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

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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,¹ and tailor-made amino acid (AA), to control 3D position of pharmacophoric moieties, closely mimicking peptide-receptor interactions.²⁻⁶ Subsequently, the development of advanced asymmetric methodologies for scalable synthesis of structurally diverse AAs is currently in high demand.⁷⁻¹⁸ For quite some time, our groups were interested in pursuing

new synthetic approaches for preparation of sterically constrained,^{19,20} phosphorus,^{21,22} and fluorine-containing²³⁻²⁵ AAs. One of the most methodologically prolific directions, inspired by the seminal work by Belokon,^{26,27} has been the chemistry of Ni(II) complexes of AAs derived Schiff bases (Scheme 1).^{28,29}

Along with other research groups,³⁰⁻³⁹ we showed that chiral nucleophilic glycine equivalents **1** can be transformed to various AAs **2** via general reactions types, such as alkyl halide alkylations,^{40,41} Michael,^{42,43} aldol,^{44,45} and Mannich^{46,47} addition reactions. Complexes **2** 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-AA_s,^{48,49} using α,ω -di-halo-alkylating reagents, highly sterically constrained (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid derivatives,^{50,51} by S_N2-S_N2' dialkylation, and kinetic resolution of unprotected α -^{52,53} and β -AA_s.⁵⁴

Using the modular design approach,^{55,56} various chiral equivalents of nucleophilic glycine **1** were developed, deriving chirality from the appropriate amino acids^{57,58} or amines.^{59,60} However, all these different types of complexes **1** share one key structural feature, the *o*-amino-benzophenone moiety. It was shown^{30-39,61} 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 *o*-amino phenyl and/or glycine moieties.

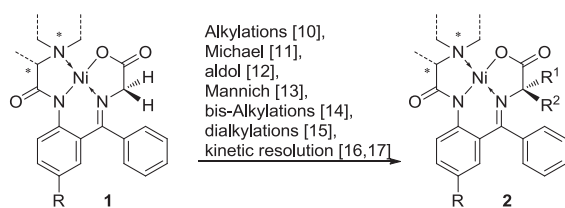
2 | MATERIALS AND METHODS

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**

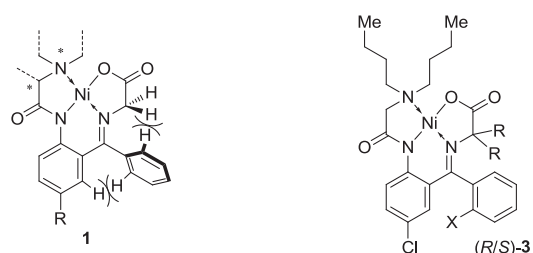


FIGURE 1 Assumingly restricted rotation of the phenyl group in Ni(II)-complexes **1** and the design of axially chiral model compounds **3**

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.

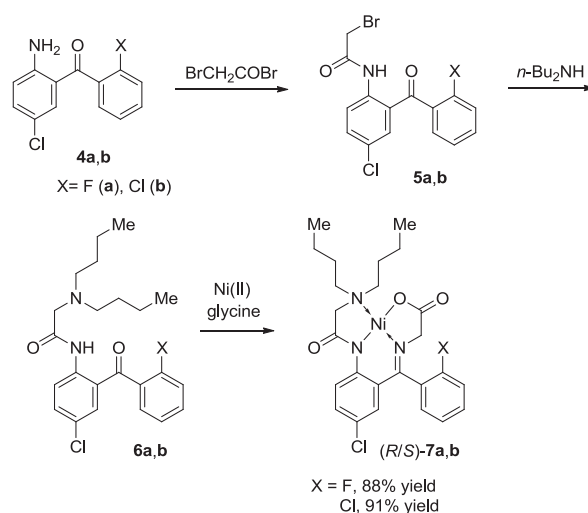
3 | RESULTS AND DISCUSSION

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,⁶² we came up with an idea to design a new type of complexes **3** (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 **3**, 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^{63,64} 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*-



SCHEME 2 Synthesis of ligands **6a,b** and axially chiral glycine Schiff base Ni(II) complexes **7a,b**

di-*n*-butylamine in the presence of Hünig's base⁶⁵ 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

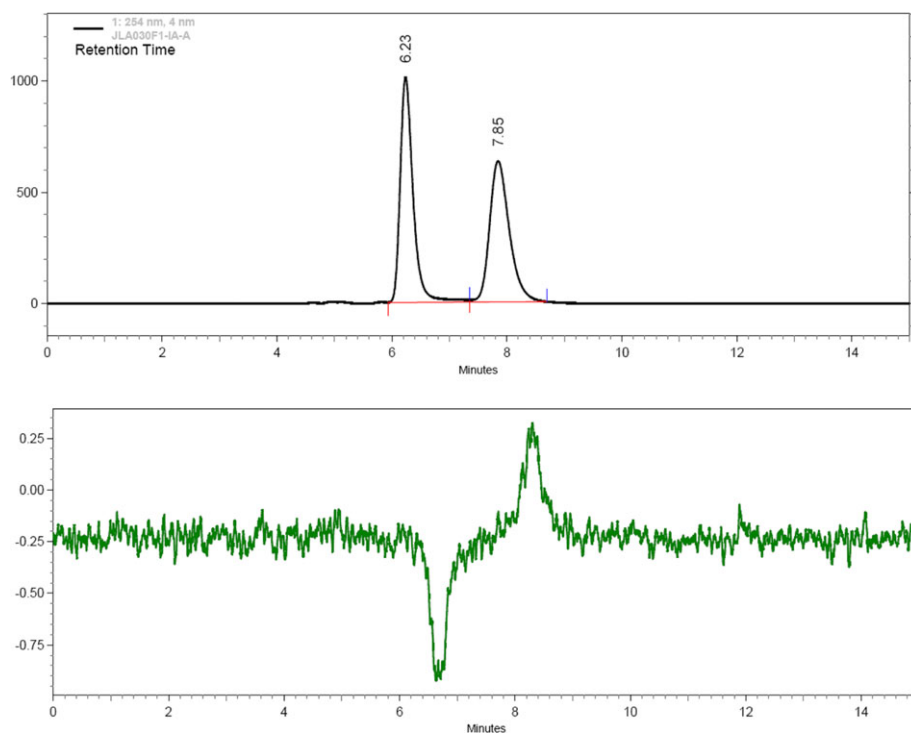


FIGURE 2 Separation of enantiomers of compound **7a** on Chiralpak IA column

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 $k_{\text{enantiomerization}} = 8.7963 \cdot 10^{-5} \text{ s}^{-1}$ (22°C, ethanol) with the ΔG^\ddagger 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 α -AAs. To this end, we performed the di-benylation of complex (*R/S*)-**7a**, as presented in Scheme 4.

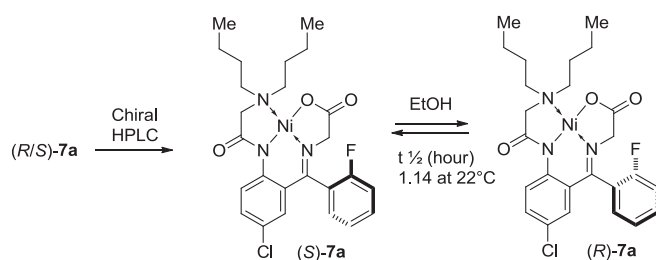
The di-benylations were conducted at ambient temperature in DMF using NaOH as base. The reactions were completed in less than 1 hour time furnishing products (*R/S*)-**8a,b** in good isolated yields. Complexes (*R/S*)-**8a,b** were purified by column chromatography and fully characterized.

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.

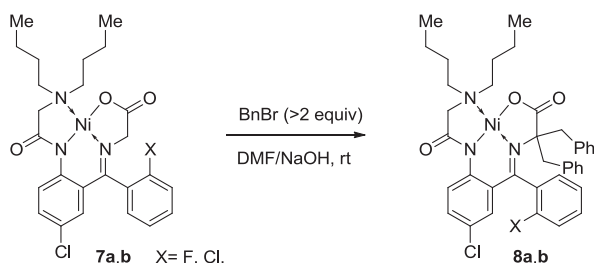
This procedure was reproduced on preparative scale (22 mg) allowing very clean isolation of about 10 mg of each individual enantiomer. However, once again, after the removal of solvents (chloroform/ethanol) the enantiomeric purity of compounds (*S*)- and (*R*)-**8a** was found to be ~90% ee, most likely, 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 $k_{\text{enantiomerization}} = 1.1445 \cdot 10^{-5} \text{ s}^{-1}$ (40°C, ethanol) with the ΔG^\ddagger 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



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

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*)- and (*S*)-**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

Method description : Chiralpak IC, Ethanol, 0,8 ml/min, DAD + CD390nm, 25°C

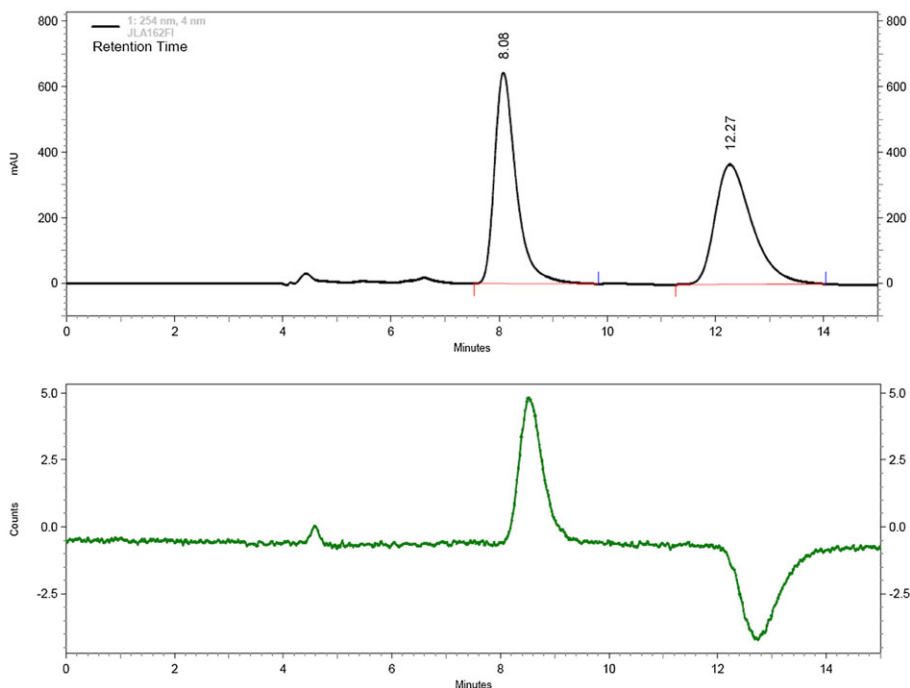
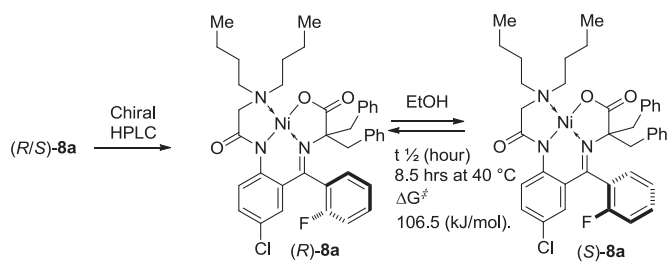


FIGURE 3 Separation of enantiomers of compound **8a** on Chiralpak IC column



SCHEME 5 Separation of enantiomers (*R*)- and (*S*)-**8a** and their racemization at 40°C in ethanol

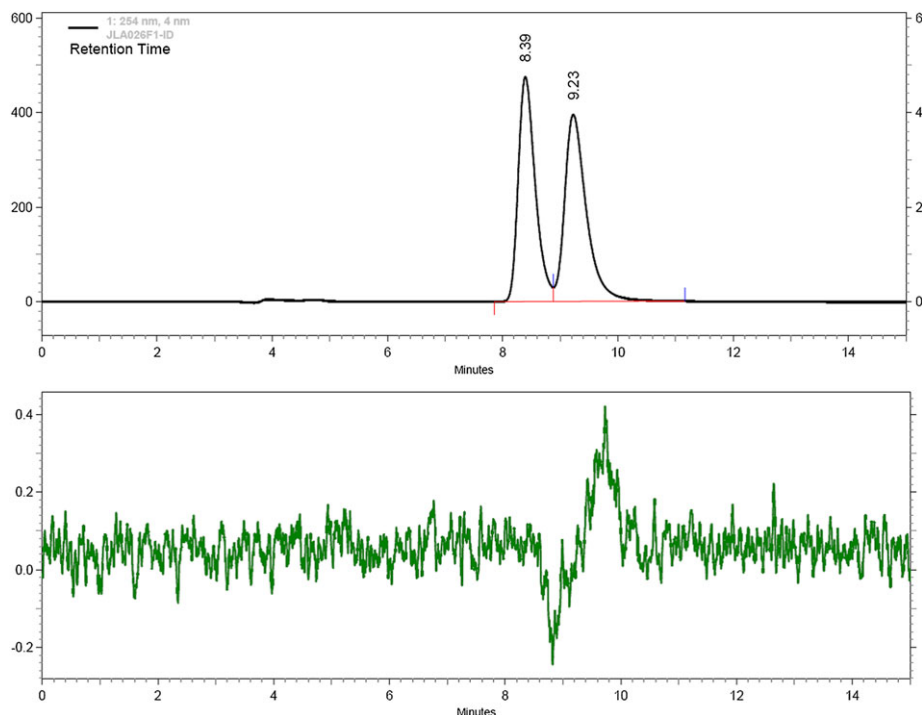


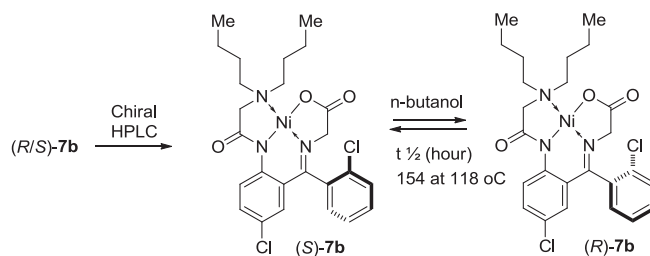
FIGURE 4 Separation of enantiomers of compound (*R/S*)-**7b** on Chiralpak ID column

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 $k_{\text{enantiomerization}} = 6.1886 \cdot 10^{-7} \text{ s}^{-1}$ (118°C, *n*-butanol) with the ΔG^\ddagger 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



SCHEME 6 Separation of enantiomers (*R*)- and (*S*)-**7b** and their racemization at 118°C in *n*-butanol

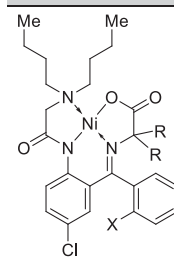
moiety. As presented in Figure 5, enantiomers of **8b** were baseline separated on Chiralpak IC column on analytical as well as preparative scale (12 mg).

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 $k_{\text{enantiomerization}} = 6.1245 \cdot 10^{-5} \text{ s}^{-1}$ with the ΔG^\ddagger 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.⁶⁶ 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.⁶⁷⁻⁶⁹ 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

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

| Complex | R | X | DG [‡] (kJ/mol) |
|-----------|----|----|--------------------------------|
| 7a | H | F | 95.2 (22°C, ethanol) |
| 7b | H | Cl | 143 (118°C, <i>n</i> -butanol) |
| 8a | Bn | F | 106.5 (40°C, ethanol) |
| 8b | Bn | Cl | 133 (132°C, chlorobenzene) |



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

Method description : Chiralpak IC, Ethanol, 0,8 ml/min, DAD + CD390nm, 25°C

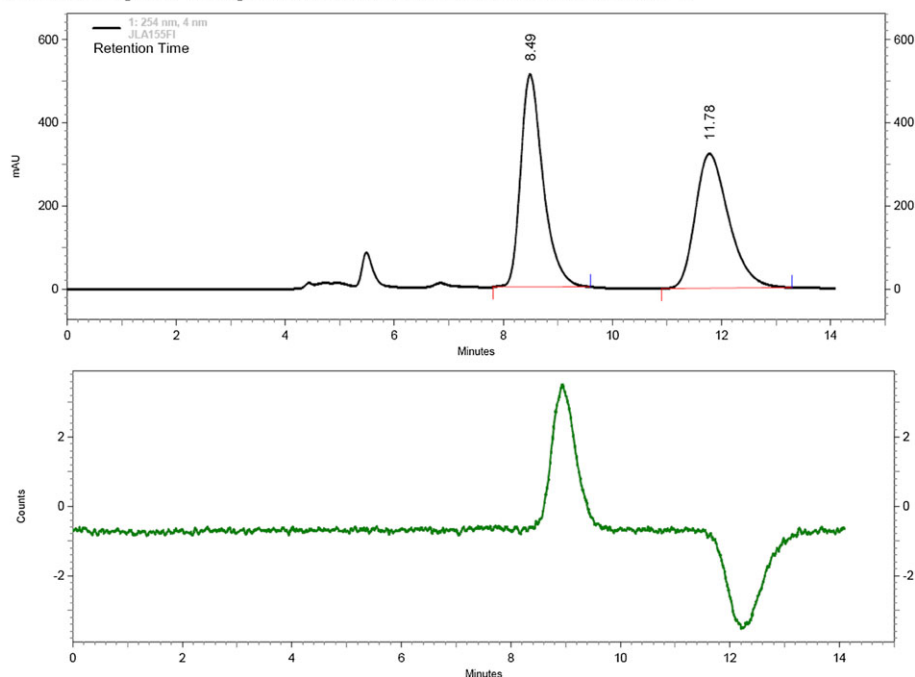
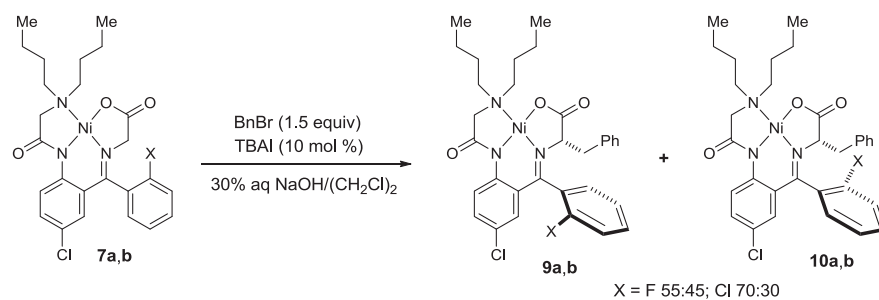


FIGURE 5 Separation of enantiomers of compound **8b** on Chiralpak IC column



SCHEME 7 Diastereoselective benzylation of glycine complexes **7a,b**

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 stereocontrol 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 benzophenone 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 analogs are configurationally permanently ($t_{1/2}$ 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

- Zhou Y, Wang J, Gu Z, et al. Next generation of fluorine-containing pharmaceuticals, compounds currently in phase II–III clinical trials of major pharmaceutical companies: new structural trends and therapeutic areas. *Chem Rev.* 2016;116:422–518.
- Gante J. Peptidomimetics—tailored enzyme inhibitors. *Angew Chem Int Ed.* 1994;33:1699–1720.
- Hruby VJ, Li G, Haskell-Luevano C, Shenderovich M. Design of peptides, proteins, and peptidomimetics in chi space. *Biopolymers.* 1997;43:219–266.
- Hruby VJ, Balse PM. Conformational and topographical considerations in designing agonist peptidomimetics from peptide leads. *Curr Med Chem.* 2000;7:945–970.
- Vagner J, Qu H, Hruby VJ. Tailoring peptidomimetics for targeting protein-protein interactions. *Curr Opin Chem Biol.* 2008; 12:292–296.
- Gibson SE, Guillo N, Tozer MJ. Synthesis of β -alkynyl α -amino acids via palladium-catalyzed alkynylation of unactivated C(sp³)-H bonds. *Tetrahedron.* 1999;55:585
- Vogt H, Brase S. Recent approaches towards the asymmetric synthesis of α,α -disubstituted α -amino acids. *Org Biomol Chem.* 2007;5:406–430.
- Kukhar VP, Sorochinsky AE, Soloshonok VA. Practical synthesis of fluorine-containing α - and β -amino acids: recipes from Kiev, Ukraine. *Future Med Chem.* 2009;1:793–819.
- Aceña JL, Sorochinsky AE, Soloshonok VA. Synthesis and physical-chemical properties of *cis*- and *trans*-1-amino-3-fluoro-3-methylcyclobutanecarboxylic acids. *Synthesis.* 2012;1591–1602.
- Bera K, Namboothiri INN. Asymmetric synthesis of quaternary α -amino acids and their phosphonate analogues. *Asian J Org Chem.* 2014;3:1234–1260.
- Metz AE, Kozlowski MC. Recent advances in asymmetric catalytic methods for the formation of acyclic α,α -disubstituted α -amino acids. *J Org Chem.* 2015;80:1–7.
- Soloshonok VA, Sorochinsky AE. Practical methods for the synthesis of symmetrically α,α -disubstituted- α -amino acids. *Synthesis.* 2010;2319–2344.
- Periasamy M, Gurubrahmam R, Sanjeevakumar N, et al. Convenient methods for the synthesis of chiral amino alcohols and amines. *Chimia.* 2013;67:23–29.

14. Popkov A, De Spiegeleer B. Chiral nickel(II) complexes in the preparation of 11C- and 18F-labelled enantiomerically pure α -amino acids. *Dalton Trans.* 2012;41:1430-1440.
15. Kim Y, Park J, Kim MJ. Dynamic kinetic resolution of amines and amino acids by enzyme-metal cocatalysis. *ChemCatChem.* 2011;3:271-277.
16. Wang J, Zhang L, Jiang H, Chen K, Liu H. Application of nickel(II) complexes to the efficient synthesis of α - or β -amino acids. *Chimia.* 2011;65:919-924.
17. So SM, Kim H, Mui L, Chin J. Mimicking nature to make unnatural amino acids and chiral diamines. *Eur J Org Chem.* 2012;229-241.
18. Turcheniuk KV, Kukhar VP, Roeschenthaler GV, Luis Acena J, Soloshonok VA, Sorochinsky AE. Recent advances in the synthesis of fluorinated aminophosphonates and aminophosphonic acids. *RSC Adv.* 2013;3:6693-6716.
19. Soloshonok VA, Tang X, Hruby VJ, Meervelt LV. Asymmetric synthesis of α,β -dialkyl- α -phenylalanines via direct alkylation of a chiral alanine derivative with racemic α -alkylbenzyl bromides. A case of high enantiomer differentiation at room temperature. *Org Lett.* 2001;3:341-343.
20. Bravo P, Capelli S, Meille SV, et al. Synthesis of optically pure (R)- and (S)- α -trifluoromethyl-alanine. *Tetrahedron: Asymmetry.* 1994;5:2009-2018.
21. Röschenthaler G-V, Kukhar VP, Kulik IB, et al. Asymmetric synthesis of phosphonotrifluoroalanine and its derivatives using *N*-tert-butanesulfinyl imine derived from fluoral. *Tetrahedron Lett.* 2012;53:539-542.
22. Turcheniuk KV, Poliashko KO, Kukhar VP, Rozhenko AB, Soloshonok VA, Sorochinsky AE. Efficient asymmetric synthesis of trifluoromethylated β -aminophosphonates and their incorporation into dipeptides. *Chem Commun.* 2012;48:11519-11521.
23. Bravo P, Farina A, Kukhar VP, et al. Stereoselective additions of α -lithiated alkyl-*p*-tolylsulfoxides to *N*-PMP(fluoroalkyl) aldimines. An efficient approach to enantiomerically pure fluoro amino compounds. *J Org Chem.* 1997;62:3424-3425.
24. Soloshonok VA, Kirilenkov AG, Kukhar VP, Resnati G. Transamination of fluorinated β -keto carboxylic esters. A biomimetic approach to β -polyfluoroalkyl- β -amino acids. *Tetrahedron Lett.* 1993;34:3621-3624.
25. Bravo P, Farina A, Frigerio M, Valdo Meille S, Viani F, Soloshonok VA. New fluorinated chiral synthons. *Tetrahedron: Asymmetry.* 1994;5:987-1004.
26. Belokon YN, Bulychev AG, Vitt SV, et al. General method of diastereo- and enantioselective synthesis of β -hydroxy- α -amino acids by condensation of aldehydes and ketones with glycine. *J Am Chem Soc.* 1985;107:4252-4259.
27. Belokon YN, Zeltzer IE, Bakhmutov VI, et al. Asymmetric synthesis of threonine and partial resolution and retroracemization of α -amino acids via copper(II) complexes of their Schiff bases with (S)-2-N-(*N'*-benzylpropyl)aminobenzaldehyde and (S)-2-N-(*N'*-benzylpropyl)aminoacetophenone. crystal and molecular structure of a copper(II) complex of glycine Schiff base with (S)-2-N-(*N'*-benzylpropyl)aminoacetophenone. *J Am Chem Soc.* 1983;105:2010-2017.
28. Sorochinsky AE, Acena JL, Moriwaki H, Sato T, Soloshonok VA. Asymmetric synthesis of α -amino acids via homologation of Ni(II) complexes of glycine Schiff bases; part 1: alkyl halide alkylations. *Amino Acids.* 2013;45:691-718.
29. Sorochinsky AE, Acena JL, Moriwaki H, Sato T, Soloshonok VA. Asymmetric synthesis of α -amino acids via homologation of Ni(II) complexes of glycine Schiff bases. Part 2: aldol, Mannich addition reactions, deracemization and (S) to (R) interconversion of α -amino acids. *Amino Acids.* 2013;45:1017-1033.
30. Nádorník M, Popkov A. Improved synthesis of the Ni(II) complex of the Schiff base of (S)-2-[N-(*N'*-benzylpropyl) amino] benzophenone and glycine. *Green Chem.* 2002;4:71-72.
31. Collet S, Bauchat P, DanionBougout R, Danion D. Stereoselective, nonracemic synthesis of ω -borono- α -amino acids. *Tetrahedron: Asymmetry.* 1998;9:2121-2131.
32. Debache A, Collet S, Bauchat P, et al. Belokon's Ni(II) complex as a chiral masked glycine for the diastereoselective synthesis of 2-substituted 1-aminocyclopropane carboxylic acids. *Tetrahedron: Asymmetry.* 2001;12:761-764.
33. Kozisek J, Fronc M, Skubak P, et al. Electronic structure of the nickel(II) complex of the Schiff base of (S)-*N*-(2-benzoylphenyl)-1-benzylprolinamide and glycine. *Sect A: Fundam Crystallogr.* 2004;60:510-516.
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.
35. Nádorník M, Langer V, Jirásko R, et al. Syntheses, X-ray, MSn, NMR and CD structure determination of nickel(II) complexes of Schiff bases of (S)-*N*-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide and aromatic α -amino acids. *Polyhedron.* 2008; 27:3477-3483.
36. Saghiyan AS, Hambardzumyan HH, Manasyan LL, Petrosyan AA, Maleev VI, Peregudov AS. Diastereoselective synthesis of anti- β -substituted α -aminobutanoic acids via Michael addition reactions of nucleophiles to new chiral Ni(II) complexes of dehydroaminobutanoic acid. *Synth Commun.* 2005;35:449-459.
37. Saghiyan AS, Manasyan LL, Geolchanyan AV, et al. Asymmetric synthesis of anti-diastereoisomers of β -heterocycle substituted (S)- α -aminobutyric acids. *Tetrahedron: Asymmetry.* 2006;17: 2743-2753.
38. Saghiyan AS, Dadayan SA, Petrosyan SG, et al. New chiral Ni^{II} complexes of Schiff's bases of glycine and alanine for efficient asymmetric synthesis of α -amino acids. *Tetrahedron: Asymmetry.* 2006;17:455-467.
39. Hung K, Harris PWR, Brimble MA. Synthesis of methyl *N*-boc-(2S,4R)-4-methylpipercolate. *J Org Chem.* 2010;75:8728-8731.
40. Tang X, Soloshonok VA, Hruby VJ. Convenient, asymmetric synthesis of enantiomerically pure 2',6'-dimethyltyrosine (DMT) via alkylation of chiral equivalent of nucleophilic glycine. *Tetrahedron: Asymmetry.* 2000;11:2917-2925.
41. Soloshonok VA, Tang X, Hruby VJ. Large-scale asymmetric synthesis of novel sterically constrained 2',6'-dimethyl- and $\alpha,2',6'$ -trimethyltyrosine and β -phenylalanine derivatives via

- alkylation of chiral equivalents of nucleophilic glycine and alanine. *Tetrahedron*. 2001;57:6375-6382.
42. Soloshonok VA, Cai C, Hruby VJ. (*S*)- or (*R*)-3-(*E*-Enoyl)-4-phenyl-1,3-oxazolidin-2-ones: ideal Michael acceptors to afford a virtually complete control of simple and face diastereoselectivity in addition reactions with glycine derivatives. *Org Lett*. 2000;2:747-750.
43. Soloshonok VA, Cai C, Hruby VJ. A practical asymmetric synthesis of enantiomerically pure 3-substituted pyroglutamic acids and related compounds. *Angew.Chem Int Ed*. 2000;39:2172-2175.
44. Soloshonok VA, Avilov DV, Kukhar VP, et al. Asymmetric aldol reactions of chiral Ni(II)-complex of glycine with aliphatic aldehydes. Stereodivergent synthesis of syn-(2*S*)- and syn-(2*R*)- β -alkylserines. *Tetrahedron: Asymmetry*. 1995;6:1741-1756.
45. Soloshonok VA, Avilov DV, Kukhar VP. Asymmetric aldol reactions of trifluoromethyl ketones with a chiral Ni(II) complex of glycine: stereocontrolling effect of the trifluoromethyl group. *Tetrahedron*. 1996;52:12433-12442.
46. Kawamura A, Moriwaki H, Rösenthaller G-V, Kawada K, Aceña JL, Soloshonok VA. Synthesis of (2*S*,3*S*)- β -(trifluoromethyl)- α,β -diamino acid by Mannich addition of glycine Schiff base Ni(II) complexes to *N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetalimine. *J Fluorine Chem*. 2015;171:67-72.
47. Soloshonok VA, Avilov DV, Kukhar VP, Meervelt LV, Mischenko N. Highly diastereoselective aza-aldol reactions of a chiral Ni(II) complex of glycine with imines. An efficient asymmetric approach to 3-perfluoroalkyl-2,3-diamino acids. *Tetrahedron Lett*. 1997;38:4671-4674.
48. Soloshonok VA, Yamada T, Ueki H, et al. Operationally convenient, efficient asymmetric synthesis of enantiomerically pure 4-aminoglutamic acids via methylene dimerization of chiral glycine equivalents with dichloromethane. *Tetrahedron*. 2006;62:6412-6419.
49. Taylor SM, Yamada T, Ueki H, Soloshonok VA. Asymmetric synthesis of enantiomerically pure 4-aminoglutamic acids via methylenedimerization of chiral glycine equivalents with dichloromethane under operationally convenient conditions. *Tetrahedron Lett*. 2004;45:9159-9162.
50. Kawashima A, Xie C, Mei H, et al. Asymmetric synthesis of (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid by sequential S_N2-S_N2' dialkylation of (*R*)-*N*-(benzyl)proline-derived glycine Schiff base Ni(II) complex. *RSC Adv*. 2015;5:1051-1058.
51. Kawashima A, Shu S, Takeda R, et al. Advanced asymmetric synthesis of (1*R*,2*S*)-1-amino-2-vinylcyclopropanecarboxylic acid by alkylation/cyclization of newly designed axially chiral Ni(II) complex of glycine Schiff base. *Amino Acids*. 2016;48:973-986.
52. Soloshonok VA, Ellis TK, Ueki H, Ono T. Resolution/deracemization of chiral α -amino acids using resolving reagents with flexible stereogenic centers. *J Am Chem Soc*. 2009;131:7208-7209.
53. Sorochinsky AE, Ueki H, Aceña JL, Ellis TK, Moriwaki H, Soloshonok VA. Chemical approach for interconversion of (*S*)- and (*R*)- α -amino acids. *Org Biomol Chem*. 2013;11:4503-4507.
54. Zhou S, Wang J, Chen X, Aceña JL, Soloshonok VA, Liu H. Chemical kinetic resolution of unprotected β -substituted β -amino acids using recyclable chiral ligands. *Angew Chem Int Ed*. 2014;53:7883-7886.
55. Ellis TK, Ueki H, Yamada T, Ohfuné Y, Soloshonok VA. Design, synthesis, and evaluation of a new generation of modular nucleophilic glycine equivalents for the efficient synthesis of sterically constrained α -amino acids. *J Org Chem*. 2006;71:8572-8578.
56. Soloshonok VA, Ueki H, Yamada T, Ohfuné Y. Application of modular nucleophilic glycine equivalents for truly practical asymmetric synthesis of β -substituted pyroglutamic acids. *Tetrahedron Lett*. 2005;46:1107-1110.
57. Jörres M, Chen X, Aceña JL, et al. Asymmetric synthesis of α -amino acids under operationally convenient conditions. *Adv Synth Catal*. 2014;356:2203-2208.
58. Bremerich M, Bolm C, Raabe G, Soloshonok VA. Design, synthesis, and evaluation of *N*-(*tert*-butyl)-alanine-derived chiral ligands—aspects of reactivity and diastereoselectivity in the reactions with α -amino acids. *Eur J Org Chem*. 2017;3211-3221.
59. Takeda R, Kawamura A, Kawashima ST, et al. Chemical dynamic kinetic resolution and *S/R* interconversion of unprotected α -amino acids. *Angew Chem Int Ed*. 2014;53:12214-12217.
60. Takeda R, Kawamura A, Kawashima A, et al. Design and synthesis of (*S*)- and (*R*)- α -(phenyl)ethylamine-derived NH-type ligands and their application for the chemical resolution of α -amino acids. *Org Biomol Chem*. 2014;12:6239-6249.
61. Nian Y, Wang J, Moriwaki H, Soloshonok VA, Liu H. Analysis of crystallographic structures of Ni(II) complexes of α -amino acid Schiff bases: elucidation of the substituent effect on stereochemical preferences. *Dalton Trans*. 2017;46:4191-4198.
62. Jörres M, Aceña JL, Soloshonok VA, Bolm C. Asymmetric carbon-carbon bond formation under solventless conditions in ball mills. *ChemCatChem*. 2015;7:1265-1269.
63. Ueki H, Ellis TK, Martin CH, Soloshonok VA. Efficient large-scale synthesis of picolinic acid-derived nickel(II) complexes of glycine. *Eur J Org Chem*. 2003;1954-1957.
64. Ueki H, Ellis TK, Martin CH, Bolene SB, Boettiger TU, Soloshonok VA. Improved synthesis of proline-derived Ni(II) complexes of glycine: versatile chiral equivalents of nucleophilic glycine for general asymmetric synthesis of α -amino acids. *J Org Chem*. 2003;68:7104-7107.
65. Moore JL, Taylor SM, Soloshonok VA. An efficient and operationally convenient general synthesis of tertiary amines by direct alkylation of secondary amines with alkyl halides in the presence of Huenig's base. *ARKIVOC*. 2005;287-292.
66. Roussel C, Blaive B, Gallo R, Metzger J, Sandström J. Dynamic stereochemistry at sp^2-sp^3 bonds part II[†]—the importance of ground-state strain in the determination of apparent spatial requirements of substituents. *Org Magnetic Resonance*. 1980;14:166-170.
67. Suzuki Y, Takahashi I, Dobashi Y, Hasegawa H, Roussel C, Kitagawa O. Relationship between rotational barriers and

- structures in N-C axially chiral 3,4-dihydroquinolin-2-one and 3,4-dihydrobenzoquinolin-2-one. *Tetrahedron Lett.* 2015;56: 132-135.
68. Belot V, Farran D, Jean M, Albalat M, Vanthuynne N, Roussel C. Steric scale of common substituents from rotational barriers of N-(*o*-substituted aryl)thiazoline-2-thione atropisomers. *J Org Chem.* 2017;82:10188-10200.
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.