Axially chiral Ni(II) complexes of $\alpha$-amino acids: Separation of enantiomers and kinetics of racemization

Wenzhong Zhang, Romuald Eto Ekomo, Christian Roussel, Hiroki Moriwaki, Hidenori Abe, Han Jianlin, Vadim A. Soloshonok

To cite this version:

HAL Id: hal-02093234
https://hal.science/hal-02093234
Submitted on 8 Apr 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
Axially chiral Ni(II) complexes of α-amino acids: Separation of enantiomers and kinetics of racemization

Wenzhong Zhang | Romuald Eto Ekomo | Christian Roussel | Hiroki Moriwaki | Hidenori Abe | Jianlin Han | Vadim A. Soloshonok

1 School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing, China
2 Aix Marseille Univ, CNRS, Centrale Marseille iSm2, Marseille, France
3 Hamari Chemicals Ltd, Osaka, Japan
4 Department of Organic Chemistry I, Faculty of Chemistry, University of the Basque Country UPV/EHU, San Sebastián, Spain
5 IKERBASQUE, Basque Foundation for Science, Bilbao, Spain

Correspondence
Christian Roussel, Aix Marseille Univ, CNRS, Centrale Marseille, iSm2, Marseille, France. Email: christian.roussel@univ-amu.fr
Jianlin Han, School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination Chemistry, Nanjing University, 22 Hankou Road, Nanjing 210093, China. Email: hanjl@nju.edu.cn
Vadim A. Soloshonok, Department of Organic Chemistry I, University of the Basque Country UPV/EHU, Paseo Manuel Lardizábal 3, San Sebastián 20018, Spain. Email: vadym.soloshonok@ehu.es

Funding information
IKERBASQUE, Basque Foundation for Science; Changzhou Jin-Feng Huang program; National Natural Science Foundation of China, Grant/Award Number: 21472082

Abstract
Herein we present design, synthesis, chiral HPLC resolution, and kinetics of racemization of axially chiral Ni(II) complexes of glycine and di-(benzyl)glycine Schiff bases. We found that while the ortho-fluoro derivatives are configurationally unstable, the pure enantiomers of corresponding axially chiral ortho-chloro-containing complexes can be isolated by preparative HPLC and show exceptional configurational stability ($t_{1/2}$ from 4 to 216 centuries) at ambient conditions. Synthetic implications of this discovery for the development of new generation of axially chiral auxiliaries, useful for general asymmetric synthesis of α-amino acids, are discussed.

KEYWORDS
amino acids, axial chirality, chiral HPLC, kinetic of racemization, rotational energy barriers

1 | INTRODUCTION

The current paradigm for successful new drugs design has two structural trends: the use of fluorinated groups, to impede the metabolic oxidation, and tailor-made amino acid (AA), to control 3D position of pharmacophoric moieties, closely mimicking peptide-receptor interactions. Subsequently, the development of advanced asymmetric methodologies for scalable synthesis of structurally diverse AAs is currently in high demand. For quite some time, our groups were interested in pursuing new synthetic approaches for preparation of sterically constrained, phosphorus, and fluorine-containing AAs. One of the most methodologically prolific directions, inspired by the seminal work by Belokon, has been the chemistry of Ni(II) complexes of AAs derived Schiff bases (Scheme 1). Along with other research groups, we showed that chiral nucleophilic glycine equivalents can be transformed to various AAs via general reactions types, such as alkyl halide alkylations, Michael, aldol, and Mannich addition reactions. Complexes can be
easily disassembled under acidic conditions to afford the target-free AAs along with recovery and recycling of the corresponding chiral ligands. This methodology was also shown to work very well for preparation of bis-AAs, using α,ω-di-halo-alkylating reagents, highly sterically constrained (1R,2S)-1-amino-2-vinylcyclopropanecarboxylic acid derivatives, by SN2−SN2′ dialkylation, and kinetic resolution of unprotected α, and β-AAs.

Using the modular design approach, various chiral equivalents of nucleophilic glycine 1 were developed, deriving chirality from the appropriate amino acids or amines. However, all these different types of complexes share one key structural feature, the α-amino-benzophenone moiety. It was shown that the benzophenone phenyl group is absolutely essential to achieve high stereocontrol of the glycine methylene homologation. It is generally assumed, as shown in Figure 1, that the phenyl group cannot freely rotate due to the steric interaction with either or both the α-amino phenyl and/or glycine moieties.

2 | MATERIALS AND METHODS

2.1 | General information

All commercial reagents were used without additional purification unless otherwise specified. All experiments were monitored by thin layer chromatography (TLC) using UV light as visualizing agent. 1H NMR (400 MHz), 13C NMR (101 MHz), and 19F NMR (376 MHz) were measured on Bruker AVANCE III-400 spectrometer. Melting points are uncorrected. Infrared spectra were obtained on Bruker Vector 22 in KBr pellets. HRMS was recorded on a LTQ-Orbitrap XL (Thermofisher, USA).

2.2 | General synthetic procedures and experimental methods synthesis of the 7a and 7b

A solution of potassium hydroxide (9.0 Eq) in methanol (7 mL/g of KOH) was added to a suspension of

**SCHEME 1** General reaction types for homologation of chiral glycine equivalent 1 to various AA derivatives 2

FIGURE 1 Assumingly restricted rotation of the phenyl group in Ni(II)-complexes 1 and the design of axially chiral model compounds 3

N-(4-chloro-2-(2-fluorobenzoyl)phenyl)-2-(dibutylamino)acetamide or N-(4-chloro-2-(2-chlorobenzoyl)phenyl)-2-(dibutylamino)acetamide (1.0 Eq), glycine (5.0 Eq), nickel nitrate hexahydrate (2.0 Eq) in methanol at 60°C to 70°C. Upon complete consumption monitored by TLC, then the reaction was quenched with H2O. The organic layer was removed, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with H2O (2 × 10 mL) and brine solution (1 × 10 mL) and dried over anhydrous Na2SO4. The solvent was evaporated to give the crude product, which was purified by flash chromatography.

2.3 | Synthesis of the 8a and 8b

To a solution of sodium tert-butoxide (2.5 Eq) in DMF (10 mL/g of complex 3a-c) were added complex 7a-b (1.0 Eq) and the corresponding alkylating reagent (2.5 Eq). The reaction was stirred at ambient temperature (room temperature water bath) for 15 minutes, and upon completion (monitored by TLC), then the reaction was quenched with H2O. The organic layer was removed, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with H2O (2 × 10 mL) and brine solution (1 × 10 mL) and dried over anhydrous Na2SO4. The solvent was evaporated to give the crude product, which was purified by flash chromatography.

2.4 | Synthesis of the 9a and 9b

To a flask containing 8a or 8b (1.0 Eq), tetrapropylammonium iodide (25 mol%), 2 mL of dichloromethane and 2 mL of 30% aqueous sodium hydroxide, benzyl bromide (1.5 Eq) was added, and the reaction mixture was stirred at room temperature. After disappearance of 8a or 8b by TLC, 10 mL of water was added, and the organic layer was extracted with CHCl3 three times. The combined organic layer was dried over magnesium sulfate. The solvent was evaporated to give the crude product, which was purified by flash chromatography.
3 | RESULTS AND DISCUSSION

Despite the key importance of this assumption for structural design and mechanistic considerations, the issue of the restricted rotation was never critically studied, due to the absence of tangible concepts of how to determine the rotation or lack of thereof. Drawing from our recent success in the synthesis of chiral ligands and the Ni(II) complexes featuring central and axial chirality, we came up with an idea to design a new type of complexes (Figure 1) bearing a single element of axial chirality by the *ortho*-substitution on the phenyl ring in question. In this work, we describe synthesis of racemic complexes, chiral chromatographic separation of the corresponding enantiomers, and kinetics of their racemization. The novelty and importance of the reported data have both theoretical and practical facets. First, we unequivocally demonstrate the evidence for relatively unhindered rotation of the benzophenone phenyl group, as well as its directional mode. Second, the results obtained allow for practical and reliable quantification of the configurational stability of this type of axial chirality, thus paving the way for a rational design of new generation of chiral ligands and Ni(II) complexes for general asymmetric synthesis of tailor-made AAs.

The major motivation to undertake this project was two-pronged. First, we sought to solve the above-stated problem of the restricted rotation of the benzophenone phenyl. We posited that this issue can be solved by using compounds 3 (Figure 1) along the following line of reasoning. The introduction of the *o*-substituent on the phenyl group in derivatives 3 would generate the element of axial chirality along the Ar–Ar bond. Next, assuming that enantiomers of complexes 3 can be separated under conditions of chiral HPLC, one can study their racemization as a function of the rotation around the Ar–Ar bond. The second goal of this work was derived from the first in a way that if, indeed, the phenyl rotation is restricted, then we could explore a rational introduction of the axial chirality on the benzophenone moiety as a novel stereocontrolling element in the structure of Ni(II) complexes. One might agree that this prospect has an enormous potential for the development of new generation of chiral ligands for general asymmetric synthesis of α-AA.

The target ligands 6a,b and axially chiral glycine Schiff base Ni(II) complexes 7a,b were prepared using modified literature procedures as presented in Scheme 2.

Commercially available *o*-amino-benzophenones 4a,b were chemo-selectively acylated with bromoacetyl bromide in acetonitrile, to furnish amides 5a,b. Compounds 5a,b were isolated, purified, and reacted next with *N,N*-di-*n*-butylamine in the presence of Hünig’s base to produce ligands 6a,b with good isolated yields. The final step, preparation of racemic Ni(II) complexes (R/S)-7a,b, was performed in MeOH using, glycine, Ni(OAc)₂, as source of Ni(II) ions, and Na₂CO₃ as a base. Complexes (R/S)-7a,b were purified by column chromatography on SiO₂ and fully characterized.

It should be noted that enantiomeric separation of compounds of type 7 was never reported, presenting obvious challenge due to their complex structure, as well as unknown configurational stability and, therefore, detectability of the corresponding enantiomers. Thus, taking advantage of available to us an entirely automated screening unit for chiral separation conditions (chiral stationary phases, solvents, temperature, and chiroptical detection) equipped for the present study with five different columns: Pirkle-type (**S,S,Ulmo), immobilized cellulose carbamates (Chiralpak IB and IC), and immobilized amylose carbamates (Chiralpak IA and ID), we finally managed to find suitable separation conditions (See Supporting Information for all optimized separations). The HPLC chart of two baseline-separated enantiomers of 7a, conducted under the optimized conditions, is presented in Figure 2.

The enantiomers (S)- and (R)-7a were cleanly separated on preparative scale (~20 mg). Quite surprisingly, after solvent evaporation the enantiomeric purity of both (S)- and (R)-7a was relatively low (~80% ee), indicating the possibility of partial racemization during the isolation/solvent evaporation procedure. Keeping this in mind, we performed the enantiomerization (racemization) energy barriers study. The racemization of an enantiomerically enriched sample was followed at a given temperature. The enantiomeric excess was monitored...
along time, and the enantiomerization rate was deduced from the slope of the first-order kinetic line. As shown in Scheme 3, the experiments revealed that for (S)- and (R)-7a, the $k_{\text{enantiomerization}} = 8.7963 \times 10^{-5} \text{ s}^{-1}$ (22°C, ethanol) with the $\Delta G^\#$ equal 95.2 (kJ/mol). These data indicate that $t_{1/2}$ racemization for compounds 7a is only 1.14 hours. In other words, the racemization occurs relatively easy at ambient temperature.

Considering that the process of racemization did not result in any detectable formation of by-products, one can postulate that the racemization is occurring via rotation of the o-F substituted phenyl ring. Consequently, taking into account that the size of a hydrogen is smaller than that of fluorine, one can claim that the relatively unhindered rotation of the phenyl group does take place as in the case of the original Ni(II) complexes 1 (Figure 1) at ambient conditions.

Thus, having determined the fact of fast rotation of the phenyl (o-F-phenyl) ring in glycine-derived complex, we were excited with an opportunity to apply the same methodology for complexes containing quaternary $\alpha$-AAs. To this end, we performed the di-benzylations of complex (R/S)-7a, as presented in Scheme 4.

The di-benzylations were conducted at ambient temperature in DMF using NaOH as base. The reactions were completed in less than 1 hour time furnishing products (R/S)-8a,b in good isolated yields. Complexes (R/S)-8a,b were purified by column chromatography and fully characterized.

For the detection and separation of the corresponding enantiomers of (R/S)-8a, we again applied our automated screening unit for chiral separation conditions allowing us to screen numerous HPLC stationary phases, among which, the Chiralpak IC gave the best separation profile. The chart of the enantiomers (R)- and (S)-8a, baseline separated on this column, is presented in Figure 3.

This procedure was reproduced on preparative scale (22 mg) allowing very clean isolation of about 10 mg of each individual enantiomer. However, once again, after the removal of solvents (chloroform/ethanol) the enantiomeric purity of compounds (S)- and (R)-8a was found to be ~90% ee, most likely, due to configurational instability of the isolated enantiomers. Racemization of enantiomers 8a was studied by heating isolated compounds in ethanol at 40°C. As presented in Scheme 5, the experiments revealed that for (S)- and (R)-8a, the $k_{\text{enantiomerization}} = 1.1445 \times 10^{-5} \text{ s}^{-1}$ (40°C, ethanol) with the $\Delta G^\#$ equal 106.5 (kJ/mol).

Accordingly, the $t_{1/2}$ racemization of compound 8a is about 8.5 hours at 40°C or 3 days at ambient temperature. Based on these data, we can conclude that while configurational stability of enantiomers 8a is significantly greater, as compared with that of 7a, their racemization is still relatively fast, occurring via rotation of the o-F-phenyl group.

The results obtained for separation and racemization of the corresponding enantiomers of complexes 7a and 8a unambiguously demonstrate that relatively unhindered
rotation of the benzophenyl phenyl group readily takes place at ambient temperature. The barrier of rotation is expectedly higher for 8a vs 7a, due to the greater steric hindrance presented by the di-benzyl-methylene vs methylene moieties.

Thus, having successfully concluded the first objective of this work, we focused on the second goal, a preliminary exploration of the axial chirality, provided by the o-substitution, as a novel stereocontrolling element in the design of Ni(II) complexes of α-AA Schiff bases.

Bearing in mind that fluorine is the second smallest, after hydrogen, atom, the case of detection and separation at room temperature of the corresponding enantiomers of complexes 7a and 8a was quite remarkable. Drawing inspiration from these data, we proceeded with similar investigation of the enantiomers of o-Cl-substituted complexes 7b and 8b. Synthesis of compounds 7b and 8b is presented in Schemes 2 and 4, correspondingly. We found that quite good baseline separation of enantiomers 7b can be achieved using Chiralpak ID column and ethanol as the mobile phase. The HPLC chart of two baseline separate enantiomers (R)-7b is presented in Figure 4.

Preparative (22 mg) separation of enantiomers (R)- and (S)-7b was conducted under similar conditions allowing preparation of about 10 mg of each enantiomer. In sharp contrast to fluorine containing derivatives 7a, enantiomers of 7b were isolated with enantiomeric excesses are higher than 99%, suggesting their much

**FIGURE 3** Separation of enantiomers of compound 8a on Chiralpak IC column

**SCHEME 3** Separation of enantiomers (S)- and (R)-7a and their racemization

**SCHEME 4** Preparation of Ni(II) complexes (R,S)-8a,b, containing quaternary α,α-di-benzyl-glycine
greater configurational stability. With each enantiomer in hand, we conducted the racemization experiment and calculation of the enantiomerization energy barriers (Scheme 6).

As presented in Scheme 6, the kinetic experiments indicated that for enantiomers (S)- and (R)-7b, the $k_{\text{enantiomerization}} = 6.1886 \times 10^{-7}$ s$^{-1}$ (118°C, n-butanol) with the $\Delta G^\circ$ equal 143 (kJ/mol). Thus, the $t_{1/2}$ racemization for compounds 7b is 154 hours at 118°C in n-butanol. Accordingly, at ambient temperature, enantiomers 7b are virtually permanently configurationally stable (216 centuries). It is worth mentioning that the barrier gap between o-F 7a and o-Cl 7b is 48 kJ/mol, which, by analogy with literature data,[66] points out that the environment of the rotating axis in compounds 7a and 7b produces a rather high sensitivity to the steric effect of the ortho-substituent, indicating highly sterically strained surroundings.

Similar chiral HPLC experiments were also conducted for racemic 8b, containing the quaternary amino acid...
moiety. As presented in Figure 5, enantiomers of 8b were baseline separated on Chiralpak IC column on analytical as well as preparative scale (12 mg).

Isolated enantiomerically pure compounds 8b were subjected to racemization by heating in chlorobenzene at 132°C. Calculation of the kinetic data revealed that for enantiomers (S)- and (R)-8b, the $k_{\text{enantiomerization}} = 6.1245 \times 10^{-5}$ s$^{-1}$ with the $\Delta G^\circ$ equal 133 kJ/mol at 132°C in chlorobenzene. Accordingly, similarly to 7b, enantiomers of 8b are configurationally permanently stable at ambient temperature (4 centuries). However, the lower rotational barrier determined for quaternary amino acid containing 8b, as compared with that of glycine complex 7b, was quite unexpected, as the higher barrier was found for 8a versus 7a. While very surprising, these results are not completely unprecedented and can be rationalized by considering the ground state strain in 8b. In this case, two benzyl substituents, as well as relatively large chlorine atom, add the steric strain in the ground state. The relationship between the higher ground state strain and the lower rotational barrier is rather a general, yet poorly recognized phenomenon, which has been overlooked in the properties of many axially chiral compounds. Summary of the energy barriers for complexes 7a,b and 8a,b is presented in Table 1.

The data discussed above on the separation of complexes 7 and 8 enantiomers and kinetics of their racemization have some important synthetic implications. In particular, the discovered configurational stability of o-Cl-substituted glycine 7b opens up an exciting opportunity of developing a new generation of chiral nucleophilic glycine equivalents possessing a structurally simple element of axial chirality as stereocontrolling function. To have a brief assessment of its efficiency, we conducted benzylation of racemic 7a,b under the phase-transfer conditions. The results are presented in Scheme 7.

As one can see from Scheme 7, the diastereoselectivity in the case of o-F-substituted derivative 7a was rather insignificant (55/45) and may reflect thermodynamic equilibrium in the final product due to the demonstrated in this work relatively unhindered rotation of the o-F-phenyl group. In sharp contrast, the benzylation of o-Cl-bearing glycine complex 7b gave reasonably good kinetic ratio of diastereomeric products 9b and 10b (70/30). We assume that diastereomers 9a,b, containing the halogen and the benzyl group on the opposite sides of the Ni(II) complex, are the major products. While the 70/30 diastereomeric ratio

![FIGURE 5](image.png)

**TABLE 1** Summary of the energy barriers for complexes 7a,b and 8a,b

<table>
<thead>
<tr>
<th>Complex</th>
<th>R</th>
<th>X</th>
<th>$\Delta G^\circ$ (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>H</td>
<td>F</td>
<td>95.2 (22°C, ethanol)</td>
</tr>
<tr>
<td>7b</td>
<td>H</td>
<td>Cl</td>
<td>143 (118°C, n-butanol)</td>
</tr>
<tr>
<td>8a</td>
<td>Bn</td>
<td>F</td>
<td>106.5 (40°C, ethanol)</td>
</tr>
<tr>
<td>8b</td>
<td>Bn</td>
<td>Cl</td>
<td>133 (132°C, chlorobenzene)</td>
</tr>
</tbody>
</table>
leaves a room for improvement, it serves well to demonstrate the novel principle of structural design of axially chiral glycine nucleophilic equivalents for general asymmetric synthesis of tailor-made α-AAs. One may assume that increase of the steric bulk of the ortho-substituent may result in the increased stereoccontrol of the glycine moiety homologation. Currently, this work is in progress and will be reported in a due course.

4 | CONCLUSION

To conclude, in this work, we successfully developed an innovative structural models to probe and quantify the rotational barriers around the Ar─Ar bond of the benzo-phenone moiety in the Ni(II) complexes of AAs Schiff bases. We demonstrate that the corresponding axially chiral ortho-fluoro derivatives, due to the small steric bulk of fluorine, are configurationally unstable suggesting rather unhindered rotation around the Ar─Ar bond. In sharp contrast, the ortho-chloro-substituted analags are configurationally permanently (t1/2 from 4 to 216 centuries) stable at ambient conditions. These findings provide for exciting opportunity of rational design of a new generation of axially chiral ligands and the corresponding Ni(II) complexes for general asymmetric synthesis of tailor-made α-AAs.

REFERENCES


SCHEME 7 Diastereoselective benzylation of glycine complexes 7a,b


34. Popkov A, Langer V, Manorik PA, Weidlich T. Long-range spin–spin interactions in the 13C-n.m.r. spectra of the nickel(II) complex of the Schiff base of (S)-N-benzylproline (2-benzoylphenyl) amide and glycine. Quantum-chemical calculations and possible donation of electron density from the π-system of the benzyl group to nickel. Transition Met Chem. 2003;28:475-481.


41. Soloshonok VA, Tang X, Hruby VJ. Large-scale asymmetric synthesis of novel sterically constrained 2′,6′-dimethyl- and α,2′,6′-trimethlytyrosine and -phenylalanine derivatives via


67. Suzuki Y, Takahashi I, Dobashi Y, Hasegawa H, Roussel C, Kitagawa O. Relationship between rotational barriers and...


69. Li JY, Chang HI, Feng CN, Wu YT. Rotation of aryl groups in 9,10-diarylphenanthrenes: does the rotational barrier become lower as the backbone becomes more crowded? *Org Lett.* 2016;18:6444-6447.