Amino Acids (2014) 46:945–952
DOI 10.1007/s00726-013-1656-0

ORIGINAL ARTICLE

Inexpensive chemical method for preparation of enantiomerically pure phenylalanine

Hiroki Moriwaki · Daniel Resch · Hengguang Li · Iwao Ojima · Ryosuke Takeda · José Luis Aceña · Vadim Soloshonok

Received: 11 October 2013 / Accepted: 17 December 2013 / Published online: 3 January 2014

Abstract Here, we report the most inexpensive procedure for chemical synthesis of enantiomerically pure phenylalanine. As a source of chirality, we use the ultimately inexpensive chiral auxiliary, 1-(phenyl)ethylamine, incorporated into the specially designed ligands which form the corresponding intermediate Ni(II) complexes with racemic phenylalanine. Diastereomerically pure Ni(II) complexes, containing either (*S*)- or (*R*)-phenylalanine, were disassembled to produce enantiomerically pure target amino acid, along with recycling the chiral ligand. All reactions were conducted under operationally convenient conditions, featuring high yields and thus underscoring attractive cost structure of this method.

Keywords Phenylalanine · Schiff bases · Ni(II) complexes · Stereogenic nitrogen · Asymmetric synthesis

H. Moriwaki · D. Resch · H. Li · I. Ojima
Department of Chemistry, Institute of Chemical Biology and Drug Discovery, State University of New York at Stony Brook, Stony Brook, NY 11794-3400, USA

H. Moriwaki · R. Takeda
Hamari Chemicals Ltd., 1-4-29 Kunijima, Higashi-Yodogawa-ku, Osaka 533-0024, Japan

J. L. Aceña · V. Soloshonok (✉)
Department of Organic Chemistry I, Faculty of Chemistry, University of the Basque Country UPV/EHU, 20018 San Sebastián, Spain
e-mail: vadym.soloshonok@ehu.es

V. Soloshonok
IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain

Introduction

Asymmetric synthesis of tailor-made α-amino acids (Soloshonok et al. 1999a) has always been in focus of organic chemistry. Besides being in the league of very special "molecules of life", amino acids play an important role in food and health care industries. In particular, production of many sophisticated pharmaceuticals is based on amino acids as source of chirality and essential functionalities (Wang et al. 2001, 2004; Breuer et al. 2004; Gallos et al. 2005). Truly immense amount of research data on synthesis of amino acids has been reported, featuring virtually all imaginable methodological approaches (O'Donnell and Eckrich 1978; Schöllkopf et al. 1981; Williams et al. 1988; Fitzi and Seebach 1988; Duthaler 1994; Soloshonok et al. 1994, 1997a, 2009a; Lygo and Wainwright 1997; Corey et al. 1997; Ooi et al. 1999; Chinchilla et al. 2000; Soloshonok 2002; Park et al. 2002, 2007; Shibuguchi et al. 2002; Solladié-Cavallo et al. 2002; Maruoka and Ooi 2003; Ma 2003; Nájera and Sansano 2007; Kukhar et al. 2009; Sorochinsky and Soloshonok 2010; Soloshonok and Sorochinsky 2010; Aceña et al. 2012, 2013; Sorochinsky et al. 2013a, b). However, high cost of preparation of amino acids via asymmetric synthesis renders the purely chemical methods prohibitively expensive for large-scale production (Fogassy et al. 2005). Therefore, the current industrial preparation of enantiomerically pure amino acids is based on chemical synthesis of racemates followed by enzymatic resolutions (Breuer et al. 2004; Soloshonok and Izawa 2009). The major advantage of biocatalytic processes is that they can be conducted under operationally convenient conditions (Ellis et al. 2003a; Soloshonok et al. 2006) and therefore have attractive cost structure. Consequently, to devise a sound synthetic methodology that can rival enzymatic reactions, one should pay due attention to the reaction

conditions and cost of the reagents. In context of practicality, the Ni(II) complex of glycine Schiff base **1** (Fig. 1) (Belokon et al. 1983, 1985a, 1998; Ueki et al. 2003a) has some attractive features. In particular, its homologation via alkyl halide alkylation (Tang et al. 2000, Qiu et al. 2000; Soloshonok et al. 2001), aldol (Soloshonok et al. 1993, 1995, 1996), Mannich (Soloshonok et al. 1997b; Wang et al. 2008) and Michael (Soloshonok et al. 1999b, 2000a, 2005a) addition reactions can be conducted at ambient temperature in commercial grade solvents. Achiral analogs of **1**, complexes **2a**,**b** (Ueki et al. 2003b) are also useful glycine equivalents for homologation under asymmetric PTC (Belokon et al. 2001, 2003) and Michael addition reactions (Soloshonok et al. 2000b, 2004; Yamada et al. 2006).

Recently, we introduced a modular design (Soloshonok et al. 2005b, c; Ellis et al. 2006) of a new generation of nucleophilic glycine equivalents of general formula **3** (Fig. 2). This approach offers remarkable structural flexibility allowing to control physicochemical properties and reactivity of the corresponding Ni(II) complexes (Ellis et al. 2003b, Yamada et al. 2008; Soloshonok et al. 2009b). Apparent success has been achieved in application of this design for preparation of ligand **4**, useful for deracemization of racemic amino acids (Soloshonok et al. 2009a) and (*S*)- to (*R*)-enantiomers interconversion (Sorochinsky et al. 2013a, b). Here, we report application of this new type of ligands/Ni(II) complexes for development of the most inexpensive chemical preparation of enantiomerically pure amino acids, demonstrated on example of phenylalanine.

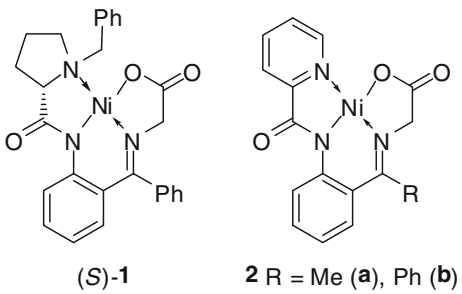


Fig. 1 Chiral **1** and achiral **2a**,**b** equivalents of nucleophilic glycine

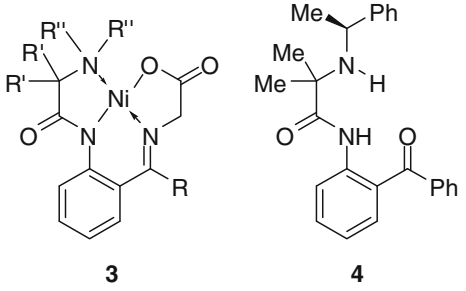


Fig. 2 New generation of Ni(II)-complexes of amino acids **3** and **4**

Materials and methods

General procedure for preparation of ligands **10a,b**

Secondary amine **9** (Soloshonok and Ueki 2010) (0.500 g, 1 equiv), *N,N*-diisopropylethylamine (1.5 equiv), alkyl halide (1.1 equiv in the case of BnBr and 3.5 equiv in the case of MeI) 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 CH_2Cl_2 and washed with 5 mL of water. The aqueous layer was washed with 3 × 5 mL fractions of CH_2Cl_2. The collected organic fractions were dried over $MgSO_4$ and the solvent was removed under vacuum to yield the crude product. Analytically pure samples of **10a,b** were obtained by column chromatography (Hex/EtOAc).

10a: Mp 80–82 °C; $[\alpha]_D^{25}$ +23.7 (*c* 1.55, $CHCl_3$). ^{1}H-NMR 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 (bs, 1H).

10b: Oil; $[\alpha]_D^{25}$ +28.1 (*c* 3.81, $CHCl_3$). ^{1}H-NMR δ 1.43 (d, J = 6.9 Hz, 3H), 1.47 (s, 1H), 3.02 (d, J = 16.8 Hz, 1H), 3.22 (d, J = 16.8 Hz, 1H), 3.36 (d, J = 12.9 Hz, 1H), 3.72 (d, J = 13.2 Hz, 1H), 3.84 (q, J = 7.2 Hz, 1H), 6.96–7.01 (m, 4H), 7.13–7.20 (m, 3H), 7.37–7.48 (m, 8H), 7.55–7.57 (m, 1H), 7.78–7.81 (m, 2H), 8.44 (dd, J = 7.5, 1.2 Hz, 1H), 11.22 (bs, 1H).

General procedure for preparation of Ni(II)-complexes **11a,b–14a,b** by the reaction of ligands **10a,b** with *rac*-phenylalanine

To a flask containing methanol solution of ligand (*S*)-**10a**,**b** (1 equiv), $NiCl_2$ (2 equiv) and racemic phenylalanine (2.0 equiv), were added K_2CO_3 (6 equiv), and the reaction mixture was stirred at 50 °C. The progress of the reaction was monitored by TLC and upon completion (consumption of ligand **10a**,**b**), the reaction mixture was poured into ice water containing 5 % acetic acid. The target product was extracted three times with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated under vacuum. After evaporation of the solvents and silica gel column chromatography, the target complexes **11a,b–14a,b** were obtained in diastereomerically pure form.

(S_C,R_N,S_C)-**11a**: Mp 164–170 °C; $[\alpha]_D^{25}$ +1711.6 (*c* 0.01, $CHCl_3$). ^{1}H-NMR δ 1.46 (3H, s), 2.25 (d, J = 7.2 Hz, 3H), 2.64 (dd, J = 13.5, 5.1 Hz, 1H), 2.86 (d, J = 16.2 Hz, 1H), 3.03 (dd, J = 13.5, 3.3 Hz, 1H), 3.07 (d, J = 16.2 Hz, 1H), 3.94 (q, J = 6.9 Hz, 1H), 4.29 (t,

J = 1.8 Hz, 1H), 6.76–6.80 (m, 2H), 7.06–7.08 (m, 1H), 7.16–7.19 (m, 2H), 7.26–7.36 (m, 5H), 7.46–7.60 (m, 7H), 8.44 (d, J = 8.4 Hz, 1H). ^{13}C-NMR δ 18.7, 38.9, 39.6, 62.4, 65.6, 71.3, 121.1, 123.6, 127.0, 127.2, 127.6, 127.7, 128.4, 128.8, 129.0, 129.1, 129.2, 130.0, 130.1, 131.5, 132.7, 133.4, 133.6, 133.7, 136.2, 142.7, 170.7, 174.7, 178.1.

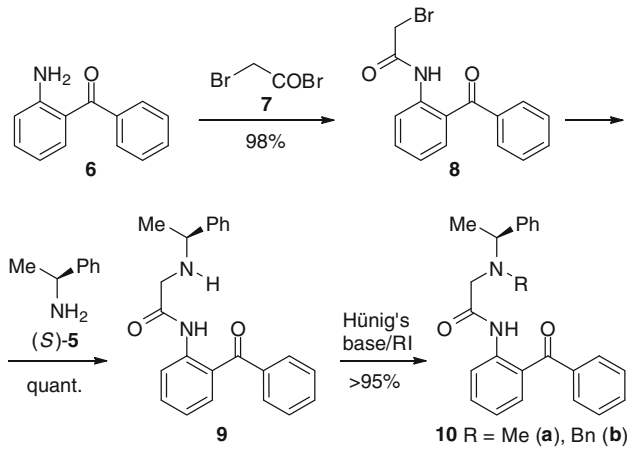
(S_C,R_N,S_C)-**11b**: Mp 228–229 °C; $[\alpha]_D^{25}$ +1417.4 (c 0.01, $CHCl_3$). ^{1}H-NMR δ 2.22 (d, J = 6.9 Hz, 3H), 2.76 (d, J = 17.1 Hz, 1H), 2.78 (d, J = 12.0 Hz, 1H), 3.10–3.30 (m, 2H), 3.95 (q, J = 6.6 Hz, 1H), 4.11 (d, J = 12.0 Hz, 1H), 4.12 (d, J = 17.1 Hz, 1H), 4.20 (t, J = 6.3 Hz, 1H), 6.57–6.61 (m, 3H), 6.94–7.18 (m, 4H), 7.21–7.38 (m, 13H), 7.49–7.53 (m, 2H), 8.07 (d, J = 7.8 Hz, 1H), 8.31 (d, J = 7.2 Hz, 2H). ^{13}C-NMR δ 20.1, 40.7, 56.3, 65.1, 65.9, 71.5, 120.4, 123.2, 125.6, 127.1, 127.4, 127.8, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.6, 129.8, 130.4, 131.5, 132.2, 133.3, 134.0, 135.0, 135.1, 135.6, 142.3, 171.3, 178.1, 178.4.

(S_C,S_N,S_C)-**12a**: Mp 216–218 °C; $[\alpha]_D^{25}$ +1550.8 (c 0.01, $CHCl_3$). ^{1}H-NMR δ 1.67 (d, J = 6.9 Hz, 3H), 2.42 (d, J = 15.9 Hz, 1H), 2.63 (s, 3H), 3.08 (dd, J = 12.0, 5.1 Hz, 1H), 3.19 (dd, J = 14.2, 4.5 Hz, 1H), 3.49 (q, J = 6.9 Hz, 1H), 3.99 (d, J = 15.9 Hz, 1H), 4.25 (t, J = 6.0 Hz, 1H), 6.77–6.88 (m, 3H), 7.08–7.11 (m, 2H), 7.21–7.35 (m, 8H), 7.40–7.43 (m, 4H), 7.51–7.54 (m, 3H), 8.65 (d, J = 8.7 Hz, 1H).

(S_C,R_N,R_C)-**13a**: Mp 104–105 °C; $[\alpha]_D^{25}$ −1634.1 (c 0.01, $CHCl_3$). ^{1}H-NMR δ 1.74 (s, 3H), 1.97 (d, J = 6.9 Hz, 3H), 2.66 (dd, J = 13.2, 5.4 Hz, 1H), 2.91 (d, J = 16.8 Hz, 1H), 2.99 (dd, J = 13.2, 3.0 Hz, 1H), 3.20 (d, J = 16.8 Hz, 1H), 3.43 (q, J = 6.9 Hz, 1H), 4.24 (t, J = 2.1 Hz, 1H), 6.76 (d, J = 4.2 Hz, 2H), 7.06 (d, J = 6.6 Hz, 1H), 7.22–7.31 (m, 6H), 7.42–7.63 (m, 10H), 8.14 (d, J = 8.4 Hz, 1H).

(S_C,R_N,R_C)-**13b**: Mp 261–264 °C; $[\alpha]_D^{25}$ −1756.4 (c 0.01, $CHCl_3$). ^{1}H-NMR δ 2.14 (d, J = 6.6 Hz, 3H), 2.71 (d, J = 16.2 Hz, 1H), 3.00–3.15 (m, 2H), 3.23 (d, J = 14.4 Hz, 1H), 3.58 (d, J = 16.2 Hz, 1H), 3.69 (d, J = 14.2 Hz, 1H), 6.67–6.72 (m, 2H), 7.00–7.24 (m, 5H), 7.26–7.75 (m, 17H). ^{13}C-NMR δ 20.1, 39.0, 60.1, 62.5, 64.6,71.1, 120.7, 124.8, 127.0, 127.2, 127.6, 128.2, 128.4, 128.6, 128.9, 129.0, 129.9, 130.9, 131.5, 131.8, 132.0, 133.0, 133.8, 136.5, 137.0, 142.3, 170.6, 175.7, 177.8.

(S_C,S_N,R_C)-**14b**: Mp 245–247 °C; $[\alpha]_D^{25}$ −1880.8 (c 0.01, $CHCl_3$). ^{1}H-NMR δ 1.54 (d, J = 6.9 Hz, 3H), 2.60–2.75 (m, 2H), 3.32 (d, J = 17.7 Hz, 1H), 3.58 (d, J = 11.7 Hz, 1H), 3.83 (t, J = 7.2 Hz, 1H), 4.32–4.38 (m, 1H), 4.33 (d, J = 16.5 Hz, 1H), 4.41 (d, J = 11.7 Hz, 1H), 5.81 (d, J = 7.5 Hz, 1H), 6.39–6.56 (m, 4H), 6.98–7.72 (m, 8H), 7.28–7.64 (m, 8H), 8.13 (d, J = 7.8 Hz, 1H), 8.20 (d, J = 8.7 Hz, 1H), 8.55 (d, J = 6.9 Hz, 2H).



Scheme 1 Synthesis of ligands **10a**,**b**

General procedure for disassembly of the Ni(II) complexes, isolation of phenylalanines (*S*)-**15**, (*R*)-**16** and recycling of chiral ligands **10a,b**

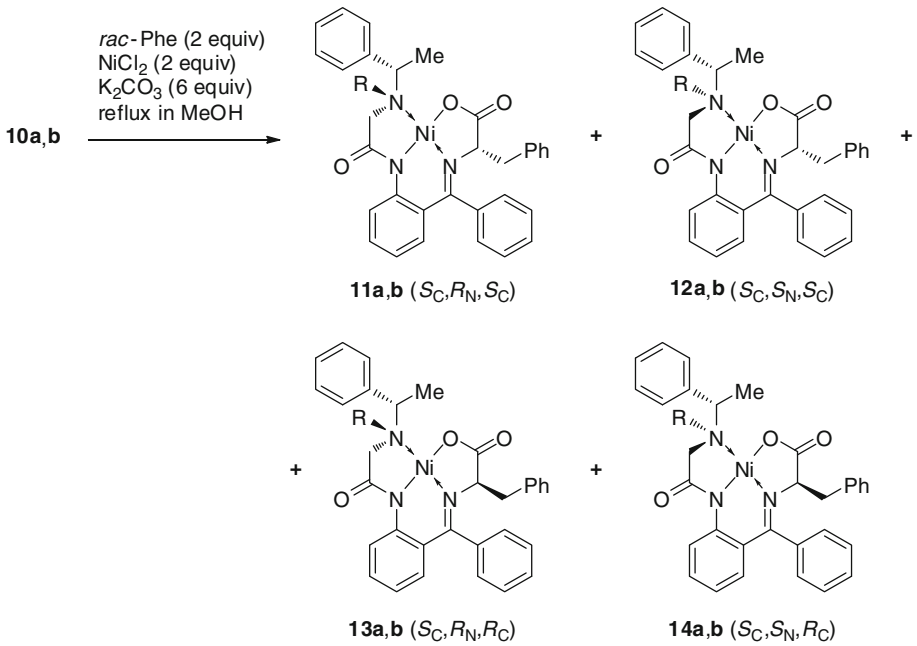
To a solution of MeOH and 3 *N* HCl at 70 °C was added complex **11a**,**b**, **13a**,**b** (14.5 mL MeOH/11 mL of 3 *N* HCl/1 g of complex **11a**,**b**, **13a**,**b**). The solution was stirred for 30 min (disappearance of red color) and then evaporated under vacuum. The residue was treated with 50 mL of DI water and 15 mL CH_2Cl_2 and then organic and aqueous layers were separated and evaporated under vacuum. Ligands **10a,b** were recovered with 95–98 % yields by the evaporation of the organic layer. Following the evaporation of aqueous layer, the crystalline residue was dissolved in the minimum amount of DI water and placed on an ion-exchange column using Dowex 50 X 2-100 resin. The column was first washed with DI water until neutral, followed by 8 % aqueous ammonium hydroxide (200 mL) to elute acids **15**, **16**. This solution was evaporated to afford target (*S*)- and (*R*)-phenylalanines in 93–95 % yield. The Ni(II) was eluted with concentrated HCl after the column was returned to neutral pH with DI water.

Results and discussion

To develop the most inexpensive chemical method for preparation of enantiomerically pure amino acids, we decided to use ultimately inexpensive chiral auxiliary, 1-(phenyl)ethylamine **5** (Juaristi et al. 1998, 1999) (Scheme 1), readily available in both enantiomeric forms. In contrast to the design of ligand **4**, bearing 2-amino-2-methylpropanoic acid, we chose the simplest case of glycine moiety, expecting high yield and uncomplicated synthesis of the target ligand.

First, *o*-aminobenzophenone **6** (Scheme 1) was acylated with 2-bromoacetyl bromide **7** (Soloshonok et al. 2007) to give product **8** in 98 % yield. Without additional

Scheme 2 Synthesis of diastereomeric complexes **11a**,**b**–**14a**,**b**



purification, compound **8** was reacted with (*S*)-amine **5** using previously reported procedure with application of Hünig's base (Moore et al. 2005), giving rise to product **9** in quantitative yield. Under the same conditions, NH functionality in **9** was alkylated to afford ligands **10a**,**b** in excellent yields.

Again, without additional purification, ligands **10a**,**b** were heated in MeOH at 50 °C, in the presence of racemic Phe, $NiCl_2$ and K_2CO_3. The formation of the corresponding Ni(II) complexes took place at relatively high rate and upon completion, the reaction mixtures were poured into icy water containing 5 % acetic acid. Analysis of the stereochemical outcome of the reactions (NMR, TLC) revealed that in the case of ligand **10a**, three diastereomeric complexes had been formed in a ratio of 9/61/30. The reaction of ligand **10b** was more stereoselective as only two major complexes were isolated in a ratio of ~63/37 with only trace amounts of the third diastereomer. Scheme 2 shows all four possible diastereomeric complexes **11**–**14** expected in the reactions under study. Stereochemical assignments of the products obtained have been made based on their crystallographic, ^{1}H-NMR data and chiroptical properties.

Thus, the major product obtained in the reaction of *N*-benzyl ligand **10b** was subjected to single crystal X-ray analysis which revealed its (S_C,R_N,S_C) absolute configuration (compound **11b**) (Figs. 3, 4). As one can see in Fig. 4, the methyl group of the (phenyl)ethylamine moiety is located in close proximity to the Ni atom, which can explain (Soloshonok et al. 1999c) its unusual down-fielded (2.22 ppm) chemical shift in its ^{1}H-NMR spectrum, as compared to uninfluenced, "normal" chemical shift of

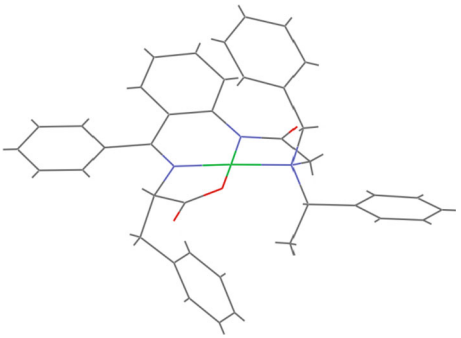


Fig. 3 Crystallographic structure of (S_C,R_N,S_C)-**11b**

about 1.5 ppm observed in the case of ligands **10a**,**b**. The case of down-fielded chemical shifts of methyl groups located above or under Ni atoms is well documented in chemistry of the compounds of this kind (Belokon et al. 1985b, 1986, 1988), and therefore can serve as a reference for the (*R*) absolute configuration of the stereogenic nitrogen in this study. Furthermore, compound (S_C,R_N,S_C)-**11b** has optical rotation +1,417.4 ($[\alpha]_D^{25}$) which is the result of non-planar, twisted structure of the chelate rings around Ni atom. In particular, the phenylalanine-containing five-membered ring and the adjacent six-membered ring are down and up, respectively, relatively to the Ni coordination plane. This twisted arrangement of the chelate rings in (S_C,R_N,S_C)-**11b** gives rise to the axial chirality of (*S*) absolute configuration, which is responsible for positive optical rotation and its remarkable magnitude. By contrast, if the phenylalanine moiety is of (*R*) configuration, the twist of the chelate rings will result in (*R*) configured axial chirality and the corresponding Ni(II) complex will have

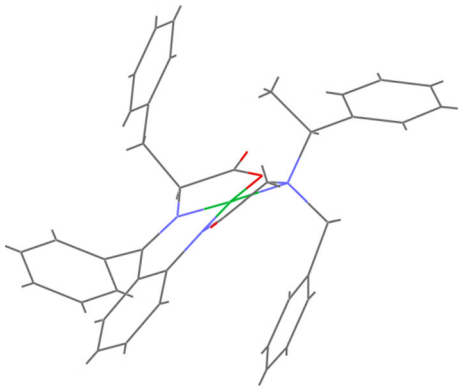


Fig. 4 Crystallographic structure of (S_C,R_N,S_C)-**11b** showing the exposure of α-(phenyl)ethylamine's methyl to the Ni(II) atom

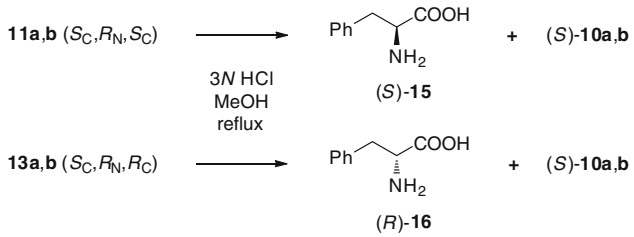
Table 1 ^{1}H-NMR and chiroptical data for diastereomeric complexes **11a**,**b**–**14a**,**b**

	Compound	Yield (%)	$[\alpha]_D^{25}$	δ (Me)
R=Me	(S_c,R_N,S_c)-**11a**	61	+1711.6	2.22
	(S_c,S_N,S_c)-**12a**	9	+1550.8	1.64
	(S_c,R_N,R_c) **13a**	30	−1634.1	1.99
	(S_c,S_N,R_c)-**14a**	0		
R=Bn	(S_c,R_N,S_c)-**11b**	63	+1417.4	2.22
	(S_c,S_N,S_c)-**12b**	0		
	(S_c,R_N,R_c)-**13b**	37	−1756.4	2.19
	(S_c,S_N,R_c)-**14b**	Trace	−1880.8	1.55

negative optical rotation of a similar magnitude (Wang et al. 2011). Consequently, the sign of optical rotation can be reliably used as a reference to assign the α-absolute configuration of the amino acid residue.

Chemical shifts of the (phenyl)ethylamine methyl group and optical rotations of the products obtained are collected in Table 1. Based on these data, we can assign the absolute configurations of all compounds obtained. Thus, in the reaction of ligand **10a** the products are (61 %) **11a** (S_C,R_N,S_C), (9 %) **12a** (S_C,S_N,S_C) and (30 %) **13a** (S_C,R_N,R_C). In the reaction of ligand **10b**, the products are (63 %) **11b** (S_C,R_N,S_C), (37 %) **13b** (S_C,R_N,R_C) and trace amount of **14b** (S_C,S_N,R_C). Obviously, for the purpose of preparation of enantiomerically pure (*S*)-phenylalanine, the complexes (S_C,R_N,S_C)-**11a** and (S_C,S_N,S_C)-**12a** can be combined, as they contain amino acid of the same (*S*) configuration.

Diastereomerically pure complexes (S_C,R_N,S_C)-**11a**, (S_C,R_N,R_C)-**13a**, (S_C,R_N,S_C)-**11b** and (S_C,R_N,R_C)-**13b** were obtained by column chromatography. Each of these products was disassembled using standard conditions shown in Scheme 3. Chiral ligands **10a**,**b** were easily recycled (∼95 %) and the target (*S*)- and (*R*)-phenylalanines were isolated using ion-exchange column in 85–90 % yields.



Scheme 3 Disassembly of Ni(II) complexes and isolation of target (*S*)- and (*R*)-phenylalanines

Regardless the incomplete diastereoselectivity in the products formation and chromatographic purification, the cost of thus prepared (*S*)- and (*R*)-phenylalanines, including silica gel, all reagents and solvents, is very attractive and well below of any other chemical approach reported thus far in the literature (Yue et al. 2007; Khamduang et al. 2009; Cárdenas-Fernández et al. 2012; Yasukawa and Asano 2012). These preliminary results clearly suggest that the approach described here has certain practical potential, which is currently being explored using various derivatives of 1-(phenyl)ethylamine and other chiral amines to improve the stereochemical outcome of the Ni(II) complexes formation and overall efficiency, generality and scalability of the method.

Conclusions

In conclusion, this work has demonstrated that simple structural design of new generation modular ligands bearing 1-(phenyl)ethylamine moiety as a source of stereochemical information, can be effectively used for quite inexpensive preparation of enantiomerically pure (*S*)- and (*R*)-phenylalanines. While the present results have some shortcomings, such as incomplete stereoselectivity and chromatographic separation, they provide an inspirational prospect for the development of improved and truly practical methodology.

Acknowledgments We thank IKERBASQUE, Basque Foundation for Science; Basque Government (SAIOTEK S-PE12UN044), Spanish Ministry of Science and Innovation (CTQ2010-19974) and Hamari Chemicals (Osaka, Japan) for generous financial support.

Conflict of interest The authors declare that they have no conflict of interest.

References

Aceña JL, Sorochinsky AE, Soloshonok VA (2012) Recent advances in asymmetric synthesis of α-(trifluoromethyl)-containing α-amino acids. Synthesis 44:1591–1602

Aceña JL, Sorochinsky AE, Moriwaki H, Sato T, Soloshonok VA (2013) Synthesis of fluorine-containing α-amino acids in

enantiomerically pure form via homologation of Ni(II) complexes of glycine and alanine Schiff bases. J Fluor Chem 155:21–38

Belokon YN, Zel'tzer E, Bakhmutov VI, Saporovskaya MB, Ryzhov MG, Yanovsky AI, Struchkov YT, Belikov VM (1983) 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*'-benzylprolyl)aminobenzaldehyde and (*S*)-2-*N*-(*N*'-benzylprolyl)aminoacetophenone. Crystal and molecular structure of a copper(II) complex of glycine Schiff base with (*S*)-2-*N*-(*N*'benzylprolyl)aminoacetophenone. J Am Chem Soc 105:2010–2017

Belokon YN, Bulychev AG, Vitt SV, Struchkov YT, Batsanov AS, Timofeeva TV, Tsyryapkin VA, Ryzhov MC, Lysova LA, Bakhmutov VI, Belikov VM (1985a) 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 107:4252–4259

Belokon YN, Maleyev VI, Vitt SV, Ryzhov MG, Kondrashov YD, Golubev SN, Vauchskii YP, Kazika AI, Novikova MI, Krasutskii PA, Yurchenko AG, Dubchak IL, Shklover VE, Struchkov YT, Bakhmutov VI, Belikov VM (1985b) Enantioselectivity of nickel(II) and copper(II) complexes of Schiff bases derived from amino acids and (*S*)-*o*-[(*N*-benzylprolyl)amino]-acetophenone or (*S*)-*o*-[(*N*-benzylprolyl)amino]benzaldehyde. Crystal and molecular structures of [Ni{(*S*)-bap-(*S*)-Val}] and [Cu{(*S*)-bap-(*S*)-Val}]. J Chem Soc Dalton Trans 17–26

Belokon YN, Bulychev AG, Ryzhov MG, Vitt SV, Batsanov AS, Struchkov YT, Bakhmutov VI, Belikov VM (1986) Synthesis of enantio- and diastereo-isomerically pure β- and γ-substituted glutamic acids via glycine condensation with activated olefins. J Chem Soc Perkin Trans 1 1865–1872

Belokon YN, Bulychev AG, Pavlov VA, Fedorova EB, Tsyryapkin VA, Bakhmutov VI, Belikov VM (1988) Synthesis of enantio- and diastereoiso-merically pure substituted prolines via condensation of glycine with olefins activated by a carbonyl group. J Chem Soc Perkin Trans 1 2075–2083

Belokon YN, Tararov VI, Maleev VI, Savel'eva TF, Ryzhov MG (1998) Improved procedures for the synthesis of (*S*)-2-[*N*-(*N*′-benzylprolyl)amino]-benzophenone (BPB) and Ni(II) complexes of Schiff's bases derived from BPB and amino acids. Tetrahedron Asymmetry 9:4249–4252

Belokon YN, Kochetkov KA, Churkina TD, Ikonnikov NS, Larionov OV, Harutyunyan S, North M, Vyskošil Š, Kagan HB (2001) Highly efficient catalytic synthesis of α-amino acids under phase-transfer conditions with a novel catalyst/substrate pair. Angew Chem Int Ed 40:1948–1951

Belokon YN, Bespalova NB, Churkina TD, Cisarova I, Ezernitskaya MG, Harutyunyan SR, Hrdina R, Kagan HB, Kocovsky P, Kochetkov KA, Larionov OV, Lyssenko KA, North M, Polasek M, Peregudov AS, Prisyazhnyuk VV, Vyskocil S (2003) Synthesis of α-amino acids via asymmetric phase transfer-catalyzed alkylation of achiral nickel(II) complexes of glycine-derived Schiff bases. J Am Chem Soc 125:12860–12871

Breuer M, Ditrich K, Habicher T, Hauer B, Keβeler M, Stürmer R, Zelinski T (2004) Industrial methods for the production of optically active intermediates. Angew Chem Int Ed 43:788–824

Cárdenas-Fernández M, López C, Álvaro G, López-Santín J (2012) L-Phenylalanine synthesis catalyzed by immobilized aspartate aminotransferase. Biochem Eng J 63:15–21

Chinchilla R, Mazón P, Nájera C (2000) Asymmetric synthesis of α-amino acids using polymer-supported Cinchona alkaloid-derived ammonium salts as chiral phase-transfer catalysts. Tetrahedron Asymmetry 11:3277–3281

Corey EJ, Xu F, Noe MC (1997) A rational approach to catalytic enantioselective enolate alkylation using a structurally rigidified and defined chiral quaternary ammonium salt under phase transfer conditions. J Am Chem Soc 119:12414–12415

Duthaler RO (1994) Recent developments in the stereoselective synthesis of α-amino acids. Tetrahedron 50:1539–1560

Ellis TK, Martin CH, Tsai GM, Ueki H, Soloshonok VA (2003a) Efficient synthesis of sterically constrained symmetrically α, α-disubstituted α-amino acids under operationally convenient conditions. J Org Chem 68:6208–6214

Ellis TK, Martin CH, Ueki H, Soloshonok VA (2003b) Efficient, practical synthesis of symmetrically α, α-disubstituted α-amino acids. Tetrahedron Lett 44:1063–1066

Ellis TK, Ueki H, Yamada T, Ohfune Y, Soloshonok VA (2006) 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 71:8572–8578

Fitzi R, Seebach D (1988) Resolution and use in α-amino acid synthesis of imidazolidinone glycine derivatives. Tetrahedron 44:5277–5292

Fogassy E, Nogradi M, Palovics E, Schindler J (2005) Resolution of enantiomers by non-conventional methods. Synthesis 1555–1568

Gallos JK, Sarli VC, Massen ZS, Varvogli AC, Papadoyanni CZ, Papasyrou SD, Argyropoulos NG (2005) A new strategy for the stereoselective synthesis of unnatural α-amino acids. Tetrahedron 61:565–574

Juaristi E, Escalante J, León-Romo JL, Reyes A (1998) Recent applications of α-phenylethylamine (α-PEA) in the preparation of enantiopure compounds. Part 1: incorporation in chiral catalysts. Part 2: α-PEA and derivatives as resolving agents. Tetrahedron Asymmetry 9:715–740

Juaristi E, León-Romo JL, Reyes A, Escalante J (1999) Recent applications of α-phenylethylamine (α-PEA) in the preparation of enantiopure compounds. Part 3: α-PEA as chiral auxiliary. Part 4: α-PEA as chiral reagent in the stereodifferentiation of prochiral substrates. Tetrahedron Asymmetry 10:2441–2495

Khamduang M, Packdibamrung K, Chutmanop J, Chisti Y, Srinophakun P (2009) Production of L-phenylalanine from glycerol by a recombinant *Escherichia coli*. J Ind Microbiol Biotechnol 36:1267–1274

Kukhar VP, Sorochinsky AE, Soloshonok VA (2009) Practical synthesis of fluorine-containing α- and β-amino acids: recipes from Kiev, Ukraine. Future Med Chem 1:793–819

Lygo B, Wainwright PG (1997) A new class of asymmetric phase-transfer catalysts derived from chincona alkaloids: application in the enantioselective synthesis of α-amino acids. Tetrahedron Lett 38:8595–8598

Ma J-A (2003) Recent developments in the catalytic asymmetric synthesis of α- and β-amino acids. Angew Chem Int Ed 42:4290–4299

Maruoka K, Ooi T (2003) Enantioselective amino acid synthesis by chiral phase-transfer catalysis. Chem Rev 103:3013–3028

Moore JL, Taylor SM, Soloshonok VA (2005) An efficient and operationally convenient general synthesis of tertiary amines by direct alkylation of secondary amines with alkyl halides in the presence of Hunig's base. ARKIVOC 287–292

Nájera C, Sansano JM (2007) Catalytic asymmetric synthesis of α-amino acids. Chem Rev 107:4584–4671

O'Donnell MJ, Eckrich TM (1978) The synthesis of amino acid derivatives by catalytic phase-transfer alkylations. Tetrahedron Lett 19:4625–4628

Ooi T, Kameda M, Maruoka K (1999) Molecular design of a C_2-symmetric chiral phase-transfer catalyst for practical asymmetric synthesis of α-amino acids. J Am Chem Soc 121:6519–6520

Park H-G, Jeong B-S, Yoo M-S, Lee J-H, Park M-K, Lee Y-J, Kim M-J, Jew S-S (2002) Highly enantioselective and practical chincona-derived phase-transfer catalysts for the synthesis of α-amino acids. Angew Chem Int Ed 41:3036–3038

Park H, Kim KM, Lee A, Ham S, Nam W, Chin J (2007) Bioinspired chemical inversion of L-amino acids to D-amino acids. J Am Chem Soc 129:1518–1519

Qiu W, Soloshonok VA, Cai C, Tang X, Hruby VJ (2000) Convenient, large-scale asymmetric synthesis of enantiomerically pure *trans*-cinnamylglycine and -α-alanine. Tetrahedron 56:2577–2582

Schöllkopf U, Groth U, Deng C (1981) Enantioselective syntheses of (*R*)-amino acids using L-valine as chiral agent. Angew Chem Int Ed Engl 20:798–799

Shibuguchi T, Fukuta Y, Akachi Y, Sekine A, Ohshima T, Shibasaki M (2002) Development of new asymmetric two-center catalysts in phase-transfer reactions. Tetrahedron Lett 43:9539–9543

Solladié-Cavallo A, Sedy O, Salisova M, Schmitt M (2002) Stereodifferentiation in a chiral 1,4-oxazin-2-one derived from 2-hydroxy-2-methyl-1-tetralone: a reagent for deracemization of amino acids. Eur J Org Chem 3042–3049

Soloshonok VA (2002) Highly diastereoselective Michael addition reactions between nucleophilic glycine equivalents and β-substituted-α, β-unsaturated carboxylic acid derivatives; a general approach to the stereochemically defined and sterically χ constrained α-amino acids. Curr Org Chem 6:341–364

Soloshonok VA, Izawa K (eds) (2009) Asymmetric Synthesis and Application of α-Amino Acids. ACS Symposium Series, vol. 1009. American Chemical Society, Washington DC

Soloshonok VA, Sorochinsky AE (2010) Practical methods for the synthesis of symmetrically α,α-disubstituted α-amino acids. Synthesis 2319–2344

Soloshonok VA, Ueki H (2010) Towards modular design of chiroptically switchable molecules based on formation and cleavage of metal–ligand coordination bonds. Synthesis 49–56

Soloshonok VA, Kukhar VP, Galushko SV, Svistunova NY, Avilov DV, Kuzmina NA, Raevski NI, Struchkov YT, Pisarevsky AP, Belokon YN (1993) General method for the synthesis of enantiomerically pure β-hydroxy-α-amino acids, containing fluorine atoms in the side chains. Case of stereochemical distinction between methyl and trifluoromethyl groups. X-ray crystal and molecular structure of the nickel(II) complex of (2S,3S)-2-(trifluoromethyl)threonine. J Chem Soc Perkin Trans 1 3143–3155

Soloshonok VA, Hayashi T, Ishikawa K, Nagashima N (1994) Highly diastereoselective aldol reaction of fluoroalkyl aryl ketones with methyl isocyanoacetate catalyzed by silver(I)/triethylamine. Tetrahedron Lett 35:1055–1058

Soloshonok VA, Avilov DV, Kukhar VP, Tararov VI, Saveleva TF, Churkina TD, Ikonnikov NS, Kochetkov KA, Orlova SA, Pysarevsky AP, Struchkov YT, Raevsky NI, Belokon YN (1995) Asymmetric aldol reactions of chiral Ni(II)-complex of glycine with aldehydes. Stereodivergent synthesis of syn-(2*S*)- and syn-(2*R*)-β-alkylserines. Tetrahedron Asymmetry 6:1741–1756

Soloshonok VA, Avilov DV, Kukhar VP (1996) Asymmetric aldol reactions of trifluoromethyl ketones with a chiral Ni(II) complex of glycine: stereocontrolling effect of the trifluoromethyl group. Tetrahedron 52:12433–12442

Soloshonok VA, Kacharov AD, Avilov DV, Ishikawa K, Nagashima N, Hayashi T (1997a) Transition metal/base-catalyzed aldol reactions of isocyanoacetic acid derivatives with prochiral ketones, a straightforward approach to stereochemically defined β, β-disubstituted-β-hydroxy-α-amino Acids. Scope and limitations. J Org Chem 62:3470–3479

Soloshonok VA, Avilov DV, Kukhar VP, Van Meervelt L, Mischenko N (1997b) 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 38:4671–4674

Soloshonok VA, Cai C, Hruby VJ, Van Meervelt L, Mischenko N (1999a) Stereochemically defined *C*-substituted glutamic acids and their derivatives. 1. An efficient asymmetric synthesis of (2*S*,3*S*)-3-methyl- and -3-trifluoromethylpyroglutamic acids. Tetrahedron 55:12031–12044

Soloshonok VA, Cai C, Hruby VJ (1999b) Asymmetric Michael addition reactions of chiral Ni(II)-complex of glycine with (*N*-*trans*-enoyl)oxazolidines: improved reactivity and stereochemical outcome. Tetrahedron Asymmetry 10:4265–4269

Soloshonok VA, Cai C, Hruby VJ, Van Meervelt L (1999c) Asymmetric synthesis of novel highly sterically constrained (2*S*,3*S*)-3-methyl-3-trifluoromethyl- and (2*S*,3*S*,4*R*)-3-trifluoromethyl-4-methylpyroglutamic acids. Tetrahedron 55:12045–12058

Soloshonok VA, Cai C, Hruby VJ (2000a) Toward design of a practical methodology for stereocontrolled synthesis of χ-constrained pyroglutamic acids and related compounds. Virtually complete control of simple diastereoselectivity in the Michael addition reactions of glycine Ni(II) complexes with N-(enoyl)oxazolidinones. Tetrahedron Lett 41:135–139

Soloshonok VA, Cai C, Hruby VJ (2000b) A unique case of face diastereoselectivity in the Michael addition reactions between Ni(II)-complexes of glycine and chiral 3-(E-enoyl)-1,3-oxazolidin-2-ones. Tetrahedron Lett 41:9645–9649

Soloshonok VA, Tang X, Hruby VJ (2001) Large-scale asymmetric synthesis of novel sterically constrained 2′,6′-dimethyl- and α,2′,6′-trimethyltyrosine and -phenylalanine derivatives via alkylation of chiral equivalents of nucleophilic glycine and alanine. Tetrahedron 57:6375–6382

Soloshonok VA, Ueki H, Tiwari R, Cai C, Hruby VJ (2004) Virtually complete control of simple and face diastereoselectivity in the Michael addition reactions between achiral equivalents of a nucleophilic glycine and (*S*)- or (*R*)-3-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones: practical method for preparation of β-substituted pyroglutamic acids and prolines. J Org Chem 69:4984–4990

Soloshonok VA, Cai C, Yamada T, Ueki H, Ohfune Y, Hruby VJ (2005a) Michael addition reactions between chiral equivalents of a nucleophilic glycine and (*S*)- or (*R*)-3-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones as a general method for efficient preparation of β-substituted pyroglutamic acids. Case of topographically controlled stereoselectivity. J Am Chem Soc 127:15296–15303

Soloshonok VA, Ueki H, Ellis TK (2005b) New generation of nucleophilic glycine equivalents. Tetrahedron Lett 46:941–944

Soloshonok VA, Ueki H, Ellis TK, Yamada T, Ohfune Y (2005c) Application of modular nucleophilic glycine equivalents for truly practical asymmetric synthesis of β-substituted pyroglutamic acids. Tetrahedron Lett 46:1107–1110

Soloshonok VA, Ohkura H, Yasumoto M (2006) Operationally convenient asymmetric synthesis of (*S*)- and (*R*)-3-amino-4,4,4-trifluorobutanoic acid. Part I: enantioselective biomimetic transamination of isopropyl 4,4,4-trifluoro-3-oxobutanoate. J Fluor Chem 127:924–929

Soloshonok VA, Ueki H, Moore JL, Ellis TK (2007) Design and synthesis of molecules with switchable chirality via formation and cleavage of metal-ligand coordination bonds. J Am Chem Soc 129:3512–3513

Soloshonok VA, Ellis TK, Ueki H, Ono T (2009a) Resolution/deracemization of chiral α-amino acids using resolving reagents with flexible stereogenic centers. J Am Chem Soc 131:7208–7209

Soloshonok VA, Ueki H, Ellis TK (2009b) New generation of modular nucleophilic glycine equivalents for the general synthesis of α-amino acids. Synlett 704–715

Sorochinsky AE, Soloshonok VA (2010) Asymmetric synthesis of fluorine-containing amines, amino alcohols, α- and β-amino

acids mediated by chiral sulfinyl group. J Fluor Chem 131:127–139

Sorochinsky AE, Ueki H, Aceña JL, Ellis TK, Moriwaki H, Sato T, Soloshonok VA (2013a) Chemical approach for interconversion of (*S*)- and (*R*)-α-amino acids. Org Biomol Chem 11:4503–4507

Sorochinsky AE, Ueki H, Aceña JL, Ellis TK, Moriwaki H, Sato T, Soloshonok VA (2013b) Chemical deracemization and (*S*) to (*R*) interconversion of some fluorine-containing α-amino acids. J Fluor Chem 152:114–118

Tang X, Soloshonok VA, Hruby VJ (2000) Convenient, asymmetric synthesis of enantiomerically pure 2′,6′-dimethyltyrosine (DMT) via alkylation of chiral equivalent of nucleophilic glycine. Tetrahedron Asymmetry 11:2917–2925

Ueki H, Ellis TK, Martin CH, Boettiger TU, Bolene SB, Soloshonok VA (2003a) 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 68:7104–7107

Ueki H, Ellis TK, Martin CH, Soloshonok VA (2003b) Efficient large-scale synthesis of picolinic acid-derived nickel(II) complexes of glycine. Eur J Org Chem 1954–1957

Wang L, Brock A, Herberich B, Schultz PG (2001) Expanding the genetic code of *Escherichia coli*. Science 292:498–500

Wang M-X, Lin S-J, Liu J, Zheng Q-Y (2004) Efficient biocatalytic synthesis of highly enantiopure α-alkylated arylglycines and amides. Adv Synth Catal 346:439–445

Wang J, Shi T, Deng G, Jiang H, Liu H (2008) Highly enantio- and diastereoselective Mannich reactions of chiral Ni(II) glycinates with amino sulfones. Efficient asymmetric synthesis of aromatic α, β-diamino acids. J Org Chem 73:5870–8563

Wang J, Lin D, Zhou S, Ding X, Soloshonok VA, Liu H (2011) Asymmetric synthesis of sterically and electronically demanding linear ω-trifluoromethyl containing amino acids via alkylation of chiral equivalents of nucleophilic glycine and alanine. J Org Chem 76:684–687

Williams RM, Sinclair PJ, Zhai W (1988) Asymmetric synthesis of β-carboxyaspartic acid. J Am Chem Soc 110:482–483

Yamada T, Okada T, Sakaguchi K, Ohfune Y, Ueki H, Soloshonok VA (2006) Efficient asymmetric synthesis of novel 4-substituted and configurationally stable analogues of thalidomide. Org Lett 8:5625–5628

Yamada T, Sakaguchi K, Shinada T, Ohfune Y, Soloshonok VA (2008) Efficient asymmetric synthesis of the functionalized pyroglutamate core unit common to oxazolomycin and neooxazolomycin using Michael reaction of nucleophilic glycine Schiff base with α, β-disubstituted acrylate. Tetrahedron Asymmetry 19:2789–2795

Yasukawa K, Asano Y (2012) Enzymatic synthesis of chiral phenylalanine derivatives by a dynamic kinetic resolution of corresponding amide and nitrile substrates with a multi-enzyme system. Adv Synth Catal 354:3327–3332

Yue H, Yuan Q, Wang W (2007) Enhancement of L-phenylalanine production by β-cyclodextrin. J Food Eng 79:878–884