Synthesis and stereochemical assignments of diastereomeric Ni(II) complexes of glycine Schiff base with (R)-2-(N-{2-[N-alkyl-N-(1-phenylethyl)-amino]acetyl}amino)benzophenone; a case of configurationally stable stereogenic nitrogen

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Abstract
A family of chiral ligands derived from α-phenylethylamine and 2-aminobenzophenone were prepared by alkylation of the nitrogen atom. Upon reaction with glycine and a Ni(II) salt, these ligands were transformed into diastereomeric complexes, as a result of the configurational stability of the stereogenic nitrogen atom. Different diastereomeric ratios were observed depending on the substituent R introduced in the starting ligand, and stereochemical assignments were based on X-ray analysis, along with NMR studies and optical rotation measurements.

Introduction
Since the beginning of organic chemistry, α-amino acids (α-AAs) have been an attractive target for synthetic chemists. The reported synthetic methods for assembling the RCH(NH2)COOH units have been explored in great detail. Structurally complex natural or tailor-made [1] α-AAs can be prepared using the currently available methodologies [2-30];
however, the chemistry of α-AAs continues to evolve [31-38]. Many of the reported synthetic methodologies have shown preference for adjusting stoichiometry or developing catalytic reactions to achieve a specific chemical and stereochemical outcome [2-30]. On the other hand, a measure of the value of a synthetic method, regardless of its stoichiometric or catalytic requirements, is the cost of the final product. In this regard, the synthetic preparation of α-AAs is far behind the biocatalytic methods that dominate their industrial production [39,40]. It was emphasized, in relatively recent reviews [39-41], that currently available, purely chemical methods for preparation of α-AAs are prohibitively expensive. The advantage of biocatalytic processes is that they can be conducted under operationally convenient conditions [42,43] and therefore are more economical. Consequently, the current emphasis in developing synthetic procedures for preparation of α-AAs is focused on simplicity of the experimental procedures and cost of the target α-AAs.

Among various chiral nucleophilic glycine equivalents, the Ni(II) complex of glycine Schiff base 1 (Figure 1) possesses some attractive characteristics that underscore its potential commercial application [44-47]. In particular, homologation of Ni(II) complex 1 via alkyl halide alkylation [48-50], aldol [51-53], Mannich [54,55] and Michael [56-58] addition reactions can be conducted at room temperature and without specially controlled conditions. Achiral derivatives of 1, compounds 2 [59,60] and 3 [61-63], show even greater features of practicability and found application in the convenient synthesis of symmetrically α,α-disubstituted α-AAs [64,65], homologation under asymmetric PTC [66,67] and Michael addition reactions [68-72]. Nevertheless, the commercial application of chiral complex 1 is rather limited. The major shortcomings of compound 1 are: problematic scale up of its synthesis, partial racemization of the N-(benzyl)proline moiety and undesirable stereochemical outcomes. To overcome these deficiencies we initiated a project aiming to design a novel and advanced structural type of Ni(II) complexes using an inexpensive and nonracemizable chiral auxiliary. As the first step in this direction, here we describe the preparation of Ni(II) complexes of glycine Schiff base with α-phenylethylamine-derived ligands. One unusual feature of these new glycine-Ni(II) complexes is that they, along with the chiral amine residue, have a configurationally stable stereogenic nitrogen, leading to formation of two diastereomers. Consequently, stereochemical assignments of the diastereomeric products, based on crystallographic data, and sense of stereochemical preferences, were an important part of this work.

Results and Discussion

Taking advantage of the recently developed new generation of modular ligands/complexes 3 [73,74], we have designed ligands 4a–f (Scheme 1) derived from α-phenylethylamine [75,76], as the source of chirality. As one can see from Scheme 1, the synthesis of ligands 4a–f involves a set of very simple reactions, occurring with virtually quantitative yields [77,78].

![Scheme 1: Synthesis of chiral ligands 4a–f.](image)

To prepare the target Gly-Ni(II) complexes, ligands 4a–f were heated in MeOH in the presence of glycine, Ni(OAc)₂ and K₂CO₃ (Scheme 2). To compare the results, all reactions were conducted under the same conditions. The reaction mixtures were poured into water and the products were simply filtered off.

The chemical and stereochemical outcomes of the reactions, presented in Table 1, were rather unexpected. First of all, one can see a clear tendency that the increase in steric bulk of the substituent R has a significant effect on the reaction rates. In the case of R = H and Me (4a,b; Table 1, entries 1 and 2) the reactions were completed in 1 hour and the corresponding Ni(II) complexes were obtained in high yields. Under the same condi-
that the complex(es) obtained in the reaction of NH (bearing ligand R = H) had unprecedentedly low solubility. During the complex formation reaction, the product(s) precipitated from the reaction mixture and were isolated by filtration. Solvents such as DMF, DMSO, and acetic acid were used in an attempt to dissolve the product without success. The stereochemical outcome in this reaction remains unclear.

Since the reactions were conducted in open atmosphere, formation of byproducts (S)-7a–f (5–20%) were observed in all cases. Compounds (S)-7a–f result from the reaction of atmospheric oxygen with the corresponding enolates derived from glycine complexes 5 and 6 and the basic reaction conditions [79,80]. Formation of 4-phenylquinazoline derivatives (S)-7a–f can be prevented by conducting the reactions in oxygen-free atmosphere. Another general trend is apparent when considering the observed optical rotations of the diastereomeric products 5 and 6. In all cases, the major diastereomers 5 had low-magnitude rotations as compared with high-magnitude dextrorotatory rotations of 6. This trend can be used to assign the configurations of products 5 and 6 and related compounds. It is interesting to note that the difference in optical rotation between diastereomers 5e and 6e was the least pronounced in the series. Most likely, some similarity in the structure of N-benzyl and N-α-(methyl)benzyl groups results in low impact on the optical rotation of diastereomers 5e and 6e.

Knowledge of one of the stereocenters in diastereomers 5 and 6 allowed us to use X-ray crystallography to determine the absolute configuration of the major product 5b [81]. The structure presented in Figure 2 shows its (S5R5) absolute configuration. Accordingly, the second product, diastereomer 6b, has (S5S5) configuration. The X-ray structure of 5b revealed the complex is not fully planar as expected. The benzophenone chelate ring system deviates from planarity by 14.4° (0.16 e.s.d.). The torsion angle of Ni2–O5–C10–C29 is +10.9° (0.16 e.s.d.).

As we have mentioned above, there is a great degree of similarity in the chiroptical properties of complexes 5b–e and 6b–e, sufficient to make the corresponding stereochemical assignments. Moreover, there is also another general trend observed in the 1H NMR spectra of compounds 5 and 6. In particular, as is evident form Figure 3, the α-phenethylamine moiety’s methyl group is located in relatively close proximity to the Ni(II) atom, causing the methyl protons to shift more downfield [82-85]. Accordingly, in all 1H NMR spectra of com-

![Scheme 2: Preparation of diastereomeric Ni(II) complexes 5a–f and 6a–f.](image)

**Table 1: Preparation of diastereomeric Ni(II) complexes 5a–f and 6a–f.**

| Entry | R     | S/6 ratio<sup>a</sup> | Yield (%) | [α]<sup>b</sup>  |
|-------|-------|------------------------|-----------|-------------------|
|       |       | 5/6                    |           | 5                 |
| 1     | H (a) | N/A<sup>c</sup>        | 87.4      | N/A<sup>c</sup>  |
| 2     | Me (b) | 57/43                  | 96.9      | +88.6             |
| 3     | Et (c) | 61/39                  | 67.7      | −150.8            |
| 4     | n-Pr (d) | 74/26                 | 70.1      | −55.0             |
| 5     | Bn (e) | 76/24                  | 31.5<sup>d</sup> | +303.6         |
| 6     | Ph(CH<sub>2</sub>)<sub>2</sub> (f) | 67/33       | 12.1<sup>e</sup> | N/A<sup>g</sup> |

<sup>a</sup>Determined by 1H NMR analysis on the crude reaction mixtures.  
<sup>b</sup>Measured in dichloromethane, 25 °C.  
<sup>c</sup>The compound could not be dissolved in any solvent.  
<sup>d</sup>The reaction was incomplete and the starting ligand was also recovered.  
<sup>e</sup>The diastereomers could not be separated.
to avoid the formation of byproducts, resulting from the oxidation complexes should be conducted under oxygen-free conditions

4) Synthesis of this type of Ni(II)

steric bulk of the substituent R on the α-phenylethylamine has a negative effect on the reaction rates and a positive configurational stability of the stereogenic nitrogen. 2) The formation of diastereomeric glycine Schiff base products due to the amino)acetamide (4b): From 4a (6.14 g, 17.23 mmol) and MeI (4.3 mL, 68.52 mmol), 4.61 g (72.4%) of 4b. White solid. Mp 80–82 °C; [α]D 25 +23.7 (c 1.55, CHCl3); 1H NMR (300 MHz, CDCl3) δ 1.54 (d, J = 6.9 Hz, 3H), 2.44 (s, 3H), 3.12 (d, J = 16.8 Hz, 1H), 3.25 (d, J = 16.8 Hz, 1H), 3.82 (q, J = 6.6 Hz, 1H), 6.87–6.92 (m, 1H), 7.15–7.22 (m, 1H), 7.25–7.28 (m, 2H), 7.50–7.72 (m, 7H), 7.73–7.92 (m, 2H), 8.69 (d, J = 8.7 Hz, 1H), 11.67 (br, 1H); 13C NMR (75 MHz, CDCl3) δ 18.4, 40.8, 58.7, 63.5, 121.5, 122.1, 125.1, 127.1, 127.6, 128.2, 130.0, 132.3, 132.5, 133.2, 138.4, 139.0, 142.8, 171.1, 197.9; HRMS: [M + H]+ calcd for C24H25N2O6, 373.1916; found, 373.1923.

3) The optimal size of the R group is n-Pr or Bn. 4) Synthesis of this type of Ni(II) complexes should be conducted under oxygen-free conditions to avoid the formation of byproducts, resulting from the oxidation of the corresponding enolates. 5) The (SCR′N) stereochemistry of the Ni(II) complexes is generally preferred. Drawing from these results, an improved design of new ligands is currently under investigation in our laboratories.

Experimental
General procedure for the preparation of ligands 4b–f
In analogous manner as previously reported [77], secondary amine 4a [78] (1 equiv), N,N-diisopropylethylamine (1.5 equiv), alkyl halide (1.5–3.5 equiv) and 10 mL of MeCN were placed in a round bottom flask and stirred at room temperature under nitrogen. After completion of the reaction (monitored by TLC), the reaction mixture was evaporated to dryness under vacuum. The residue was dissolved in 5 mL of CH2Cl2 and washed with 5 mL of water. The aqueous layer was washed with 3 × 5 mL fractions of CH2Cl2. The collected organic fractions were dried over MgSO4 and the solvent was removed under vacuum to yield the crude product. Analytically pure samples of 4b–f were obtained by column chromatography (Hex/EtOAc).

(5)-N-(2-benzoylphenyl)-2-(methyl-(1-phenylethyl)-

Combining together the crystallographic, chiroptical and 1H NMR data of compounds 5 and 6, we can confidently assign the (SCR′N) absolute configuration to all products 5b–e and (SCR′N) stereochemistry to the complexes 6b–e.

Conclusion
In conclusion, this exploratory work has revealed that: 1) Application of α-phenylethylamine as the source of stereochemistry information in the novel Ni(II) complexes, results in the formation of diastereomeric glycine Schiff base products due to the configurational stability of the stereogenic nitrogen. 2) The steric bulk of the substituent R on the α-phenylethylamine residue has a negative effect on the reaction rates and a positive influence on the stereochemical outcome. 3) The optimal size of the R group is n-Pr or Bn. 4) Synthesis of this type of Ni(II) complexes should be conducted under oxygen-free conditions to avoid the formation of byproducts, resulting from the oxidation of the corresponding enolates. 5) The (SCR′N) stereochemistry of the Ni(II) complexes is generally preferred. Drawing from these results, an improved design of new ligands is currently under investigation in our laboratories.

General procedure for the preparation of Ni(II) complexes 5b–f and 6b–f
To a flask containing a methanol solution of ligand 4b–f (1 equiv), Ni(OAc)2·4H2O (2 equiv) and glycine (5.0 equiv), was added K2CO3 (9 equiv), and the reaction mixture was stirred at 60–70 °C. The progress of the reaction was monitored by TLC and upon completion (consumption of the reagent 4), the reaction mixture was poured into ice water. The target product was extracted three times with CH2Cl2. The combined organic layer was dried over anhydrous MgSO4 and evaporated under vacuum. After evaporation of the solvents, the target complexes 5b–f and 6b–f were obtained in diastereomerically pure form by separation on silica-gel column chromatography. 6b: From 4b (512 mg, 1.375 mmol), 647.3 mg (96.9 %) of a 57:43 mixture of 5b and 6b. Data of 5b: Red solid. Mp
Supporting Information
Supporting Information File 1
Experimental data for compounds 4c-f, 5c-e and 6c-e.
[http://www.beilstein-journals.org/bioc/content/supplementary/1860-5397-10-41-S1.pdf]

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References
1. Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Van Meerwold, L.; Mischenko, N. Tetrahedron 1999, 55, 12031–12044. doi:10.1016/S0040-4020(99)00711-5
2. Schößkopf, U.; Groth, U.; Deng, C. Angew. Chem., Int. Ed. Engl. 1981, 20, 798–799. doi:10.1002/anie.198107981
3. Williams, R. M.; Sinclair, P. J.; Zhai, W. J. Am. Chem. Soc. 1986, 110, 482–483. doi:10.1021/ja010160a027
4. Fitzi, R.; Seebach, D. Tetrahedron 1988, 44, 5277–5292. doi:10.1016/S0040-4020(01)80639-6
5. O’Donnell, M. J.; Eckrich, T. M. Tetrahedron Lett. 1978, 19, 4625–4628. doi:10.1016/S0040-4020(01)85688-4
6. Soloshonok, V. A.; Hayashi, T.; Ishikawa, K.; Nagashima, N. Tetrahedron Lett. 1994, 35, 1055–1058. doi:10.1016/S0040-4020(01)79964-3
7. Lygo, B.; Wainwright, P. G. Tetrahedron Lett. 1997, 38, 8595–8598. doi:10.1016/S0040-4020(97)10293-3
8. Corey, E. J.; Xu, F.; Noe, M. C. J. Am. Chem. Soc. 1997, 119, 12414–12415. doi:10.1021/ja973137Y
9. Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Ishikawa, K.; Nagashima, N.; Hayashi, T. J. Org. Chem. 1997, 62, 3470–3479. doi:10.1021/jo9623402
10. Ooi, T.; Kameda, M.; Maruoka, K. J. Am. Chem. Soc. 1999, 121, 8519–8520. doi:10.1021/ja991062w
11. Chinchilla, R.; Mazoín, P.; Nájera, C. Tetrahedron: Asymmetry 2000, 11, 3277–3281. doi:10.1016/S0957-4166(00)00317-7
12. Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. Angew. Chem., Int. Ed. 2002, 41, 3036–3038. doi:10.1002/1521-3773(20020816)41:16<3036::AID-Anie3036>3.0.CO;2-3
13. Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. Tetrahedron Lett. 2002, 43, 9539–9543. doi:10.1016/S0040-4039(02)02416-4
14. Solładí-Cavalo, A.; Sedó, O.; Salisova, S.; Schmitt, M. Eur. J. Org. Chem. 2002, 3042–3049. doi:10.1002/1099-0690(200209)2002:17<3042::AID-EJOC3042>3.0.CO;2-S
15. Park, H.; Kim, K. M.; Lee, A.; Ham, S.; Nam, W.; Chin, J. J. Am. Chem. Soc. 2007, 129, 1518–1519. doi:10.1021/ja077724g
16. Soloshonok, V. A.; Ellis, T. K.; Ueki, H.; Ono, T. J. Am. Chem. Soc. 2009, 131, 7208–7209. doi:10.1021/ja902605g
17. Sorochinsky, A. E.; Ueki, H.; Aceña, J. L.; Ellis, T. K.; Moriwaki, H.; Sato, T.; Soloshonok, V. A. J. Fluorine Chem. 2013, 152, 114–118. doi:10.1016/j.jfluchem.2013.02.022
18. Sorochinsky, A. E.; Ueki, H.; Aceña, J. L.; Ellis, T. K.; Moriwaki, H.; Sato, T.; Soloshonok, V. A. Org. Biomol. Chem. 2013, 11, 4503–4507. doi:10.1039/c3ob05451a
19. Duthaler, R. O. Tetrahedron 1994, 50, 1539–1600. doi:10.1016/0040-4020(94)90840-1
20. Maruoka, K.; Ooi, T. Chem. Rev. 2003, 103, 3013–3028. doi:10.1021/cr020020e
21. Ma, J.-A. Angew. Chem., Int. Ed. Eng. 2003, 42, 4290–4299. doi:10.1002/anie.200301600
22. Nájera, C.; Sansano, J. M. Chem. Rev. 2007, 107, 4654–4671. doi:10.1021/cr050580o
23. Soloshonok, V. A. Curr. Org. Chem. 2002, 6, 341–364. doi:10.2174/1385272024605014
24. Kukhar, V. P.; Sorochinsky, A. E.; Soloshonok, V. A. Future Med. Chem. 2009, 1, 793–819. doi:10.1555/fmc.09.70
25. Sorochinsky, A. E.; Soloshonok, V. A. J. Fluorine Chem. 2010, 131, 127–139. doi:10.1016/j.jfluchem.2009.09.015
26. Soloshonok, V. A.; Sorochinsky, A. E. Synthesis 2010, 2319–2344. doi:10.1055/s-0029-1220013
27. Aceña, J. L.; Sorochinsky, A. E.; Soloshonok, V. A. Synthesis 2012, 44, 1591–1602. doi:10.1055/s-0031-1289756
28. Aceña, J. L.; Sorochinsky, A. E.; Moriwaki, H.; Sato, T.; Soloshonok, V. A. J. Fluorine Chem. 2013, 155, 21–38. doi:10.1016/j.jfluchem.2013.06.004
29. Sorochinsky, A. E.; Aceña, J. L.; Moriwaki, H.; Sato, T.; Soloshonok, V. A. Amino Acids 2013, 45, 681–718. doi:10.1007/s00726-013-1539-4
30. Sorochinsky, A. E.; Aceña, J. L.; Moriwaki, H.; Sato, T.; Soloshonok, V. A. Amino Acids 2013, 45, 1017–1033. doi:10.1007/s00726-013-1580-3
77. Moore, J. L.; Taylor, S. M.; Soloshonok, V. A. ARKIVOC 2005, No. vi, 287–292. doi:10.3998/ark.5550190.0006.624
78. Soloshonok, V. A.; Ueki, H. Synthesis 2010, 49–56. doi:10.1055/s-0029-1217090
79. Soloshonok, V. A.; Ueki, H. J. Am. Chem. Soc. 2007, 129, 2426–2427. doi:10.1021/ja0671215
80. Soloshonok, V. A.; Acerfa, J. L.; Ueki, H.; Han, J. Beilstein J. Org. Chem. 2012, 8, 1920–1928. doi:10.3762/bjoc.8.223
81. CCDC 943686 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.
82. Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Van Meervelt, L. Tetrahedron 1999, 55, 12045–12058. doi:10.1016/S0040-4020(99)00710-3
83. Belokon, Y. N.; Bulychev, A. G.; Ryzhov, M. G.; Vitt, S. V.; Batsanov, A. S.; Struchkov, Y. T.; Bakhmutov, V. I.; Belikov, V. M. J. Chem. Soc., Perkin Trans. 1 1986, 1865–1872. doi:10.1039/p19860001865
84. Belokon, Y. N.; Bulychev, A. G.; Pavlov, V. A.; Fedorova, E. B.; Tsryapkin, V. A.; Bakhmutov, V. I.; Belikov, V. M. J. Chem. Soc., Perkin Trans. 1 1988, 2075–2083. doi:10.1039/P19880002075
85. Belokon, Y. N.; Maleyev, V. I.; Vitt, S. V.; Ryzhov, M. G.; Kondrashov, Y. D.; Golubev, S. N.; Vauchskii, Y. P.; Kazika, A. I.; Novikova, M. I.; Krasutskii, P. A.; Yurchenko, A. G.; Dubchak, I. L.; Shklover, V. E.; Struchkov, Y. T.; Bakhmutov, V. I.; Belikov, V. M. J. Chem. Soc., Dalton Trans. 1985, 17–26. doi:10.1039/dt8850000017

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