArH), 7.98 (d, *J* = 8.4 Hz, 1H, ArH), 8.16 (d, *J* = 8.3 Hz, 1H, ArH), 8.44 (d, *J* = 9.1 Hz, 1H, ArH), 8.88 (d, *J* = 8.3 Hz, 1H, ArH). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 34.8 (CH_2S), 37.8 (SCH_2Ph), 59.2 (CH_2-$NCOCH_2$), 61.5 (CH_2 of azepine), 66.9 (CH_2 of azepine), 69.8 (α-CH of Cys part), 125.26 (ArC), 125.28 (ArC), 126.0 (ArC), 126.35 (ArC), 126.44 (ArC), 126.8 (ArC), 127.2 (ArC), 127.38 (ArC), 127.45 (ArC), 127.46 (ArC), 127.9 (ArC), 128.2 (ArC), 128.4 (ArC), 128.5 (ArC), 128.6 (ArC), 128.8 (ArC), 129.00 (ArC), 129.02 (ArC), 129.18 (ArC), 129.22 (ArC), 129.4 (ArC), 130.2 (ArC), 131.1 (ArC), 131.2 (ArC), 131.5 (ArC), 132.3 (ArC), 132.4 (ArC), 132.7 (ArC), 133.7 (ArC), 134.0 (ArC), 135.4 (ArC), 136.0 (ArC), 137.3 (ArC), 141.4 (ArC), 170.0, 174.5, 176.8 (CN and 2 x CO). IR (KBr) 1249, 1319, 1462, 1648, 1677, 3056, 3452 cm^{-1}. MS (ESI) *m/z* found 816 $[M + H]^+$, 838 $[M + Na]^+$. HRMS calcd for $C_{47}H_{37}ClN_3NiO_3S$ $[M + H]^+$: 816.1598, found 816.1572, calcd for $C_{47}H_{36}ClN_3NaNiO_3S$ $[M + Na]^+$: 838.1417, found 838.1396.

Alkylation of (*R*)(*R*)-12 with methyl iodide: preparation of dehydroalanine 14 : To a suspension of the Ni(II) complex of *S*-benzyl-cysteine (*R*)(*R*)-**12** (50 mg, 0.06 mmol, 1.0 eq.) in THF (1.0 mL, 20 v/w) were added sodium hydride (60% dispersion in mineral oil, 7.2 mg, 0.18 mmol, 3.0 eq.) and methyl iodide (25.5 mg, 0.18 mmol, 3.0 eq.) at 0 °C under an argon atmosphere. The mixture was stirred for 30 min at rt, and then was quenched by pouring icy 5% aqueous acetic acid (40 mL) and extracted with ethyl acetate (15 mL). The solution was dried over Na_2SO_4 and evaporated to give a residue. The residue was purified by silica gel column chromatography (heptane/AcOEt = 5/1) to afford (*R*)-**14** as a dark-red solid (45 mg, quant.).
mp 287.3 °C (dec.) (IPE/heptane). $[\alpha]_D^{25}$ = +875 (*c* = 0.029, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.75 (d, *J* = 12.1 Hz, 1H, one of azepine CH_2N), 3.43 (d, *J* = 15.6 Hz, 1H, one of azepine CH_2N), 3.77 and 3.94 (ABq, *J* = 13.7 Hz, each 1H, acetanilide $NCOCH_2$), 4.20 (d, *J* = 15.6 Hz, 1H, one of azepine CH_2N), 4.64 (d, *J* = 12.1 Hz, 1H, one of azepine CH_2N), 5.65 (d, *J* = 1.2 Hz, 1H, $C=CH_2$), 6.93 (d, *J* = 2.5 Hz, 1H, $C=CH_2$), 7.02-7.21 (m, 2H, ArH), 7.26-7.35 (m, 3H, ArH), 7.43-7.56 (m, 8H, ArH), 7.94-8.02 (m, 3H, ArH), 8.11 (d, *J* = 8.4 Hz, 1H, ArH), 8.47 (d, *J* = 8.4 Hz, 1H, ArH), 8.55 (d, *J* = 9.2 Hz, 1H, ArH). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 58.3 (CH_2-$NCOCH_2$), 61.1 (CH_2 of azepine), 65.0 (CH_2 of azepine), 115.7 ($C=CH_2$), 124.8 ($C=CH_2$), 126.1 (ArC), 126.2 (ArC), 126.4 (ArC), 126.48 (ArC), 126.52 (ArC), 127.4 (ArC), 127.7 (ArC), 128.0 (ArC), 128.4 (ArC), 128.5 (ArC), 128.8 (ArC), 128.9 (ArC), 129.07 (ArC), 129.10 (ArC), 129.5 (ArC), 130.7 (ArC), 131.0 (ArC), 131.3 (ArC), 133.4 (ArC), 133.5 (ArC), 133.7 (ArC), 134.0 (ArC), 134.6 (ArC), 135.66 (ArC), 135.70 (ArC), 142.2 (ArC), 146.9 (ArC), 168.7, 169.8, 174.3 (CN and 2 x CO). IR (KBr) 1248, 1323, 1459, 1655, 1678, 2966, 3442 cm^{-1}. MS (ESI) *m/z* found 692 $[M + H]^+$, 714 $[M + Na]^+$. HRMS calcd for $C_{40}H_{29}ClN_3NiO_3$ $[M + H]^+$: 692.1251, found 692.1260, calcd for $C_{40}H_{28}ClN_3NaNiO_3$ $[M + Na]^+$: 714.1082, found 714.1070.

Alkylation of (*R*)(*S*)-7 with benzyl chloromethyl sulfide : To a suspension of the Ni(II) complex of alanine (*R*)(*S*)-**7** (100 mg, 0.14 mmol, 1.0 eq.) in THF (2 mL, 20 v/w) were added sodium hydride (60% dispersion in mineral oil, 17.3 mg, 0.43 mmol, 3.0 eq.) and benzyl chloromethyl sulfide (27.3 mg, 0.16 mmol, 1.1 eq.) at 0 °C under an argon atmosphere. The mixture was stirred for 0.5 h at rt, additional benzyl chloromethyl sulfide (27.3 mg, 0.16 mmol, 1.1 eq.) was added to the mixture at rt, and then stirred for 1.0 h. The mixture was quenched by pouring water (2 mL) and ethyl acetate (2 mL), then separated. The aqueous phase was extracted with ethyl acetate (2 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), then concentrated in vacuo to give a crude alkylated Ni(II) complex as a mixture of (*R*)(*R*)-**16** and (*R*)(*S*)-**16** in a ratio of 84:16, respectively. The crude Ni(II) complex was purified by silica gel column chromatography (CH_2Cl_2/acetone = 80/1 as a eluent) to afford (*R*)(*R*)-**16** major (190 mg, 31%, a red orange solid) as a former fraction and (*R*)(*S*)-**16** minor (42 mg, 7%, a red orange solid) as a later fraction.
The data of (*R*)(*R*)-**16** (major) were reported on patent (WO2014188783).
(*R*)(*S*)-**16** (minor): mp 190.7 °C (dec.) (toluene/heptane). $[\alpha]_D^{25}$ = +875 (*c* = 0.100, $CHCl_3$). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.13 (s, 3H, α-Me) 2.58 (d, *J* = 12.9 Hz, 1H, CCH_2S), 2.70 (d, *J* = 12.0 Hz, 1H, one of azepine CH_2N), 2.88 (d, *J* = 12.9 Hz, 1H,

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$CCCH_2S$), 3.61 and 3.73 (ABq, *J* = 15.6 Hz, each 1H, SCH_2Ph), 3.90 (d, *J* = 13.4Hz, 1H, one of azepine CH_2N) 3.90 and 4.03 (ABq, *J* = 13.4 Hz, each 1H, acetanilide $NCOCH_2$), 4.27 (d, *J* = 13.4 Hz, 1H, one of azepine CH_2N), 4.69 (d, *J* = 12.0 Hz, 1H, one of azepine CH_2N), 6.66 (d, *J* = 2.4 Hz, 1H, ArH), 6.90 (d, *J* = 7.7 Hz, 1H, ArH), 7.05-7.10 (m, 1H, ArH), 7.15-7.56 (m, 16H, ArH), 7.91 (d, *J* = 8.1 Hz, 1H, ArH), 7.98 (d, *J* = 8.1 Hz, 1H, ArH), 7.99 (d, *J* = 8.3 Hz, 1H, ArH), 8.44 (d, *J* = 8.4 Hz, 2H, ArH), 8.45 (d, *J* = 8.4 Hz, 1H, ArH). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 28.0 (α-Me), 37.9 (CH_2S), 42.2 (SCH_2Ph), 58.3 (CH_2-$NCOCH_2$), 60.7 (CH_2 of azepine), 63.4 (CH_2 of azepine), 76.9 (quaternaly α-C), 124.9 (ArC), 125.8 (ArC), 125.9 (ArC), 126.1 (ArC), 126.4 (ArC), 126.5 (ArC), 127.0 (ArC), 127.3 (ArC), 127.4 (ArC), 127.5 (ArC), 127.7 (ArC), 127.8 (ArC), 128.1 (ArC), 128.3 (ArC), 128.4 (ArC), 128.6 (ArC), 128.9 (ArC), 129.1 (ArC), 129.3 (ArC), 129.8 (ArC), 130.1 (ArC), 130.5 (ArC), 131.1 (ArC), 131.4 (ArC), 131.7 (ArC), 132.2 (ArC), 132.7 (ArC), 133.7 (ArC), 133.8 (ArC), 135.2 (ArC), 135.3 (ArC), 135.8 (ArC), 138.0 (ArC), 140.4 (ArC), 172.1, 174.3, 180.8 (CN and 2 x CO). IR (KBr) 1159, 1244, 1352, 1463, 1649, 1649, 1676, 2918, 3057, 3449 cm^{-1}. MS (ESI) *m/z* found 830 $[M + H]^+$, 852 $[M + Na]^+$. HRMS calcd for $C_{48}H_{39}ClN_3NiO_3S$ $[M + H]^+$: 830.1754, found 830.1752, calcd for $C_{48}H_{38}ClN_3NaNiO_3S$ $[M + Na]^+$: 852.1574, found 852.1573.

Preparation of *S*-benzyl-2-methyl-L-cysteine, (*R*)-9 : To a suspension of the Ni(II) complex (*S*)(*R*)-**18** (1.20 g, 1.60 mmol) in methanol (12 mL, 10 v/w) was added 6N HCl (1.33 mL, 7.98 mmol, 5eq.) and the whole was heated at 40 °C for 6 h. Upon disappearance of the red color of the stating complex, the reaction mixture was concentrated to dryness. To the residue were added ethylenediaminetetraacetic acid disodium salt dihydrate (594 mg, 1.60 mmol), isopropyl acetate (12 mL, 10 v/w) and water (12 mL, 10 v/w), and then basified to pH 12-13 using 12N aqueous sodium hydroxide solution, stirred and separated. The resulting organic phase was washed with water (12 mL, 10 v/w) and brine (12 mL, 10 v/w), dried (Na_2SO_4), and concentrated to afford the recovered ligand (910 mg, quant.). The combined aqueous phase was evaporated to 10 v/w. The aqueous phase was washed with isopropyl acetate (12 mL, 10 v/w). The water phase was neutralized to pH 7-6 to give a precipitate. The precipitate was filtrated and washed with water to afford *S*-benzyl-2-methyl-L-cysteine, (*R*)-**9** (257 mg, 71%).
mp 234.4 °C (dec.) (water). IR (KBr) 1108, 1232, 1270, 1367, 1453, 1583, 1619, 2987, 3450 cm^{-1}. MS (ESI) *m/z* found 226 $[M + H]^+$, 248 $[M + Na]^+$. HRMS calcd for $C_{11}H_{16}NO_2S$ $[M + H]^+$: 226.0902, found 226.0906, calcd for $C_{11}H_{15}NNaO_2S$ $[M + Na]^+$: 248.0721, found 248.0725.

NMR data for the HCl salt of *S*-benzyl-2-methyl-L-cysteine, (*R*)-**9**
^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.49 (s, 3H, α-Me), 2.94 and 3.02 (ABq, *J* = 14.3 Hz, each 1H, CCH_2S), 3.83 (s, 2H, SCH_2Ph), 7.21-7.38 (m, 5H, ArH), 8.65 (brs, 3H, NH_3^+). ^{13}C-NMR (50.3 MHz, DMSO-d_6): δ 21.8 (α-Me), 36.5 (CCH_2S), 37.4 (SCH_2Ph), 59.5 (quaternaly α-C), 127.1 (ArC), 128.4 (ArC), 128.9 (ArC), 138.0 (ArC), 171.7 (CO_2H).

Preparation of *S*-benzyl-*N*-(*tert*-butoxycarbonyl)-2-methyl-L-cysteine DCHA salt, (*R*)-19 : To a suspension of the (*R*)-**9** (250 mg, 1.11 mmol) in DMF (10 mL, 40 v/w) was added tetramethylammonium hydroxide (211 mg, 1.17 mmol), di-*tert*-butyl dicarbonate ($(Boc)_2O$, 303 mg, 1.39 mmol) and the mixture was stirred for 8 h. The reaction mixture was quenched by 1M aqueous citric acid solution to pH 3-4. Resulting mixture was extracted with ethyl acetate (5 mL, 3 times). The combined organic phase was washed with water (10 mL, 3 times), dried (Na_2SO_4) and concentrated to give yellow oil (161 mg) which was dissolved in isopropyl ether (5 mL) and heptane (5 mL). To this solution was added dicyclohexylamine (DCHA, 97 mg, 1.01 mmol) and the whole was stirred at rt for 1.0 h. The crystalline solid thus formed was collected by filtration and dried in vacuo at 50 ºC to afford *S*-benzyl-*N*-(*tert*-butoxycarbonyl)-2-methyl-L-cysteine DCHA salt ((*R*)-**19**, 462 mg, 83%) as a white crystal.
mp 170.1 °C (IPE/heptane). $[\alpha]_D^{25}$ = –13.56 (*c* = 0.100, $CHCl_3$). ^{1}H-NMR (200 MHz, DMSO-d_6): δ 1.14-1.32 (m, 10H), 1.29 (s, 3H α-Me), 1.37 (s, 9H, *t*-Bu), 1.47-1.72 (m, 6H, cyclohexyl), 1.90-2.19 (m, 4H, cyclohexyl), 2.88 (d, *J* = 13.1 Hz, 1H, CCH_2S), 3.10 (d, *J* = 13.1 Hz, 1H, CCH_2S), 2.85-3.13 (m, 2H, $(CH)_2N$), 3.59 and 3.69 (ABq, *J* = 13.0 Hz, each 1H, SCH_2Ph), 6.66 (s, 1H, NH), 7.18-7.38 (m, 5H, ArH), 8.93 (brs, 1H, $(CH)_2NH_2^+$). ^{13}C-NMR (50.3 MHz, $CDCl_3$): δ 23.9 (α-Me), 24.1 (cyclohexyl C), 24.9 (cyclohexyl C), 28.3 (cyclohexyl C), 29.2 (cyclohexyl C), 35.8 (CCH_2S), 37.5 (SCH_2Ph), 51.8 ($(CH)_2NH$), 59.0 (quaternaly α-C), 77.1 ($OCMe_3$), 126.5 (ArC), 128.1 (ArC), 128.7 (ArC), 139.6 (ArC), 153.5 ($NHCO_2$), 174.4 (CO_2H). IR (KBr) 1055, 1163 1351, 1384, 1572, 1713, 2361, 2857, 2935, 3421 cm^{-1}. MS (ESI) *m/z* found 348 $[M + Na]^+$. HRMS calcd for $C_{16}H_{23}NNaO_4S$ $[M + Na]^+$: 348.1245, found 348.1242.

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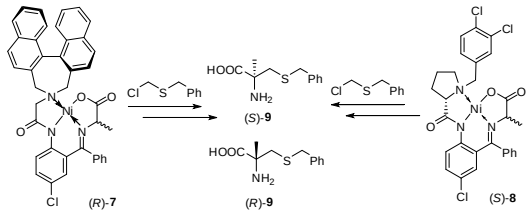

We demonstrate that the thiomethylation of the Ni(II) complexes of alanine Schiff bases, is viable and practically attractive approach affording the target α-(methyl)-cysteine containing derivatives.

Key Topic* Asymmetric synthesis

Junya Yamamoto, Aki Kawashima, Akie Kawamura, Hidenori Abe, Hiroki Moriwaki, Norio Shibata, and Vadim A. Soloshonok**

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Operationally Convenient and Scalable Asymmetric synthesis of (2*S*)- and (2*R*)-α-(Methyl)cysteine Derivatives via Alkylation of Chiral Alanine Schiff Base Ni(II) Complexes

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