

Asymmetric Synthesis of 4,4-(Difluoro)glutamic Acid via Chiral Ni(II)-Complexes of Dehydroalanine Schiff Bases. Effect of the Chiral Ligands Structure on the Stereochemical Outcome

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Four differently substituted chiral Ni(II)-complexes of dehydroalanine Schiff base were prepared and reacted with BrCF₂COOEt/Cu under the standard reaction conditions. The observed diastereoselectivity was found to depend on the degree and pattern of chlorine substitution for hydrogen in the structure of the dehydroalanine complexes. The unsubstituted complex gave the ratio of diastereomers (S)(2S)/(S)(2R) of 66/34. On the

other hand, introduction of chlorine atoms in the strategic positions on the chiral ligands allowed to achieve a practically attractive diastereoselectivity of (~98.5/1.5). Diastereomerically pure major product was disassembled to prepare 9-fluorenylmethoxycarbonyl (Fmoc) derivative of (S)-4,4-difluoroglutamic acid.

Though pharmaceutical molecules span a wide range of structures, two major common traits emerge upon analysis. One of them is ever increasing number of medicinal compounds containing fluorine.^[1] In fact, fluorine editing or fluorine scan is currently a well-established platform in new drug development^[2] allowing for high degree of rational control over physicochemical and biological properties.^[3] The second trend is biological application of tailor-made amino acids (AAs)^[4] as structural scaffolds to mimic 3D structure of targeted receptors.^[5] The growing acceptance of peptides and modified

peptides as drugs,^[6] indicates that the role of tailor-made AAs in the drug design will continue to grow. In line with these key structural features, fluorine-containing amino acids are in high demand in nearly every sector of medicinal chemistry and drug design.^[7] Chemistry of fluoro-AAs and their derivatives is comprehensively covered in monograph^[8] and more recent review articles.^[9,10] Our long-standing interest in tailor-made AAs, focuses mostly on fluorinated α -^[11] and β -AAs,^[12] but also includes phosphorus-containing^[13] and conformationally constrained derivatives^[14] as well as their not-linear chiroptical properties, such self-disproportionation of enantiomers.^[15] Methodologically, along with other research groups, we are developing chemistry of Ni(II) complexes of AA Schiff bases (Scheme 1), derived from chiral tridentate ligands, as a general approach for asymmetric synthesis of various tailor-made AAs.^[9e,16]

In particular, Ni(II) complexes of glycine Schiff base **1**, derived from (S)- or (R)-proline-containing ligands, can be conventionally transformed to the derivatives of higher AAs via alkyl halide alkylation,^[17] aldol,^[18] Mannich,^[19] Michael^[20] addition reactions, as well as various multi-step transformations.^[21] Homologation products **2** are conveniently disassembled under acidic conditions to afford the target AAs **3** along with recovery and reuse of the corresponding chiral ligands. By contrast, the homologation of dehydroalanine Schiff bases complexes (S)-**4** is a significantly less studied area of this chemistry. Thus, only a handful of examples^[16,22] of additions to (S)-**4**, limited mostly to NH and OH nucleophiles, have been reported so far. One may agree that reactions of dehydroalanine complexes (S)-**4**, via intermediates **5**, would allow preparation of structural types of AAs unavailable by homologation of glycine derivatives (S)-**1**. However, the reactivity and synthetic potential of chiral equivalents of electrophilic dehydroalanine (S)-**4** remains virtually unexplored. Recently we reported the reactions of achiral Ni(II) complexes of dehydroalanin **7**^[23] with BrCF₂COOEt provid-

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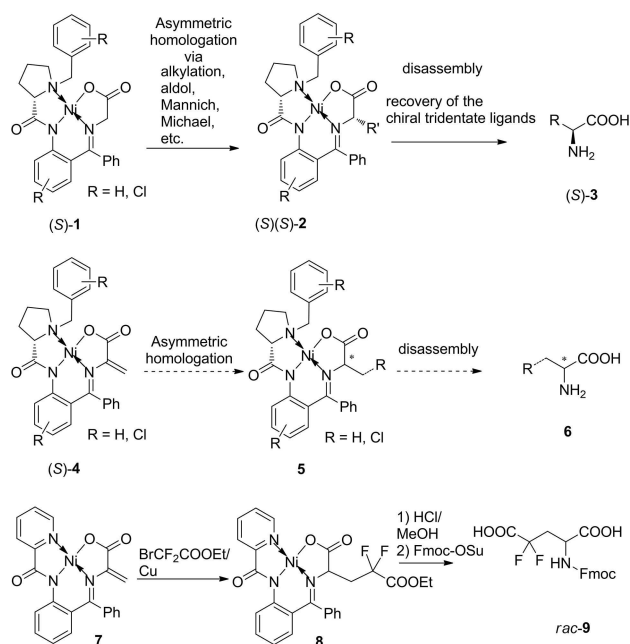
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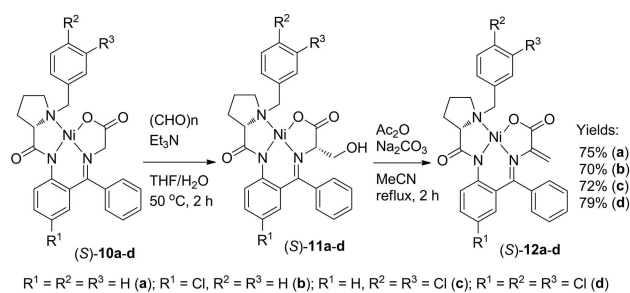
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Scheme 1. Asymmetric homology of chiral glycine (S)-1 and dehydroalanine (S)-4 Schiff bases.

ing direct access to 4,4-(difluoro)glutamic acid **9**^[24] via intermediate **8**. Besides the synthetic value, the previous work^[23] has demonstrated that Cu(II) species are compatible with Ni(II)-chelated starting materials and the dehydroalanine Schiff bases are sufficiently electrophilic to react with BrCuCF₂COOEt. In the present work we extend these findings to the series of chiral dehydroalanine equivalents (S)-4 and evaluate the level of stereochemical outcome as a function of dehydroalanine complexes structure. Furthermore, we describe a convenient procedure for asymmetric synthesis of preparation of *N*-Fmoc-4,4-(difluoro)glutamic acid, a valuable building block in medicinal chemistry and drug design.^[24,25]

Syntheses of the requisite tridentate chiral ligands^[26] and glycine Schiff base complexes **10a–d**^[27] was performed according to the literature procedures (Scheme 2). The transformation of the glycine moiety in **10a–d** to dehydroalanine residue of **12a–d** was accomplished by two-step procedure by analogy with the literature data^[22] and the method used in the previous



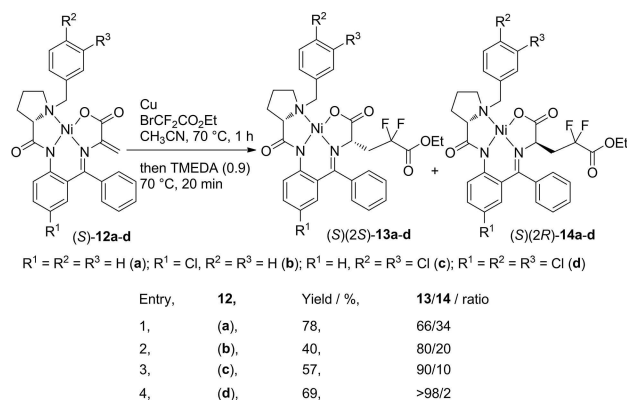
Scheme 2. Two-step synthesis of known (S)-12a,c and new (S)-12b,d dehydroalanine Schiff base Ni(II) complexes from glycine derivatives (S)-10a–d.

work.^[23] Starting glycine complexes **10a–d** were treated with formaldehyde in the presence of triethylamine to furnish intermediate serine containing compounds **11a–d**. Dehydration of **11a–d** to **12a–d** takes place via in situ formation the corresponding esters followed by the elimination of acetic acid in acetonitrile under reflux. Dehydroalanine complexes **12a**^[22a] and **12c**^[22e] are known compounds, while derivatives **12b** and **12d** have not been previously described.

Our interest in studying the reaction of four different dehydroalanine complexes **12a–d** stems from the reports^[28] that in the case of glycine complexes **10**, a seemingly insignificant structural modifications with chlorine atoms or other halogen or alkyl substituents, results in a noticeable differences in the stereochemical outcome of their reactions with various electrophiles. In particular, it was shown^[29] that **10d** provides for the most optimal parallel displaced type of aromatic interactions between *o*-amino-benzophenone and Pro *N*-benzyl rings controlling the stereochemical outcome.^[30] Consequently, it was rather important to investigate whether or not this trend would hold true for the new platform of dehydroalanine Schiff base complexes in the reactions with nucleophiles.

As presented in Scheme 3, the reactions of complexes **12a–d** with BrCF₂COOEt was conducted in the presence of activated Cu powder in acetonitrile. The progress of the additions was monitored by TLC.

The reaction conditions were optimized using dehydroalanine complex (S)-12d allowing to define the following settings: 6 equivalents of the activated Cu powder, 3 equivalents of bromodifluoroacetate, 0.9 equivalents of tetramethylene ethylenediamine (TMEDA) in acetonitrile at 70 °C. Under these conditions, the reactions proceeded quite rapidly, being virtually completed in about 20 min of the reaction time. The additions of BrCF₂COOEt/Cu with a series of dehydroalanine complexes (S)-12a–d were conducted under the same conditions to assess the relationships between the complexes' structure and the level of the stereochemical outcome. The results reported in Scheme 3 were absolutely exciting as the levels of the asymmetric induction clearly correlated with the degree and pattern of chlorine substitution for hydrogen in the



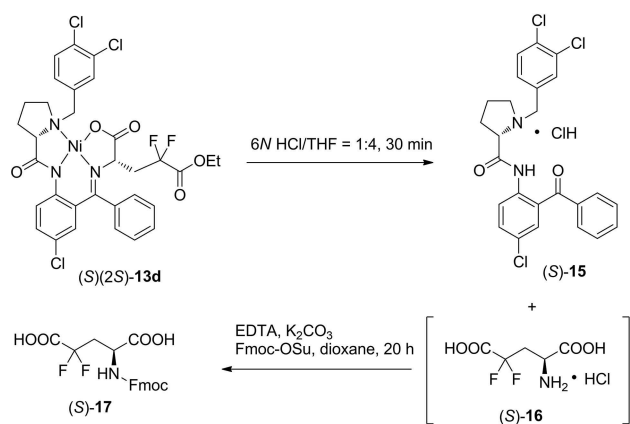
Scheme 3. Reactions of dehydroalanine Schiff base Ni(II) complexes (S)-12a–d with BrCF₂COOEt/Cu.

structure of complexes (S)-12a–d. Thus, unsubstituted dehydroalanine complex gave the ratio of diastereomers (S)(2S)-13a/(S)(2R)-14a of 66/34. Introduction of a chlorine atom in the *p*-position of the *o*-amino-benzophenone moiety allowed to increase the diastereomeric ratio to 80/20. On the other hand, the presence of two chlorine atoms in the *p*- and *m*-position of the *N*-benzyl moiety was found to be more effective in controlling the stereochemical outcome increasing the ratio of (S)(2S)-13c/(S)(2R)-14c to 90/10. Finally, the chlorination of both of the *o*-amino-benzophenone and *N*-benzyl moieties gave the best result affording diastereomers (S)(2S)-13d and (S)(2R)-14d with practically attractive diastereoselectivity of >98/2 (~98.5/1.5).

Considering the above mentioned work,^[29,30] these results, while quite spectacular, were not entirely unexpected. In particular, the superior stereocontrolling properties of the trichloro derivatives of glycine complexes (S)- or (R)-1 (Scheme 1) have been convincingly demonstrated.^[28,30] The trend of the stereocontrolling properties observed in the present work is likely suggesting that the previously determined aromatic interactions between the *o*-amino-benzophenone and the *N*-benzyl rings are of greater general importance. Nevertheless, the direct comparison of all four differently substituted derivatives have never been conducted before emphasizing the methodological importance of the results obtained.

As a final synthetic step in this work, we performed disassembly of Ni(II) complex (S)(2R)-13d as presented in Scheme 4.

Major diastereomer (S)(2S)-13d, obtained as described in Scheme 3, was additionally purified by column chromatography to remove the residual amounts of minor product (S)(2R)-14d. Diastereomerically pure (S)(2S)-13d was subjected to the action of 6 N HCl in THF (1:5) at ambient temperature. The red-colored mixture gradually changed to a green solution indicating the disassembly of the starting (S)(2S)-13d complex and formation of NiCl₂. The precipitate of chiral ligand (S)-15 was removed by filtration and the solution was concentrated and treated with EDTA to chelate the Ni(II) ions. The protection of the in situ formed hydrochloric salt of (S)-16 was performed



Scheme 4. Disassembly of major diastereomer (S)-13d, recycling of chiral ligand (S)-15 and preparation of Fmoc-derivative (S)-17.

using Fmoc-OSu in dioxane at ambient temperature in the presence of K₂CO₃.

In summary, four differently substituted chiral Ni(II)-complexes of dehydroalanine Schiff base were prepared and their addition reactions with BrCF₂COOEt/Cu were studied under the standard reaction conditions. The observed diastereoselectivity rather remarkably was found to depend on the degree and pattern of chlorine substitution for hydrogen in the structure of the starting dehydroalanine complexes. While the unsubstituted complex gave the ratio of diastereomers (S)(2S)-13a/(S)(2R)-14a of 66/34, introduction of chlorine atoms in the *p*-position of the *o*-amino-benzophenone and the *p*- and *m*-positions of the *N*-benzyl moieties led to gradual increase of the stereochemical outcome allowing to achieve a synthetically attractive value of >98/2 diastereomeric ration. These results clearly suggest the similarity between chiral Ni(II) complexes of dehydroalanine and glycine in the nature of the stereocontrol being governed by the parallel displaced type of aromatic interactions between *o*-amino-benzophenone and Pro *N*-benzyl rings. Preparation of Fmoc derivative of (S)-4,4-difluoroglutamic acid by disassembling of the major diastereomer was successfully performed.

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Keywords: asymmetric synthesis · tailor-made amino acids · fluorine · Schiff bases · Ni(II)-complexes

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