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REVIEW ARTICLE

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

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Abstract This review provides a comprehensive treatment of literature data dealing with asymmetric synthesis of α-amino-β-hydroxy and α,β-diamino acids via homologation of chiral Ni(II) complexes of glycine Schiff bases using aldol and Mannich-type reactions. These reactions proceed with synthetically useful chemical yields and thermodynamically controlled stereoselectivity and allow direct introduction of two stereogenic centers in a single operation with predictable stereochemical outcome. Furthermore, new application of Ni(II) complexes of α-amino acids Schiff bases for deracemization of racemic α-amino acids and (*S*) to (*R*) interconversion providing additional synthetic opportunities for preparation of enantiomerically pure α-amino acids, is also reviewed. Origin of observed diastereo-/enantioselectivity in the aldol, Mannich-type and deracemization reactions, generality and limitations of these methodologies are critically discussed.

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Introduction

The present review is the second part of a series that cover synthetic applications of Ni(II) complexes of glycine Schiff bases for preparation of various enantiomerically pure α-amino acids (Sorochinsky et al. 2013a). In general, Ni(II) complexes of glycine Schiff bases have been used to synthesize enantiomerically pure α-amino acids via *C*-alkylation reactions (Tang et al. 2000; Ellis et al. 2003a; Taylor et al. 2004) as well as aldol, Mannich-type and Michael addition reactions (Cai et al. 2004; Yamada et al. 2006, 2008). The subject of the first part was highly diastereoselective alkylations of chiral or achiral Ni(II) complexes of glycine Schiff bases as general practical methodology for asymmetric synthesis of α-amino acids. In the present review, the focus is on aldol and Mannich-type reactions of Ni(II) complexes of the glycine Schiff bases. In the most commonly used version aldol reactions of chiral Ni(II) complex of the Schiff base derived from (*S*)-2-[*N*-(*N*′-benzylprolyl)amino]benzophenone and glycine with achiral carbonyl compounds provide powerful and versatile method for the asymmetric synthesis of α-amino-β-hydroxy acids. The structural complexity of these amino acids with two vicinal chiral centers represents a synthetic challenge, especially the synthesis of enantiomerically pure materials. Chiral Ni(II) complex of the glycine Schiff base in the reactions with carbonyl compounds provides high level of stereocontrol at the α-stereogenic carbon of the newly formed amino acid moiety being much less effective in controlling absolute configuration at the β-position.

However, at high reaction pH the rearrangement of the intermediate aldol condensation product, when the ionized hydroxyl group of the product substitutes the ionized carboxyl group in the main coordination plane of the Ni(II) complex, resulted in synthetically useful stereochemical outcome of *syn*-(2*R*)-configured products starting from (*S*)-chiral auxiliary. On the other hand, only a few examples employing chiral Ni(II) complex of glycine in the Mannich-type reactions with imines for asymmetric synthesis of α,β-diamino acids have been reported. Additionally, this review discusses applications of a new type of "NH" Ni(II)-complexes Schiff bases of glycine containing a configurationally unstable stereogenic nitrogen suitable for both deracemization of *rac*-α-amino acids and (*S*) to (*R*) interconversion. These new "NH" type of glycine equivalents provide optimal differences in stereochemistry and physicochemical properties of diastereomeric Ni(II) complexes allowing for their easy separation.

Aldol addition reactions

One of the general strategies for homologation of nucleophilic glycine equivalents is aldol reactions with carbonyl compounds allowing efficient, stereoselective access to α-amino-β-hydroxy acids. The structure of Ni(II) complexes of glycine Schiff bases, due to relatively high C–H acidity of the α-protons of the amino acid fragment, allows the use of a wide range of weak and strong bases under various conditions for the aldol reaction with carbonyl compounds. For example, the condensation of Ni(II) complexes of glycine Schiff base with 2-[*N*-(benzylprolyl)amino]benzophenone (*S*)-**1** (Belokon et al. 1998; Ueki et al. 2003) or 2-[*N*-(benzylprolyl)amino]acetophenone (*S*)-**2** and formaldehyde in methanol at 50 °C in the presence of Et_3N provided Ni(II) complexes (2*S*)-**3** and (2*S*)-**4** with diastereomeric excess 83–96 %, estimated either by ^1H NMR or by chiral GLC analysis of the (*S*)-serine recovered from the complexes after decomposition with aqueous HCl (Belokon et al. 1985) (Scheme 1). In addition, CD spectra of the complexes were used to assign the absolute configuration of the α-carbon of the amino acid moiety. The reaction was completed after 5 h when the equilibrium was reached according to TLC data. It should be noted that condensation of formaldehyde with corresponding alanine Ni(II) complexes in the presence of Et_3N did not proceed at all.

Condensation of Ni(II) complex (*S*)-**1** and aromatic aldehydes **5** was found to take place in the presence of Et_3N in MeOH at ambient temperature to give all four possible diastereomeric Ni(II) complexes **6–9** (Soloshonok et al. 1991a, 1992a, 1993a, b) (Scheme 2). The reactions rate was rather slow with 90 % conversion being obtained after several days except for pentafluorobenzaldehyde **5h**. The condensation of pentafluorobenzaldehyde **5h** using DABCO as catalyst in $CHCl_3$ was completed in 2 h. This difference in reactions rate was explained by considering high electrophilicity of the carbonyl group in pentafluorobenzaldehyde **5h**. While mixture of major diastereomers (2*S*,3*R*)-**6** and (2*S*,3*S*)-**7** containing α-(*S*)-phenylserines was easily separated by chromatography in 80 % combined yield, diastereomers (2*R*,3*R*)-**8** and (2*R*,3*S*)-**9** were formed in minor amounts.

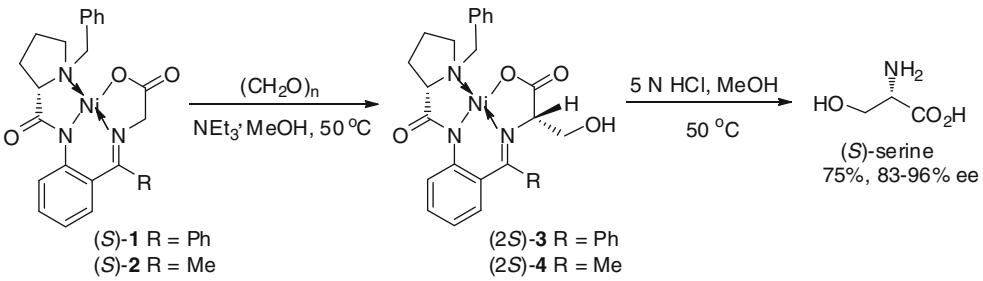
The ratio of (2*S*,3*R*)-**6** and (2*S*,3*S*)-**7** diastereomeric Ni(II) complexes was significantly affected by the substituent pattern of the aromatic aldehydes. Selectivity, as a ratio of diastereomers (2*S*,3*R*)-**6** and (2*S*,3*S*)-**7**, ranged from 1:1 to 1.8:1 in the case of *para*-substituted benzaldehydes, *ortho*-fluorobenzaldehyde and pentafluorobenzaldehyde, whereas introduction of large substituents in the *ortho*-position of aromatic ring increased (2*S*,3*R*)/(2*S*,3*S*) ratio to 10:1 (Table 1).

After separation of diastereoisomeric complexes (2*S*,3*R*)-**6f–h** by preparative chromatography on SiO_2 and subsequent disassembly with aqueous HCl in MeOH, free β-(2-trifluoromethylphenyl)serine (2*S*,3*R*)-**10f**, β-(2-difluoromethoxyphenyl)serine (2*S*,3*R*)-**10g** and β-(pentafluorophenyl)serine (2*S*,3*R*)-**10h** were isolated by ion-exchange chromatography in 79, 77 and 81 % yield, respectively (Scheme 3). This procedure also allowed recovery of the chiral ligand (*S*)-2-[*N*-(benzylprolyl)amino]benzophenone [(*S*)-BPB] which can be reused for the preparation of starting glycine complex (*S*)-**1**.

Ni(II) complex (*S*)-**1** was shown to react easily in $CHCl_3$ in the presence of DABCO with polyfluorinated aliphatic aldehydes **11** giving rise to the corresponding diastereomeric Ni(II) complexes (2*S*,3*R*)-**12** and (2*S*,3*S*)-**13** (Scheme 4). Similar to the reactions of aromatic aldehydes, the stereoselectivity in the α-position of newly formed amino acids was high, while the configuration of the β-carbon was virtually uncontrolled giving rise to the diastereomeric Ni(II) complexes (2*S*,3*R*)-**12** and (2*S*,3*S*)-**13** in a ratio of 1/1 (Soloshonok et al. 1993a, b).

The mechanism of aldol reaction of aromatic aldehydes **5** and polyfluorinated aliphatic aldehydes **11** with Ni(II) complex (*S*)-**1** in the presence of Et_3N or DABCO as a base consists of abstraction of the α-proton from glycine moiety of Ni(II) complex (*S*)-**1** followed by addition of the resulting carbanion to the carbonyl group of aldehydes. The condensation products have usual structure of Ni(II)–amino acid complexes with coordinated carboxylate group and pseudoaxial orientation of the amino acid chain. The condensation is a reversible process and the position of equilibrium is influenced by nature of the corresponding aldehyde and reaction conditions. Similar to the alkylation (Qiu et al. 2000; Soloshonok et al. 2001; Ellis et al. 2003b) and Michael addition reactions (Soloshonok et al. 1999,

Scheme 1 .



Scheme 2 .

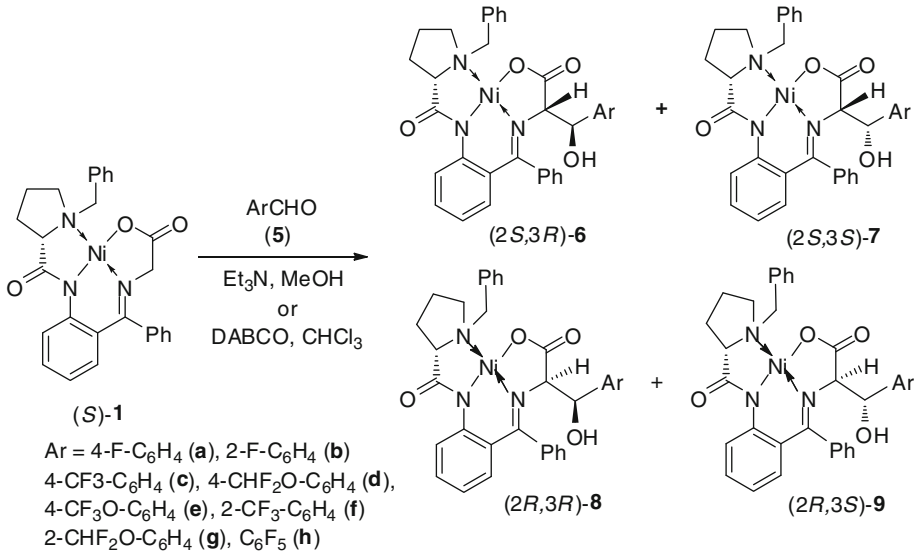


Table 1 Reactions of Ni(II) complex (*S*)-**1** with aromatic aldehydes ArCHO **5** in the presence of Et_3N

Entry	Ar	Reaction time	Ratio (2*S*,3*R*)/(2*S*,3*S*)[a]
1	4-F-C_6H_4 (a)	4 days	1.7/1
2	2-F-C_6H_4 (b)	4 days	1.6/1
3	4-CF_3-C_6H_4 (c)	3 days	1.8/1
4	4-CHF_2O-C_6H_4 (d)	3 days	1.5/1
5	4-CF_3O-C_6H_4 (e)	3 days	1.8/1
6	2-CF_3-C_6H_4 (f)	3 days	10/1
7	2-CHF_2O-C_6H_4 (g)	3 days	10/1
8	C_6F_5 (h)	2 h	1/1

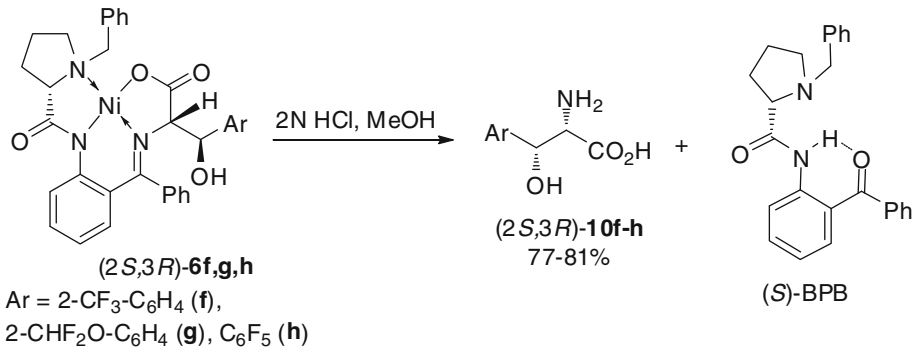
[a] Complexes were isolated in 80 % combined yield

2000, 2004), the (*S*) absolute configuration of the *N*-benzylproline residue in (*S*)-**1** induces the thermodynamically favorable diastereomer with (*S*) stereochemistry of the α-carbon atom of the amino acid moiety. The unfavorable interaction of the amino acid chain with the phenyl group at the C=N bond is responsible for instability of corresponding (*R*) diastereomer. However, under low pH there was no significant thermodynamic diastereoselectivity of the process at the β-carbon atom of the amino acid moiety. High (2*S*,3*R*)/(2*S*,3*S*) ratio in the cases of *ortho*-substituted aromatic aldehydes could be explained by weak electrostatic (Soloshonok et al. 1994a, b) attractive interaction of the central metal ion with fluorine-containing *ortho*-substituents stabilizing (2*S*,3*R*)-configuration of the side chain. While the target β-hydroxy amino acids can be prepared by this method, its preparative value is relatively low as it requires the chromatographic separation of the diastereomers. It should be mentioned that there is an alternative approach to this type of fluorinated phenylserines via Hayashi gold(I)-catalyzed asymmetric aldol reaction of isocyanoacetate derivatives with fluorinated benzaldehydes (Soloshonok and Hayashi 1994a, b; Soloshonok et al. 1996a).

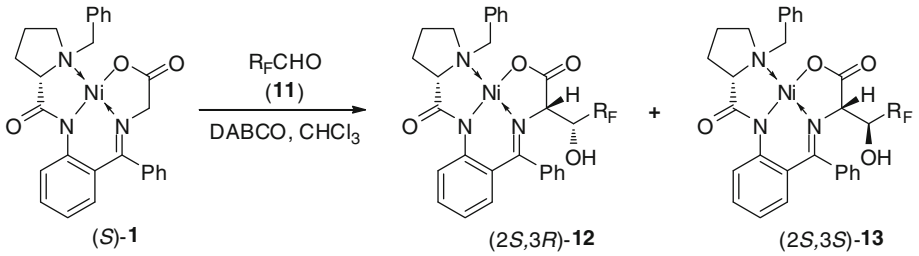
Under catalysis of MeONa, Ni(II) complexes (*S*)-**1** and (*S*)-**2** underwent condensation with formaldehyde in methanol giving rise to Ni(II) complexes (2*R*)-**3** and (2*R*)-**4** as the major products (Scheme 5), while complex (2*S*)-**3** and (2*S*)-**4** predominated at low pH in the presence of Et_3N (Belokon et al. 1985, 1988; Qin et al. 2006) (see Scheme 1). Further disassembly of the complexes (2*R*)-**3** and (2*R*)-**4** gave (*R*)-serine with an enantiomeric excess up to 89 %. The synthesis of (*S*)-serine was accomplished employing Ni(II) complex (*R*)-**1** as a recoverable chiral auxiliary.

On the other hand, condensation of formaldehyde with alanine Ni(II) complex (*S*,*S*)-**14** at high concentration of

Scheme 3 .



Scheme 4 .



MeONa in the reaction mixture afforded products (2*S*)-**15** and (2*R*)-**15** in ratio 1.25:1 and high combined chemical yield (Belokon et al. 1991, 2001a) (Scheme 6). Attempts to improve the diastereoselectivity of the condensation by changing reaction conditions failed. Both enantiomerically pure α-methylserines could be obtained by chromatographic separation of diastereomeric complexes (*S*)-**15** and (*R*)-**15** and disassembly under an acidic condition in high yields.

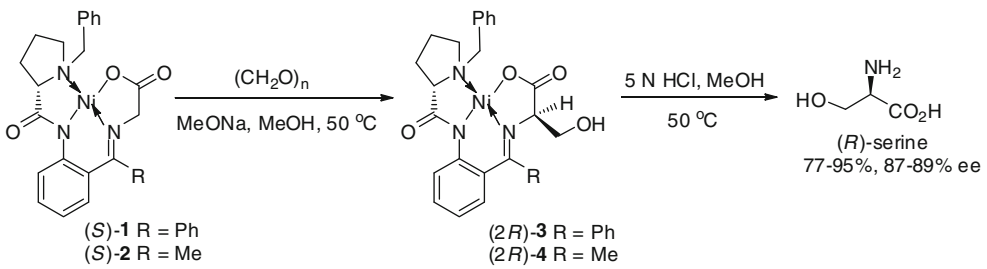
Detailed analysis of the aldol reaction of Ni(II) complex (*S*)-**1** with aliphatic aldehydes **16** in the presence of excess of MeONa in MeOH has shown that stereochemical outcome significantly depended on reaction time (Belokon et al. 1990; Soloshonok et al. 1995). Under high pH of solution almost pure Ni(II) complexes (2*S*,3*R*)-**17** were initially formed and after 24 h initial product were transformed into complexes (2*R*,3*S*)-**19** with up to 90 % diastereomeric excess alone with minute amount of additional Ni(II) complexes (2*R*,3*R*)-**18** and (2*S*,3*S*)-**20** via a cascade of C–C bond breaking and forming reactions (Scheme 7).

At the early stage of aldol reactions length and bulkiness of aliphatic aldehydes had little influence on stereochemical outcome (Table 2). By contrast, steric bulk of aliphatic aldehydes had critical influence on diastereomeric purity of complexes (2*R*,3*S*)-**19** as the final products of aldol reactions. Thus, reactions of *i*-PrCHO **16e** and *t*-BuCHO **16f** at room temperature gave corresponding products with only 49 and 15 % de, respectively.

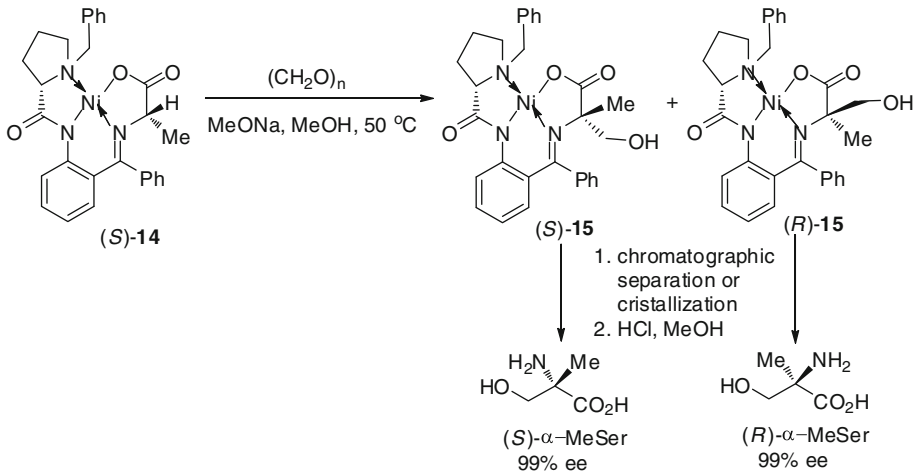
The enantiomerically pure α-amino-β-hydroxy acids (2*S*,3*R*)-**21** and (2*R*,3*S*)-**22** could be obtained from corresponding pure diastereomers (2*S*,3*R*)-**17** and (2*R*,3*S*)-**19** isolated by chromatography on silica gel and disassembled with 2 N HCl (Scheme 8).

Similar influence of reaction time on stereochemical outcome of the aliphatic aldehydes condensation with Ni(II) complex (*S*)-**1** was observed in the presence of NaH as a base in THF (Belokon et al. 2001b). The rate of equilibration between the diastereomeric complexes decreased when the reaction was conducted in aprotic solvents allowing isolation of initially formed Ni(II)

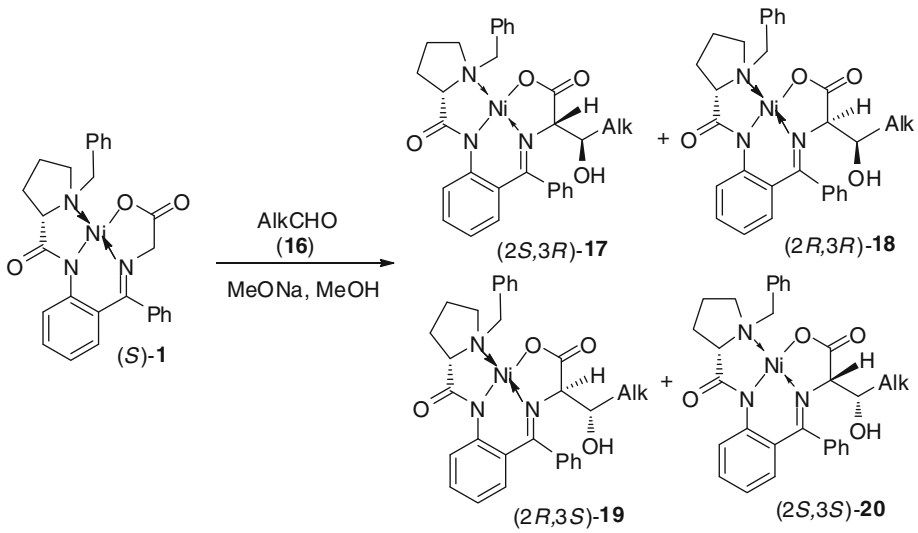
Scheme 5 .



Scheme 6 .



Scheme 7 .

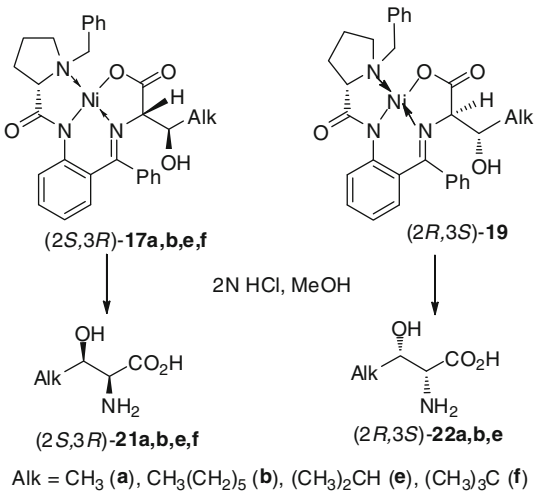


Alk = CH_3 (**a**), $CH_3(CH_2)_5$ (**b**), $CH_3(CH_2)_7$ (**c**), $(CH_3)_2CHCH_2$ (**d**), $(CH_3)_2CH$ (**e**), $(CH_3)_3C$ (**f**)

Table 2 MeONa-promoted aldol reaction of aliphatic aldehydes **16** with Ni(II) complex (*S*)-**1**

Entry	Aldehyde **16**	Time	Ratio (2*S*,3*R*)-**17**/(2*R*,3*S*)-**19**	Yield (%)[a]
2	CH_3CHO (b)	0.5 min	95/5	82
3	CH_3CHO (b)	24 h	5/95	78
4	$CH_3(CH_2)_5CHO$ (c)	0.5 min	91/9	94
5	$CH_3(CH_2)_5CHO$ (c)	24 h	11/85	78
6	$CH_3(CH_2)_7CHO$ (d)	0.5 min	>95/<5	78
7	$CH_3(CH_2)_7CHO$ (d)	24 h	10/90	76
8	$(CH_3)_2CHCH_2CHO$ (e)	0.5 min	97/3	94
9	$(CH_3)_2CHCH_2CHO$ (e)	24 h	9/91	75
10	$(CH_3)_2CHCHO$ (f)	3 min	90/10	99.6
11	$(CH_3)_2CHCHO$ (f)	3 h	25.5/74.5	–
12	$(CH_3)_3CCHO$ (g)	10 min	>98/< 2	97
13	$(CH_3)_3CCHO$ (g)	240 h	42.5/57.5	–

[a] Combined yield of all diastereomeric complexes



Scheme 8 .

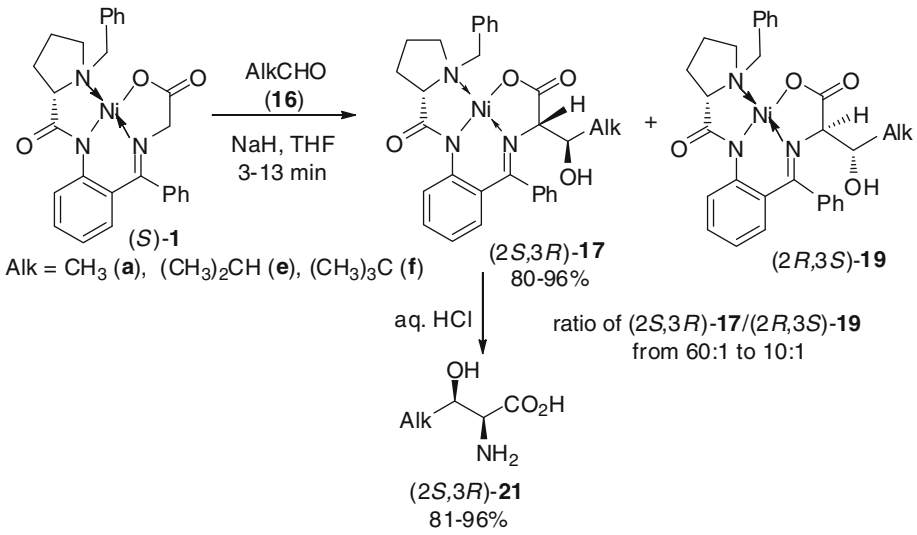
complexes (2*S*,3*R*)-**17** precipitated after treatment of reaction mixture with cold aqueous acetic acid (Scheme 9). The diastereomeric Ni(II) complexes were obtained with ratio of (2*S*,3*R*)-**17**/(2*R*,3*S*)-**19** ranging from 60:1 to 10:1. Sodium hydride was found to give better results than other bases such as *tert*-BuOK and *tert*-BuLi in terms of both chemical yield and diastereoselectivity.

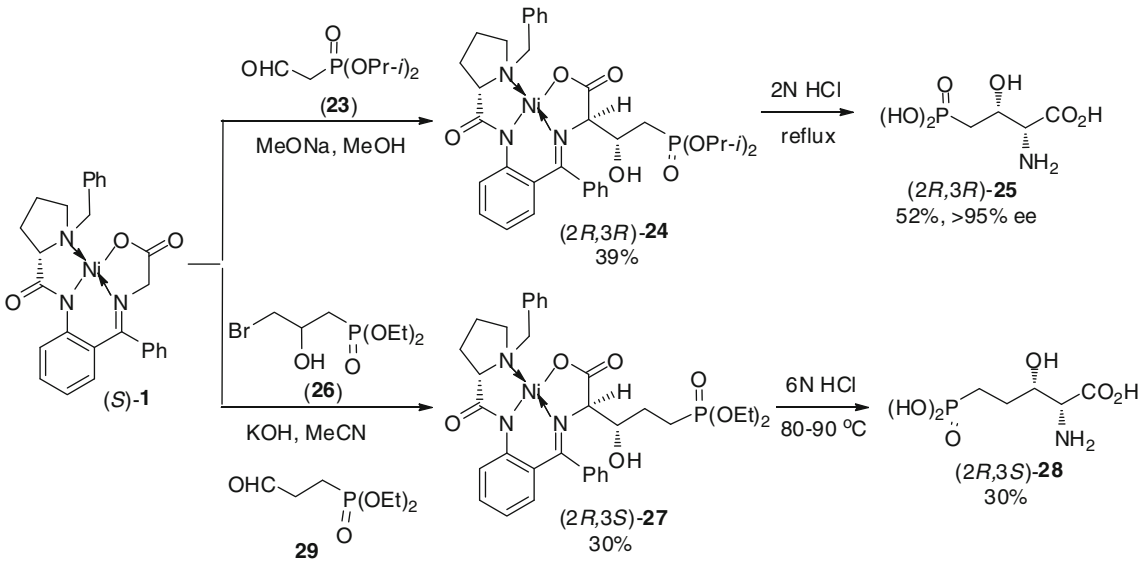
The aldol reactions of Ni(II) complex (*S*)-**1** provided opportunities for the synthesis of biologically important phosphorus-functionalized α-amino-β-hydroxy acids. It was found that condensation with diisopropyl (2-oxoethyl)phosphonate **23** and diethyl 3-bromo-2-hydroxypropylphosphonate **26** under strong basic conditions yielded Ni(II) complexes (2*R*,3*R*)-**24** and (2*R*,3*S*)-**27** as major products (Soloshonok et al. 1992b, 1994c) (Scheme 10). Isomerization of bromohydrin **26** under reaction conditions into aldehyde **29** was supposed to explain the stereochemistry of Ni(II) complex (2*R*,3*S*)-**27**. Ni(II) complexes after chromatographic separation were transformed into free 2-amino-3-hydroxy-4-phosphonobutyric (2*R*,3*R*)-**25** and 2-amino-3-hydroxy-5-phosphonopentanoic (2*R*,3*S*)-**28** acids by reflux in hydrochloric acids that allows simultaneous hydrolysis of phosphonate and ester groups.

Using analogs of Ni(II) complex (*S*)-**1** that contained electron-withdrawing Cl- or F-substituents as well as electron-donating Me-groups in various position of the benzyl group of the proline chiral auxiliary allowed to increase the diastereoselectivity and rate of the aldol reactions with formaldehyde and acetaldehyde under strongly basic conditions (Belokon' et al. 2002; Saghiyan et al. 2006a, b, 2010). The best enantiomeric excess of corresponding serine of (*R*) and threonine of (2*R*,3*S*)-absolute configuration were observed with Ni(II) complexes (*S*)-**30** modified by introduction of chlorine or fluorine atoms at the *ortho*-position of the aromatic ring of the *N*-benzylproline residue (Scheme 11). The enantiomeric purity of (*R*)-serine increased from 90 % in the case of Ni(II) complex (*S*)-**1** to 97–99 % in case of (*S*)-**30**. The same tendency was observed for the synthesis of (2*R*,3*S*)-threonine with increasing in the selectivity from 90 to 95–97 %.

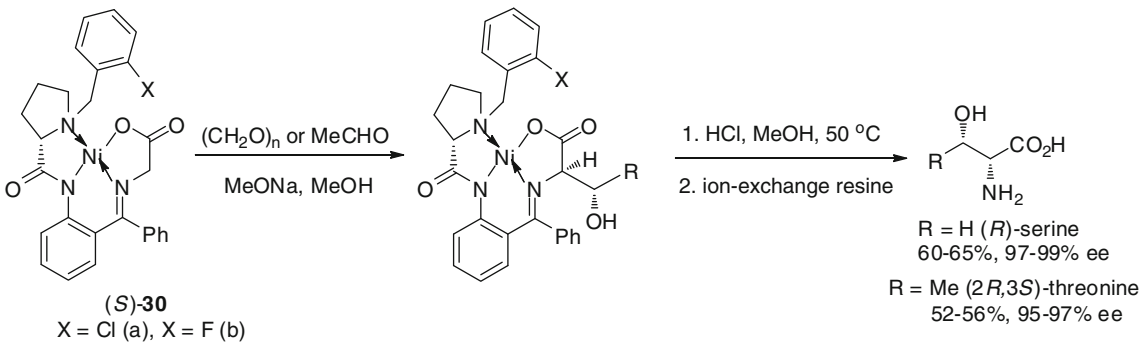
The use of excess of MeONa as a base for aldol reaction of Ni(II) complex (*S*)-**1** with aromatic aldehydes **5** resulted in a significant increase in the stereoselectivity of the process affording Ni(II) complexes (2*R*,3*S*)-**9** and (2*S*,3*R*)-**6** with considerable predominance of (2*R*,3*S*) isomer along with minute amounts of additional diastereomeric Ni(II) complexes (2*S*,3*S*)-**7** and (2*R*,3*R*)-**8** (Soloshonok et al. 1991b, 1993a, b) (Scheme 12). The aldol additions of aromatic aldehydes **5** followed by the equilibration of the resulting diastereomers was complete within 10 min and only insignificant change in the ratio of the products was

Scheme 9 .





Scheme 10 .



Scheme 11 .

Scheme 12 .

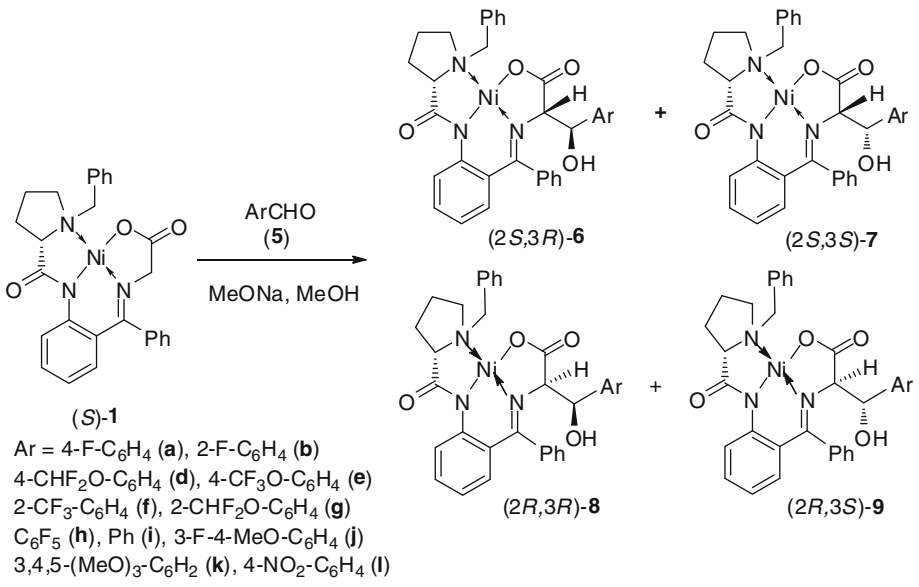


Table 3 Condensation of ArCHO **5** with Ni(II) complex (*S*)-**1** catalyzed by MeONa

Entry	Ar	Ratio (2*R*,3*S*)-**9**/(2*S*,3*R*)-**6**[a]	
		10 min	1 h
1	4-F-C_6H_4 (a)	96/4	96/4
2	2-F-C_6H_4 (b)	96/4	96/4
3	4-CHF_2O-C_6H_4 (d)	87/13	93/7
4	4-CF_3O-C_6H_4 (e)	88/12	92/8
5	2-CF_3-C_6H_4 (f)	89/11	90/10
6	2-CHF_2O-C_6H_4 (g)	88/12	90/10
7	C_6F_5 (h)	1/1[b]	8/1[c]
8	Ph (i)	95/5	95/5
9	3-F-4-MeO-C_6H_4 (j)	100/0	100/0
10	3,4,5-$(MeO)_3$-C_6H_2 (k)	100/0	100/0
11	4-NO_2-C_6H_4 (l)	83/17	90/10

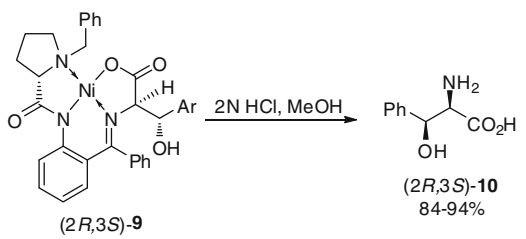
[a] Combined yield of complexes was 70–82 %

[b] Ratio 2*S*,3*S*/2*S*,3*R*

[c] Mixture of complexes containing pentafluorophenylserine and 4-methoxytetrafluorophenylserine

observed after 1 h from the start of the reaction. When complete equilibrium was reached the reaction mixture was neutralized by aqueous AcOH and the complexes were extracted by $CHCl_3$.

The position of substituent in the aromatic ring did not influence the stereochemical result of the reaction and in the cases of 2- and 4-fluorobenzaldehydes as well as 2- and 4-difluoromethoxybenzaldehydes the ratio of diastereomeric complexes (2*R*,3*S*)-**9**/(2*S*,3*R*)-**6** was practically the same (Table 3). On the other hand, introduction of electron-withdrawing substituent on aromatic ring increased the formation of minor diastereomers (2*S*,3*R*)-**6**. When Ni(II) complex (*S*)-**1** was reacted with 4-nitrobenzaldehyde the ratio of (2*R*,3*S*)-**9**/(2*S*,3*R*)-**6** was 90/10 while with benzaldehyde ratio 95/5 was obtained. In the case of aromatic aldehydes with electron-donating substituents minor diastereomers did not form at all. In contrast, the reaction of perfluorobenzaldehyde **5h** with Ni(II) complex (*S*)-**1** after 10 min afforded mixture of complexes (2*S*,3*S*)-**7** and



(2*R*,3*S*)-**9**

(2*R*,3*S*)-**10**
84-94%

Ar = 4-F-C_6H_4 (**a**), 2-F-C_6H_4 (**b**), 4-CHF_2O-C_6H_4 (**d**), 4-CF_3O-C_6H_4 (**e**), 2-CF_3-C_6H_4 (**f**), 2-CHF_2O-C_6H_4 (**g**), C_6F_5 (**h**), Ph (**i**), 3-F-4-MeO-C_6H_4 (**j**), 3,4,5-$(MeO)_3$-C_6H_2 (**k**), 4-NO_2-C_6H_4 (**l**)

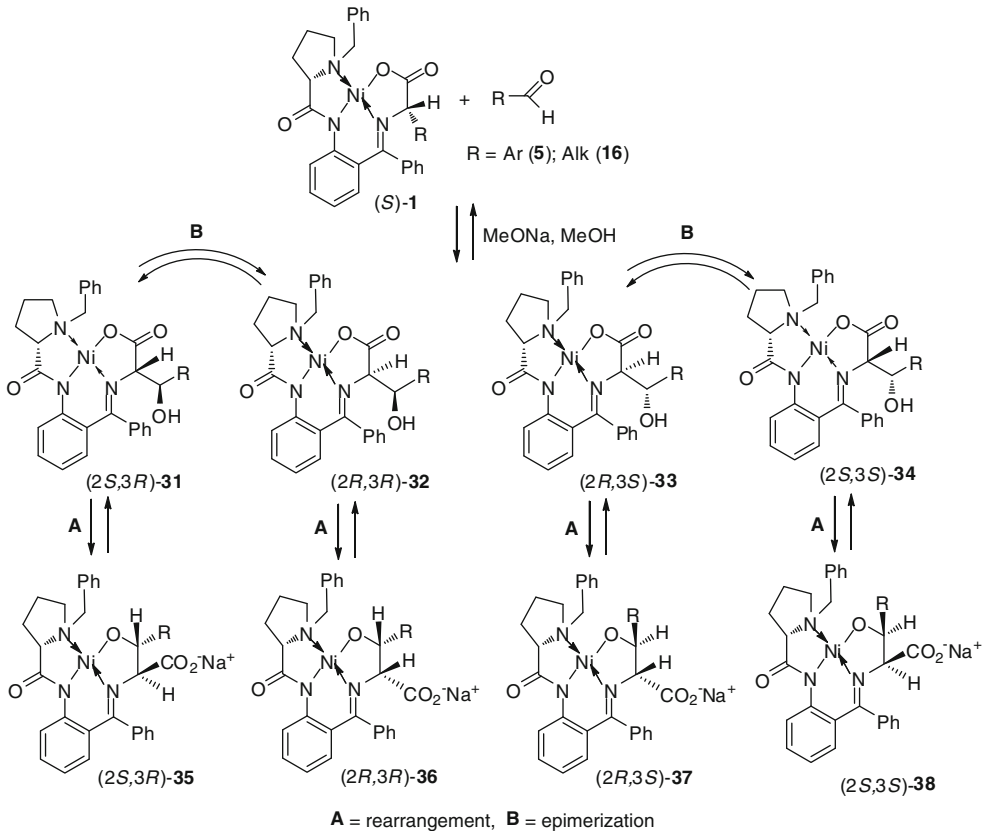
Scheme 13 .

(2*S*,3*R*)-**6** in ratio 1:1. Subsequent epimerization of initial products for 7 h gave rise to a mixture of complexes (2*R*,3*S*)-**9** and (2*S*,3*R*)-**6** in ratio 8:1. Nucleophilic substitution of fluorine atom in *para* position of pentafluorophenyl ring by MeO group was also observed in the course of condensation.

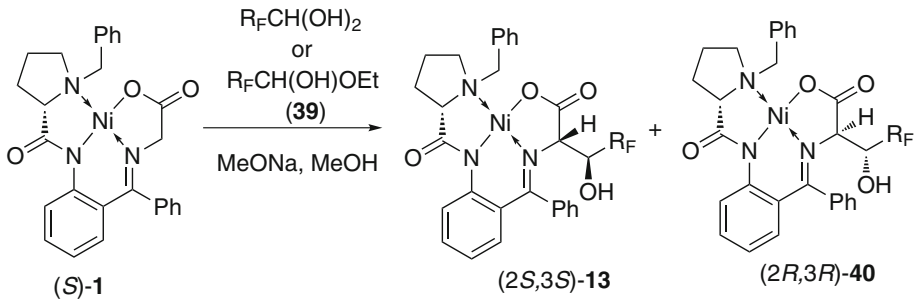
In all cases Ni(II) complexes (2*R*,3*S*)-**9** were isolated in diastereomerically pure form followed by acidic disassembly gave rise to amino acids (2*R*,3*S*)-**31** in 84–94 % yield (Scheme 13).

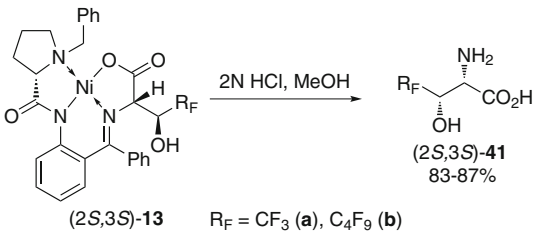
Regarding the mechanism of the aldol reaction between Ni(II) complex (*S*)-**1** and aromatic **5** or aliphatic **16** aldehydes at high pH, preferable formation of complexes (2*R*,3*S*)-**33** cannot be understood on the basis of the usual structure of the Ni(II)-amino acid complexes with coordinated carboxylate group (Scheme 14). The possible reaction pathway involves ionization of the side chain hydroxyl group and the rearrangement of the intermediate aldol condensation products **31**–**34**, where the ionized hydroxyl group substitutes the ionized carboxyl group in the main coordination sphere of Ni(II) leading to complexes **35**–**38**. Due to the rigid five-membered ring, the stereochemistry of the amino acid residue, and therefore both stereogenic centers, were effectively controlled by thermodynamic preference for *trans*-relationship of the carboxylate and aromatic or alkyl groups. Moreover, the thermodynamically favorable orientation of the carboxylate group opposite to the phenyl ring of the *N*-benzyl substituent for the isomer with (*R*) configuration of the α-carbon atom and the unfavorable steric interaction of the carboxylate with the *N*-benzyl group in the case of the (*S*) isomer explains formation of the complex (2*R*,3*S*)-**37** as final thermodynamically controlled product at a high pH of the reaction medium. When the pH was decreased, the complex having (2*R*,3*S*)-**37** structure becomes protonated and rearranges into the structure with coordinated carboxy group (2*R*,3*S*)-**33**. The introduction of electron-withdrawing substituent on the phenyl ring of aromatic aldehydes lowered the basicity of the hydroxy group and led to the destabilization of rearranged complexes (2*R*,3*S*)-**37**. By contrast, electron-donating substituents increased the basicity of the hydroxyl group and increased the stability of complexes (2*R*,3*S*)-**37**. Additionally thermodynamically controlled low ratio of complexes (2*R*,3*S*)-**37**/(2*S*,3*R*)-**35** in the reactions of (*S*)-**1** with *iso*-PrCHO and *tert*-BuCHO could be explained by specific changes in geometry of chelate rings of hydroxy group coordinated complexes due to steric demands of *iso*-propyl and *tert*-butyl groups. The molecular mechanic calculations have shown that distance between the carboxylic group and the metal center in complexes (2*S*,3*R*)-**35** becomes shorter than in complexes (2*R*,3*S*)-**37** as the size of amino acids moiety has increased. Thus, electrostatic attractive interaction between the negatively charged

Scheme 14 .

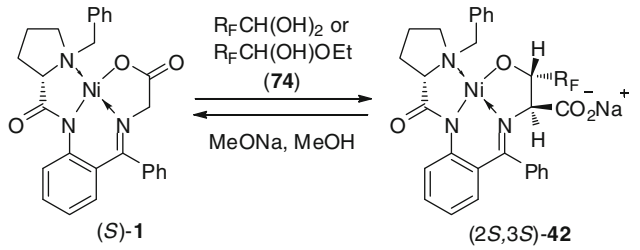


Scheme 15 .





Scheme 16 .



Scheme 17 .

oxygen atom of the carboxylic group and positively charged metal in complexes (2*S*,3*R*)-**35** is sufficient to overcome the steric non-bonded interaction rendering the complexes (2*S*,3*R*)-**35** energetically almost similar to (2*R*,3*S*)-**37** for *tert*-BuCHO condensation with Ni(II) complex (*S*)-**1**.

The condensation of Ni(II) complex (*S*)-**1** with hemiacetals or hydrates of polyfluorinated aldehydes **39** has also

been subject of investigation (Soloshonok et al. 1991c, 1993a, b). It was found that reactions in MeONa solution gave no products at room temperature. However, heating of reaction mixture at 50 °C for 10 min led to the formation of the corresponding diastereomeric complexes (2*S*,3*S*)-**13** and (2*R*,3*R*)-**40** in ratio 96:4 and high combined yield (Scheme 15). For the complete conversion of Ni(II) complex (*S*)-**1** a 10 % excess of hemiacetals or hydrates of polyfluorinated aldehydes **39** was required.

Ni(II) complexes (2*S*,3*S*)-**13a**, **b** were isolated in diastereomerically pure form by chromatography and their disassembly with 2 N HCl afforded amino acids (2*S*,3*S*)-**41** which were isolated on Dowex-50 without loss of optical purity (Scheme 16).

In the case of polyfluoroalkyl aldehydes, combined effects of the electrostatic and steric features of the polyfluoroalkyl group (Bravo et al. 1994; Kanai et al. 2003; Soloshonok et al. 1993b; Soloshonok and Ono 1996) influence the stereochemical outcome of aldol reactions. The electrostatic attraction between the positively charged metal and negatively charged polyfluoroalkyl group of the amino acid moiety located on the side of coordination plane opposite to the *N*-benzyl substituent could be the main reason for energetic stabilization of hydroxy group coordinated complexes **42** as revealed by molecular mechanics calculations (Scheme 17).

Aldol addition reactions of ketones with Ni(II) complexes of glycine Schiff bases are generally unpractical due to the unfavorable electronic as well as steric characteristics shifting the equilibrium to the starting compounds. For example, condensation of excess of acetone with Ni(II) complexes of glycine Schiff bases could be conducted in 1.3–1.7 M MeONa at ambient temperature to give (*R*)-β-hydroxyvaline in 54–56 % chemical yield and 70–72 % diastereoselectivity, suggesting that the selectivity in this reaction was relatively poor. Aldol addition with acetophenone completely failed, presumably due to less electrophilic nature (Belokon et al. 1985). In sharp contrast, alkyl trifluoromethyl ketones **43** were found to react easily with Ni(II) complex (*S*)-**1** providing straightforward access to α-amino-β-hydroxy-β-alkyl-β-trifluoromethyl carboxylic acids (2*S*,3*S*)-**46** unavailable by other methods (Soloshonok et al. 1996b, c) (Scheme 18).

After optimization of reaction conditions the aldol condensation of Ni(II) complex (*S*)-**1** with trifluoromethyl ketones **43** bearing *n*-alkyl, substituted alkyl and phenylacetylenyl groups in the presence of 3 mol of DBU proceeded at a very high rate furnishing products (2*S*,3*S*)-**44** in over 95 % diastereomeric excesses along with minor products (2*R*,3*R*)-**45** regardless of the length of the alkyl chain (Table 4). Complete conversion of Ni(II) complex (*S*)-**1** into aldol products was achieved by using 2 mol excess of the starting ketones **43**. The only exception was highly electrophilic phenylacetylenyl trifluoromethyl ketone **43f**. In this case the use of NEt_3 as a base allowed to prepare the corresponding Ni(II) complex (2*S*,3*S*)-**44f** in 56 % yield. Detailed analysis of *n*-heptyl trifluoromethyl ketone **43c** condensation with Ni(II) complex (*S*)-**1** has shown that stereoselectivity depended on reaction time increasing from 74 to over 98 % de within 1 h. These results suggested that the observed (2*S*,3*S*) diastereoselectivity was thermodynamically controlled. Complexes (2*S*,3*S*)-**44a, c–e** were isolated in a diastereomerically pure form and treated with HCl in MeOH to give enantiomerically pure 3-substituted 3-trifluoromethylserines (2*S*,3*S*)-**46a, c–e** (Scheme 18).

By analogy with condensation of aromatic **5**, aliphatic **16** aldehydes and hemiacetals or hydrates of polyfluoroalkyl aldehydes **14** with Ni(II) complex (*S*)-**1**, trifluoromethyl ketones **43**, at high pH of the reaction medium gave four hydroxyl coordinated complexes **47–50** (Scheme 19). Thermodynamic preference for hydroxy coordinated

Scheme 18 .

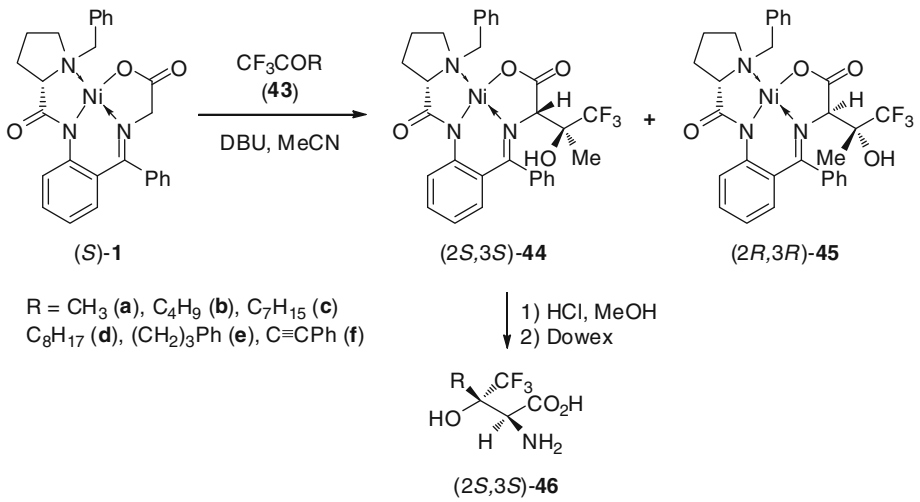


Table 4 Aldol reaction of Ni(II) complex (*S*)-**1** with trifluoromethyl ketones **43**

Entry	Ketone **43**	Time (h)	de (%)	Yield (%)[a]
1	CF_3COCH_3 (**a**)	0.25	95	75
2	CF_3COCH_3 (**a**)	1	>98	73
3	$CF_3COC_4H_9$ (**b**)	0.25	98	71
4	$CF_3COC_7H_{15}$ (**c**)	0.25	74	
5	$CF_3COC_7H_{15}$ (**c**)	0.5	92	
6	$CF_3COC_7H_{15}$ (**c**)	1	>98	70
7	$CF_3COC_8H_{17}$ (**d**)	1	>98	75
8	$CF_3COC_3H_6Ph$ (**e**)	1	96	87
9	$CF_3COCCPh$ (**f**)[b]	0.5	90	56

The reactions were carried out in MeCN at room temperature. Ratio Ni(II) complex (*S*)-**1**/ketone/DBU = 1/2/3

[a] Isolated yield of diastereomerically pure complexes (2*S*,3*S*)-**44**

[b] The reaction in MeCN in the presence of NEt_3

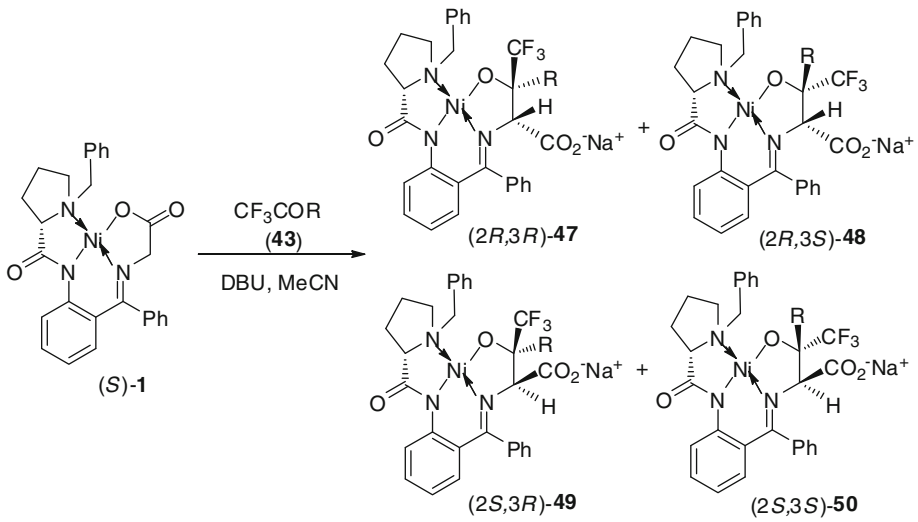
complex (2*S*,3*S*)-**50**, which upon neutralization of the reaction medium gives carboxy coordinated complex (2*S*,3*S*)-**44**, is a result of favorable *trans*-disposition of carboxylate and trifluoromethyl groups pointed down from the benzyl on the proline nitrogen. This orientation of the trifluoromethyl group is the most sterically favorable and allows for the electrostatic attractive interaction between trifluoromethyl group and Ni(II) atom. The steric and electrostatic demands of the trifluoromethyl group are more pronounced in controlling the stereochemistry of these reactions than steric effect of alkyl or acetylenic substituents.

Mannich addition reactions

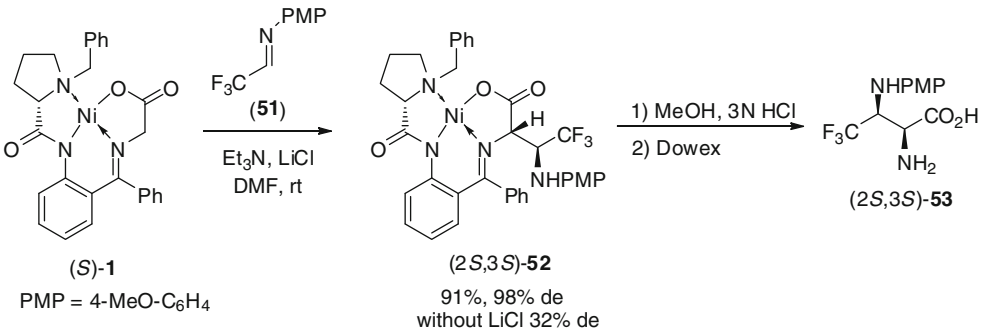
The nucleophilic addition of glycine equivalents to imines and related compounds plays main role for preparing α,β-diamino acid derivatives. According to this strategy Ni(II) complex (*S*)-**1** has been applied in the base-mediated Mannich-type reaction with *N*-*p*-methoxyphenyl (PMP)-protected aldimine of trifluoroacetaldehyde **51** leading to adduct (2*S*,3*S*)-**52** (Soloshonok et al. 1997) (Scheme 20). The PMP-protective group provides geometric homogeneity of the imine functionality, induces reasonably high electrophilicity to the C=N double bond and allows the imine nitrogen to form coordinated transition states. Furthermore, it can be readily cleaved to afford free target amine functionality. The Mannich additions of the Ni(II) complex (*S*)-**1** to PMP-protected aldimine **51** proceeded slowly in the presence of Et_3N in DMF solution giving rise to a mixture of diastereomeric complexes in ratio 66/34. In the mixture of products isomer (2*S*,3*S*)-**52** was predominantly formed. The addition of LiCl to the reaction mixture significantly enhanced the rate of the reaction allowing conversion of starting Ni(II) complex (*S*)-**1** to product (2*S*,3*S*)-**52** in 2 h with excellent stereoselection and very high chemical yields. The target 4,4,4-trifluoro-2,3-diaminobutanoic acid (2*S*,3*S*)-**53** was isolated from Ni(II) complex (2*S*,3*S*)-**52** in high chemical yield by treatment of its solution in MeOH with 3 N HCl followed by isolation via ion-exchange chromatography. The mechanism of this addition reaction involves the formation of highly organized transition states in which the lithium cation played a key role chelating the glycine enolate oxygen as well as imine nitrogen. The observed virtually complete stereochemical outcome of Mannich reaction was controlled by the trifluoromethyl group similar to that of aldol reactions of fluorinated carbonyl compounds.

In another case, PMP-protected α-imino ester **54** acted as electrophile in the Mannich reaction with Ni(II) complex (*S*)-**1** (Wang et al. 2010) (Scheme 21). The Mannich addition took place in the presence of 1.2 Equiv. of DBU at room

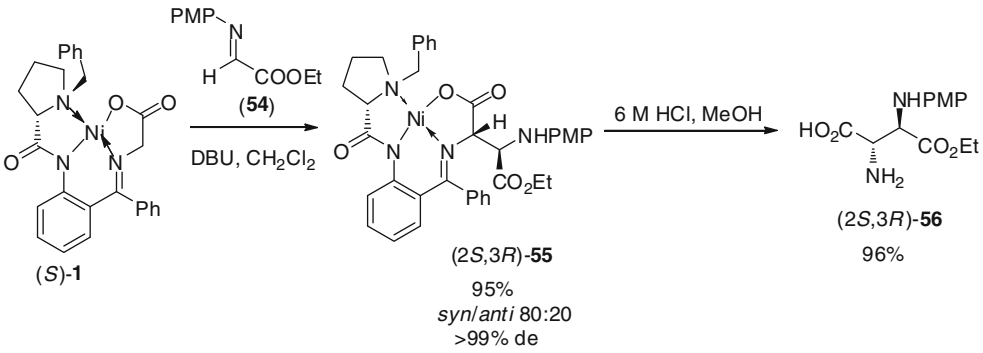
Scheme 19 .



Scheme 20 .



Scheme 21 .

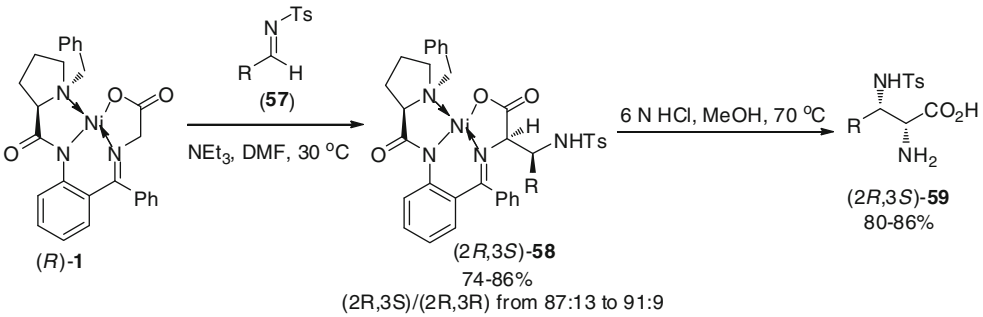


temperature in dichloromethane providing adduct (2*S*,3*R*)-**55** in highly stereoselective fashion, structure of which was supported by single-crystal X-ray crystallographic analysis. Improvement of *syn*/*anti* selectivity was achieved when the reaction was carried out at low temperatures but also with a lower yield. Attempts to improve the stereochemical outcome by changing base or solvent were unsuccessful. Complex (2*S*,3*R*)-**55** was disassembled by heating in methanol and 6 *M* aqueous HCl to give the 3-aminoaspartate derivative (2*S*,3*R*)-**56** in 96 % yield. The PMP group provided orthogonal protection of the amino group allowing ready manipulation in further synthetic elaborations.

Recently, within the same general approach, the enolate generated from Ni(II) complex (*R*)-**1** and Et_3N reacted with electrophilic aromatic and heterocyclic *N*-sulfonyl imines **57** to afford complexes (2*R*,3*S*)-**58** as major products (Song et al. 2011) (Scheme 22). The reactions proceeded smoothly in DMF and excellent yield was obtained within 30 min at 30 °C. Ratio of (2*R*,3*S*) and (2*R*,3*R*) diastereomers was from 87:13 to 91:9 according to ^{1}H NMR analysis of the crude reaction mixtures. The steric repulsion between the substituting group at 3-C and the neighboring phenyl group at the C=N bond was responsible for this preference. Satisfactory yield (74 %) and diastereoselectivity [(2*R*,3*S*)/(2*R*,3*R*) ratio 78:22] were also obtained in the reaction with adipic imine **57g**. α,β-Diamino acids (2*R*,3*S*)-**59** were generated by hydrolysis of the Ni(II) complexes (2*R*,3*S*)-**58** with 6 N HCl in MeOH and isolated by ion-exchange chromatography with excellent yield and *syn*-selectivity.

Readily available *N*-Boc-α-amido sulfones **60** have also been employed instead of imines in the reaction with Ni(II) complex (*S*)-**1**. Application of DBU as a base allowed for

Scheme 22 .



R = Ph (**a**), 4-MeO-C_6H_4 (**b**), 4-Me-C_6H_4 (**c**), 3-NO_2-C_6H_4 (**d**), 2-Cl-C_6H_4 (**e**), 2-Furyl (**f**), $(CH_3)_2CHCH_2$ (**g**)

the smooth reaction of Ni(II) complex (*S*)-**1** and in situ generated imines, giving rise to Mannich products (2*S*,3*R*)-**61** in diastereoselectivity up to 99 % while moderate diastereoselectivity was observed with other bases such as, NaH, *t*-BuOK, and NaOH (Wang et al. 2008) (Scheme 23). The *syn*-diastereomers were obtained as the major products based on an X-ray analysis. Further optimization of the reaction conditions revealed that DBU as a base and acetone as a solvent at ambient temperature afforded the best combination of yield and selectivity. In general, aryl and heterocyclic *N*-Boc-*a*-amido sulfones **60** were quite reactive providing for high enantio- and diastereoselectivity of the corresponding products regardless of the electronic effect of substituents. Upon examination of the reaction scope, it was found that less reactive aliphatic substrates gave good to high diastereoselectivity but showed low yields. It was also found that asymmetric Mannich reaction could also be applied for *N*-Cbz-α-amido sulfones as well as Ni(II) complex (*R*)-**1**, significantly expanding the scope of the reactions. Acidic hydrolysis of Ni(II) complex (2*S*,3*R*)-**61a** under standard conditions finally yielded 2,3-diamino-3-phenylpropanoic acid (2*S*,3*R*)-**62**. Stereochemical mechanism of the Mannich reaction was proposed and supported by quantum chemical calculations.

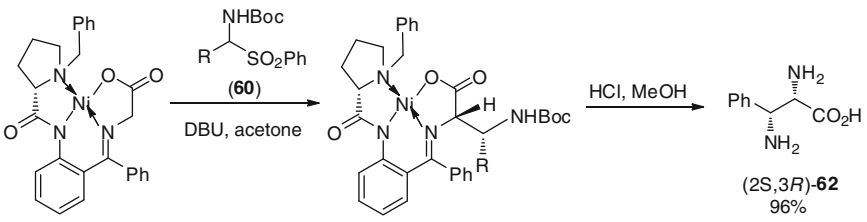
Deracemization and (*S*) to (*R*) interconversion of α-amino acids

Recently new structural type of the Ni(II) complexes of α-amino acid Schiff bases have been reported (Soloshonok et al. 2005a, b; Ellis et al. 2006) as useful reagents for deracemization and α-interconversion of α-amino acids. When reactions of ligand (*R*)-**63** containing a configurationally stable stereogenic carbon in addition to the configurationally unstable stereogenic nitrogen with racemic amino acids **64** were conducted at 60–70 °C in methanol in the presence of potassium hydroxide as a base and nickel nitrate as the metal source only two (*R*,R_N)(*S*)-**65** and (*R*,S_N)(*S*)-**66** of the four possible diastereomeric products were formed (Soloshonok et al. 2009) (Scheme 24). Furthermore, the thermodynamic diastereoselectivity strongly favored the diastereomers (*R*,R_N)(*S*)-**65** over (*R*,S_N)(*S*)-**66**. Application of this method to β-branched amino acids valine and phenylglycine was less successful. In these cases the major (*R*,R_N)(*S*) diastereomers favored with a ratio of 1.5/1. The significant difference in chromatographic behavior between diastereomeric complexes allowed for their efficient separation on SiO_2 even on a large scale. Diastereomerically pure major products (*R*,R_N)(*S*)-**65** were disassembled under the standard conditions HCl in MeOH to furnish the enantiomerically pure amino acids (*R*)-**64** along with quantitative recycling of the chiral ligand (*R*)-**63**.

Despite relatively low reaction rates of Ni(II) complex formation between chiral ligand (*S*)-**63** and racemic ω-CF_3 containing amino acids **67**, diastereoselectivity of the reactions was very good favoring formation of the products (*S*,S_N)(*R*)-**68** in 75–79 % yields (Sorochinsky et al. 2013b) (Scheme 25). When the ligand **63** was used of the opposite (*R*) configuration, this deracemization process produced the corresponding complexes with (*R*, R_N)(*S*) stereochemistry with very similar diastereoselectivity and yields. Diastereomerically pure complexes were disassembled in a usual manner to afford the enantiomerically pure amino acids (*R*)-**67** in 63–66 % yield. Taking into account that racemic amino acids **67** can be made using simple and established procedures (Tsushima et al. 1988), this approach can compete with the asymmetric synthesis (Wang et al. 2011) rendering the corresponding enantiomerically pure amino acids readily available for systematic medicinal chemistry studies and peptide design.

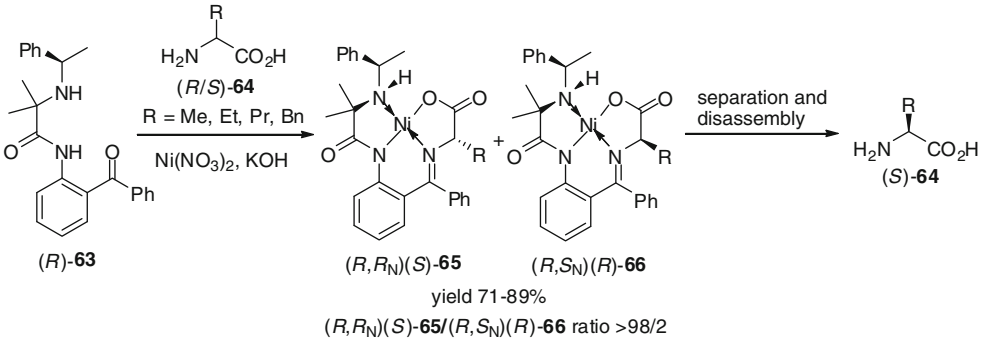
Chiral ligand **63** of (*S*) configuration has also been used for interconversion of easily available from inexpensive natural sources (*S*)-amino acids to (*R*)-enantiomers. Thus, reactions of ligand (*S*)-**63** with amino acids (*S*)-**64a–f** in

Scheme 23 .

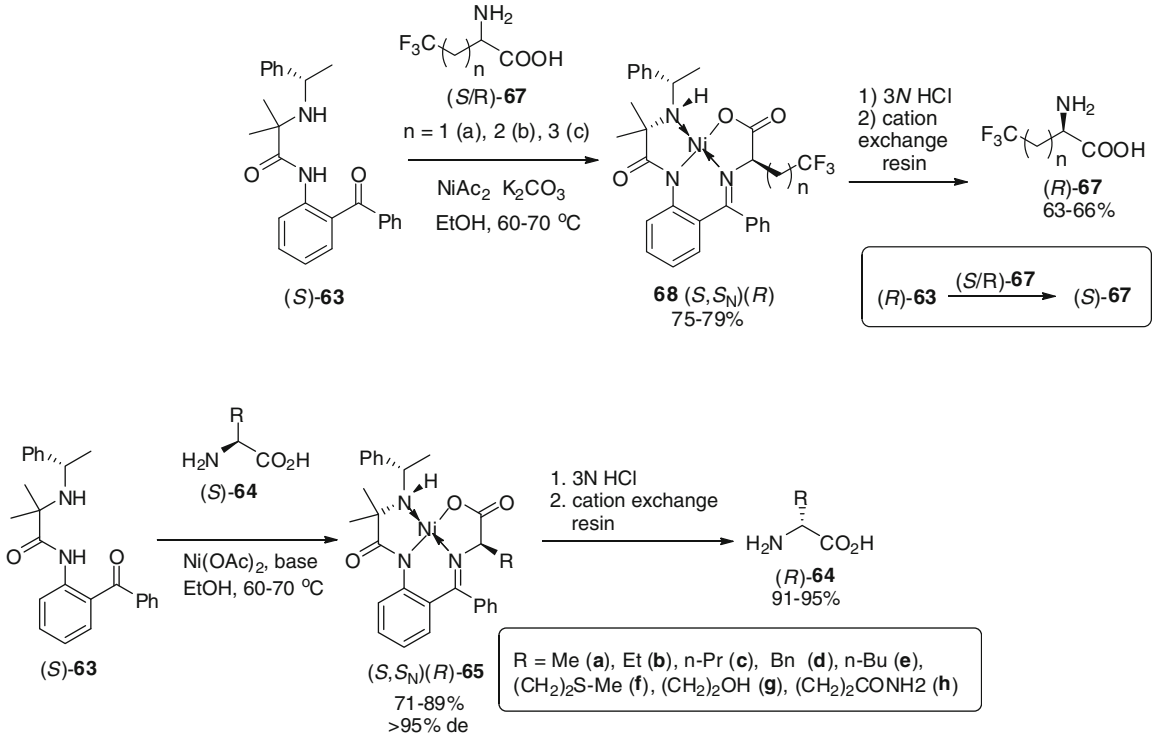


R = 2-Me-C_6H_4 (**a**), 3-Me-C_6H_4 (**b**), 4-Me-C_6H_4 (**c**), 4-MeO-C_6H_4 (**d**), 4-NO_2-C_6H_4 (**e**), 4-F-C_6H_4 (**f**), 4-Cl-C_6H_4 (**g**), 4-Br-C_6H_4 (**h**), 2-furyl (**i**), 3-thiophenyl (**j**), 2-naphthyl (**k**), 2-quinoline (**l**)

Scheme 24 .

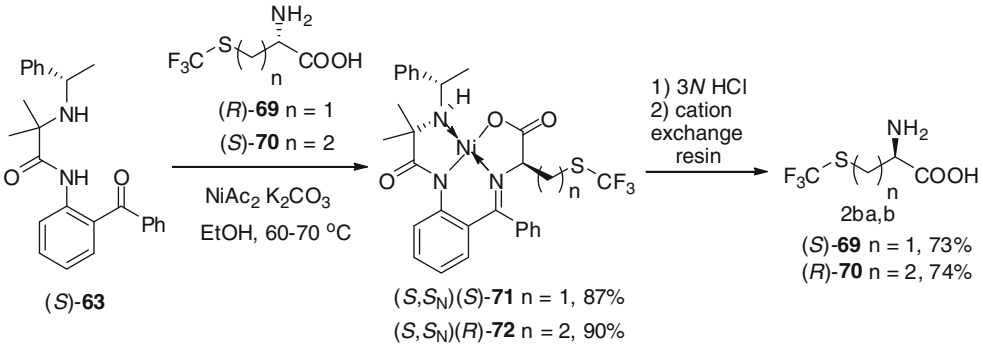


Scheme 25 .



Scheme 26 .

Scheme 27 .



ethanol in the presence of potassium carbonate and nickel acetate were completed within 24 h providing for a high level of asymmetric induction in controlling the stereochemistry of the products $(S,S_N)(R)$-**65-d** (Sorochinsky et al. 2013c) (Scheme 26). The use of DBU as a base for these reactions allowed for preparation of homoserine-

and glutamine-containing complexes (S,S_N)(R)-**65g, h**. Further disassembly of complexes (S,S_N)(R)-**65** afforded enantiomerically pure (R) configured α-amino acids **64** in 91–95 % yield.

Under the standard thermodynamically controlled conditions, reactions of chiral ligand (S)-**63** with fluorinated amino acids (R)-**69** and (S)-**70** easily prepared from naturally occurring and inexpensive (R)-cysteine and (S)-methionine (Soloshonok et al. 1992c; Kieltsch et al. 2007, 2008; Capone et al. 2008) gave rise to complexes (S,S_N)(S)-**71** and (S,S_N)(R)-**72** with high diastereoselectivity and in 87 and 90 % yield, respectively (Sorochinsky et al. 2013b) (Scheme 27). Disassembling of complexes (S,S_N)(S)-**71** and (S,S_N)(R)-**72** purified by column chromatography allowed preparation of new (R)-stereoisomers of S-CF_3 derivatives **69** and **70** in good isolated yields.

Conclusions

This review has demonstrated that aldol reactions between chiral Ni(II) complexes of glycine Schiff bases and carbonyl compounds offer practical, general and synthetically efficient approach for preparing various α-amino-β-hydroxy acids and their derivatives in enantiomeric pure form. Furthermore, the recently developed asymmetric Mannich reaction of chiral Ni(II) complex of glycine Schiff base with imines provides a new strategy for the construction of diverse α,β-diamino acid derivatives useful in organic and medicinal chemistry. Further methodological development to increase the stereoselectivity of the Mannich reactions of chiral Ni(II) complexes of glycine Schiff bases and construction of quaternary stereocenters in this family of molecules with valuable biological properties deserve further systematic study. The use of new type of "NH" Ni(II)-complexes of Schiff base of glycine containing a configurationally unstable stereogenic nitrogen is reliable method for both separation of enantiomers of *rac*-α-amino acids and interconversion of (S)-α-amino acids to the corresponding (R)-α-enantiomers via formation of diastereomeric derivatives with optimal differences in stereochemistry and physicochemical properties allowing for their easy separation. The recovery of the chiral ligands and their reuse for preparation of the starting Ni(II) complexes without any loss in enantiomeric purity and reactivity is another attractive practical aspect of these procedures suitable for larger scale preparations of various amino acids in an enantiomerically pure form.

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

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