Amino Acids (2013) 45:691–718
DOI 10.1007/s00726-013-1539-4

REVIEW ARTICLE

Asymmetric synthesis of α-amino acids via homologation of Ni(II) complexes of glycine Schiff bases; Part 1: alkyl halide alkylations

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Received: 16 April 2013 / Accepted: 17 June 2013 / Published online: 6 July 2013

Abstract Alkylations of chiral or achiral Ni(II) complexes of glycine Schiff bases constitute a landmark in the development of practical methodology for asymmetric synthesis of α-amino acids. Straightforward, easy preparation as well as high reactivity of these Ni(II) complexes render them ready available and inexpensive glycine equivalents for preparing a wide variety of α-amino acids, in particular on a relatively large scale. In the case of Ni(II) complexes containing benzylproline moiety as a chiral auxiliary, their alkylation proceeds with high thermodynamically controlled diastereoselectivity. Similar type of Ni(II) complexes derived from alanine can also be used for alkylation providing convenient access to quaternary, α,α-disubstituted α-amino acids. Achiral type of Ni(II) complexes can be prepared from picolinic acid or via recently developed modular approach using simple secondary or primary amines. These Ni(II) complexes can be easily mono/bis-alkylated under homogeneous or phase-transfer catalysis conditions. Origin of diastereo-/enantioselectivity in the alkylations reactions, aspects of practicality, generality and limitations of this methodology is critically discussed.

Keywords Amino acids and peptides · Unnatural amino acids · Asymmetric synthesis · Chiral auxiliary · Organometallic compounds · Nickel

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Introduction

The asymmetric synthesis of α-amino acids (α-AAs) continues to be a subject of intense current research interest and ever increasing technological importance in major areas of chemical industries dealing with health care and food production. In particular, pharmaceutical and agrochemical industries heavily depend on the progress in amino acids availability and large-scale production. It would not be overstatement to say that the price of pharmaceuticals and the rate of the development of new drug candidates practically reflect the current methodological state in the area of asymmetric synthesis of amino acids (Izumi et al. 1978; Coppola and Schuster 1987).

Although a significant progress in this area has been already achieved (Duthaler 1994; Maruoka and Ooi 2003; Ma 2003; Nájera and Sansano 2007; Soloshonok and Sorochinsky 2010; Aceña et al. 2012), a general and cost-effective access to structurally varied α-AAs, on relatively large scale, has not been reached thus far. To name just a few of the most relevant synthetic strategies, the asymmetric hydrogenation of α,β-dehydro-α-amino acid derivatives (Etayo and Vidal-Ferrán 2013) or the Strecker reaction (Wang et al. 2011a) has produced outstanding results in the last decades. However, both methods cannot

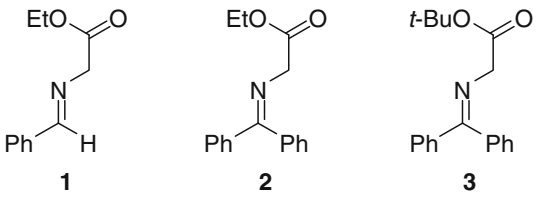


Fig. 1 Achiral nucleophilic glycine equivalents

be successfully applied to the synthesis of all types of α-AAs.

In this respect, the alkylation of nucleophilic equivalents of glycine and higher amino acids is probably the most practical and direct method for the synthesis of structurally varied and/or conformationally restricted, sterically constrained α-AAs. One of the most useful types of achiral nucleophilic glycine equivalents is imines derived from glycine esters **1** and **2** (Fig. 1) introduced for homologation of glycine into various higher amino acids (Stork et al. 1976). This area was revolutionized by O'Donnell who demonstrated that imine **3**, derived from benzophenone and *tert*-butyl ester of glycine, can be alkylated with high enantioselectivity using cinchona alkaloids-derived phase-transfer catalysts (O'Donnell and Eckrich 1978; O'Donnell et al. 1988, 1989; O'Donnell 2001, 2004). Subsequent work by many research groups (Corey et al. 1997; Chinchilla et al. 2000; Park et al. 2002; Shibuguchi et al. 2002), most notably by Lygo (Lygo and Wainwright 1997; Lygo et al. 2001, 2002, Lygo and Andrews 2004) and Maruoka (Ooi et al. 1999, 2003; Hashimoto and Maruoka 2007; Ooi and Maruoka 2007; Shirakawa and Maruoka 2013) have expanded the synthetic utility of this glycine equivalent through the design of new and more efficient catalysts, mostly quaternary ammonium salts, leading to enantioselectivities usually higher than 99 %. One problem still associated with this methodology is the inherent hydrolytical instability of Schiff base and products of its homologation, resulting in incomplete chemical yields.

Another milestone in the asymmetric synthesis of α-AAs is the application of chiral derivatives of glycine. The most remarkable examples are Schöllkopf bislactims **4** (Schöllkopf et al. 1981; Schöllkopf 1983a, b; Undheim 2008), Williams diarylmorpholinones **5** (Sinclair et al. 1986; Williams et al. 1988; Williams and Im 1991; Sebahar and Williams 2000) and Seebach imidazo- and oxazolidinones **6** (Fitzi and Seebach 1988; Seebach et al. 1996) (Fig. 2). In these cyclic templates, one of the faces of the corresponding in situ prepared enolate is effectively sterically shielded providing for virtually complete stereoselectivity. Acyclic nucleophilic glycine equivalents, such as Myers glycinamide **7** (Myers et al. 1997) and Evans oxazolidinone **8** (Evans and Weber 1986), have also been successfully applied for the synthesis of α-amino acids.

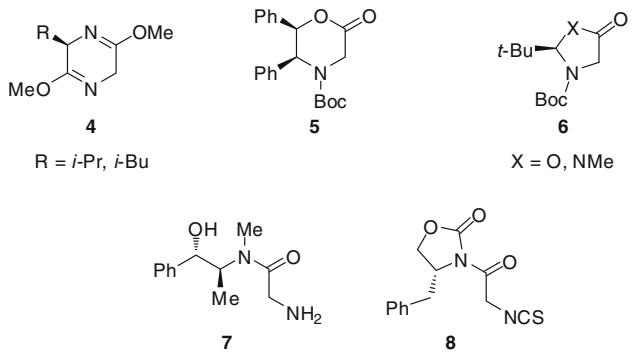
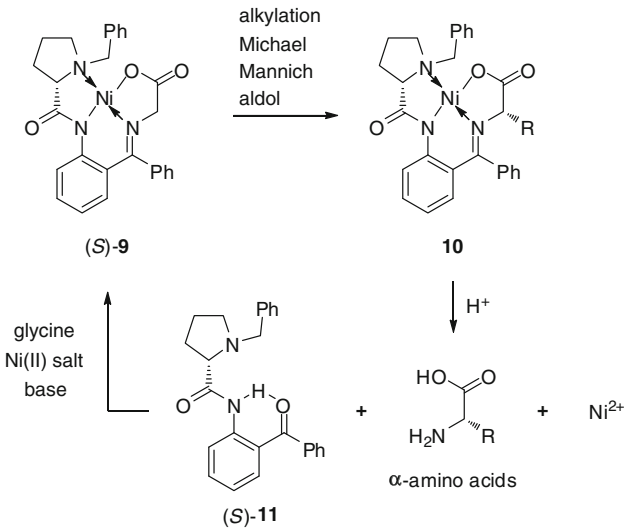


Fig. 2 Chiral nucleophilic glycine equivalents

However, the main disadvantage of compounds **4**–**8** is the low C–H acidity of the glycine methylene moiety, which requires the use of strong bases, such as *n*-BuLi, low temperatures, usually −78 °C, and anhydrous conditions to form the corresponding enolates. Furthermore, preparation of these derivatives requires multi-step sequences, rendering them relatively expensive, in particular for application on a large scale.

Transition metal complexes derived from glycine Schiff bases constitute a convenient template for an easy functionalization of the glycine moiety. Belokon et al. (1983) described Cu(II) complexes of glycine and other amino acids using (*S*)-2-[*N*-(*N*′-benzylprolyl)amino]-benzophenone (BPB, (*S*)-**11**) as chiral ligand and studied their reactivity, in particular aldol addition reactions. Further development of this approach revealed that the corresponding Ni(II) complex (*S*)-**9** is more practical due to its higher stability and overall reactivity (Belokon et al. 1985a). In addition, the paramagnetic character of the Cu(II) complexes impedes their analysis using NMR techniques. The most synthetically appealing features of Ni(II) complex (*S*)-**9** include its easy preparation from available and inexpensive starting materials and generally highly diastereoselective functionalization of the glycine moiety. In particular, the homologation of the glycine complex (*S*)-**9** can be conducted via the following major types of reactions: alkyl halide alkylations, the subject of this review, Michael (Soloshonok et al. 1999, 2000a, b, 2005a), aldol (Soloshonok et al. 1993, 1995, 1996a, b) and Mannich (Soloshonok et al. 1997) addition reactions (Scheme 1). All these reactions can be conducted under operationally convenient reaction conditions (Boyall et al. 2002; Soloshonok and Berbasov 2004; Moore et al. 2005; Soloshonok et al. 2006a, b; Yasumoto et al. 2007), at ambient temperature or moderate heating, commercial grade solvents and, in most of cases, just in the open air. The decomposition or disassembly of the homologation products **10** is also operationally convenient, requiring heating of products **10** in a mixture of methanol and 3 N



Scheme 1 Strategies for the homologation of the glycine complex (*S*)-**9**

HCl. Finally, isolation of the target amino acids can be achieved using in situ derivatization or by use of ion-exchange chromatography on Dowex-type resins. It is very important to emphasize that at the disassembly step, the chiral ligand (*S*)-**11** can be quantitatively recovered and, in most cases, reused to produce new portions of the glycine complex (*S*)-**9**.

Complex (*S*)-**9** is a red, crystalline compound and can be purified by crystallization or chromatography on SiO_2. Crystal structure analysis of (*S*)-**9** reveals that the complex is square planar, neutral with two positive charges at the central Ni ion neutralized by two negative charges (CON^- and COO^-) of the tetradentate ligand (Kožíšek et al. 2004). Crystallographic data and theoretical calculations suggest that in one of the low-energy conformations, the benzyl group is located above the metal in the coordination plane. It is assumed that possible weak interaction between the Ni atom and the benzyl group can additionally stabilize the conformation of the complex in which the benzyl group is fixed above the central Ni atom and reduces the distance between the plane of the benzyl group and the nickel atom (Popkov et al. 2003). Consequently, much work has been focused on the preparation of analogs of (*S*)-**9** at the benzyl moiety with the aim of improving the diastereoselective outcome of the alkylation reactions.

A second type of Ni(II) complexes derived from glycine are based on achiral ligands. For instance, Belokon et al. (1997) and Soloshonok et al. reported the preparation of Ni(II) complexes **12** and **13** derived from 2-(*N*-(α-picolyl)amino)benzophenone (PABP) and -acetophenone, respectively (Fig. 3). Complexes **12** and, in particular, **13** were found to be excellent achiral glycine equivalents in the Michael addition reactions with chiral oxazolidinone-

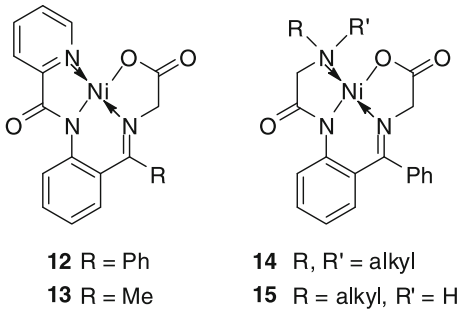
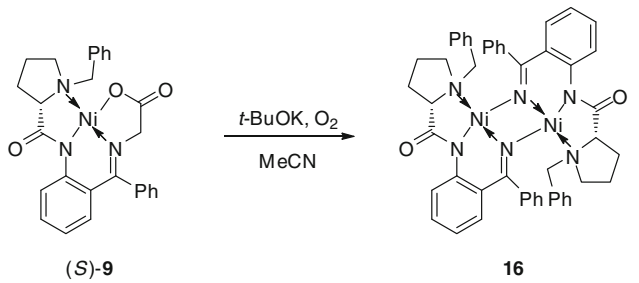


Fig. 3 Achiral Ni(II) complexes of glycine Schiff bases

derived Michael acceptors (Soloshonok et al. 2000c, d, 2004; Cai et al. 2004), providing for very efficient synthesis of various sterically constrained β-substituted amino acids (Qiu et al. 2001; Soloshonok 2002) used for total synthesis of oxazolomicine antibiotics (Yamada et al. 2008) and new thalidomide derivatives (Yamada et al. 2006; Soloshonok et al. 2009a). Another type of achiral Ni(II) complexes **14** and **15** was recently introduced by Soloshonok et al. (2005b, c, 2009b). The major advantage of complexes **14** and **15** is their easy modular assembly and structural flexibility allowing to tailor virtually any desired reactivity and physicochemical properties. In addition, the cost of preparing complexes **14** and **15** is much lower compared to those derived from *N*-benzylproline or picolinic acid. Both types of achiral complexes **12**–**15** are suitable for diastereo- or enantioselective homologation reactions, using chiral reagents or catalysts, respectively.

Discussing general features of Ni(II) complexes **9**, **12**–**15** reactivity, it should be mentioned that when their synthesis or their homologation is conducted under strongly basic conditions and in the presence of oxygen, one unusual oxidative reaction takes place (Scheme 2). It is assumed that in situ generated enolate react with molecular oxygen to trigger a cascade of transformations resulting in the formation of binuclear Ni(II) complexes **16** (Soloshonok and Ueki 2007). These products possess an inherent helical chirality and their chiroptical properties can be applied in the area of chiral nano-technology (Soloshonok et al. 2010).

Despite the large number of contributions reported thus far on the synthetic applications of Ni(II) complexes of glycine and other α-AAs, it is surprising the lack of review articles covering this important area. In fact, the only general review published by Belokon (1992) was a result of a symposium presentation. Later on, Soloshonok reported the progress in Michael additions to Ni(II) complexes of glycine (Soloshonok 2002; Soloshonok et al. 2009b), and very recently Popkov accounted for their applications in the synthesis of radiolabelled compounds (Popkov and De Spiegeleer 2012). Accordingly, the general aim of this



Scheme 2 Synthesis of binuclear Ni(II) complex with inherent helical chirality

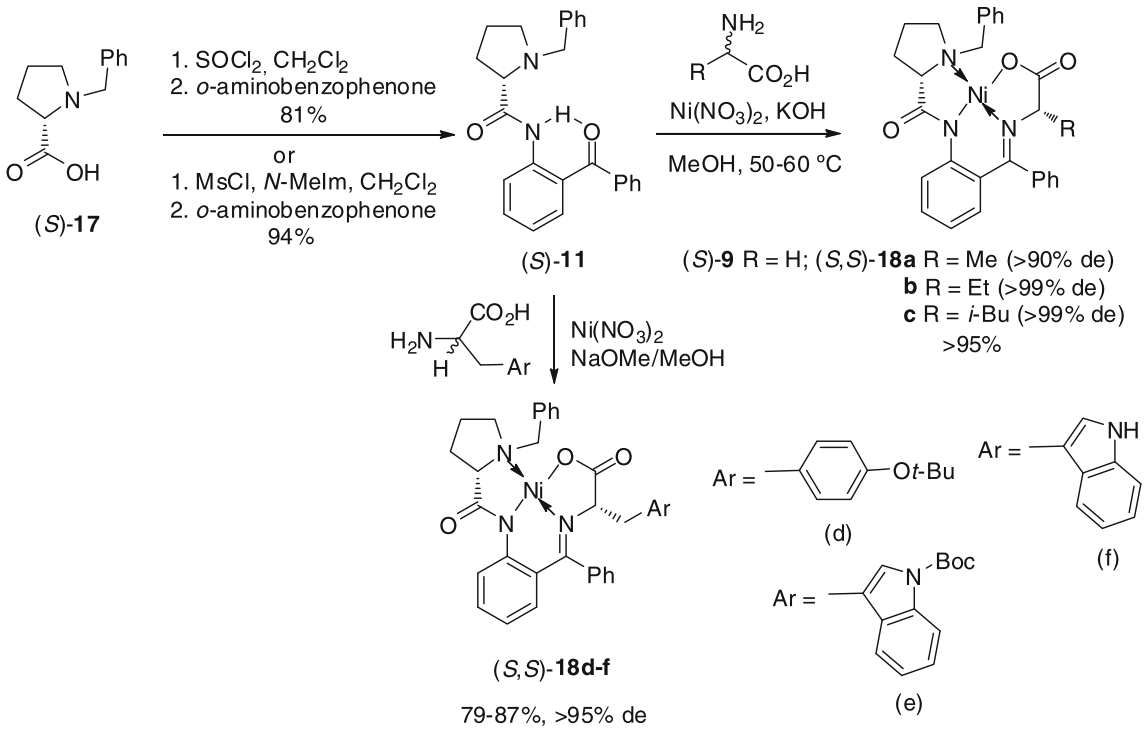
review is to cover the most direct homologation reactions on these glycine equivalents, i.e. alkylations, providing a comprehensive outlook of this important transformation leading to α-AAs after disassembling the corresponding alkylated Ni(II) complexes. The specific aspects shown are the synthesis of the starting nickel complexes, their differences in reactivity and the differences in alkylation conditions (homogeneous vs. heterogeneous), as well as those topics related with the diastereo- and/or enantioselectivity of the reactions.

Synthesis of Ni(II) complexes of Schiff's bases derived from *o*-amino-benzo-/aceto-phenones and α-amino acids

The Ni(II) complexes of the Schiff bases derived from (*S*)-2-[*N*-(*N*′-benzylprolyl)amino]benzophenone (BPB) (*S*)-**11** and glycine or higher α-amino acids can be prepared on large scale by a simple sequence of reactions starting from *N*-benzylproline (BP) (*S*)-**17** (Scheme 3). In the original procedure published by Belokon et al. (1988, 1998) (*S*)-**17** is converted in situ to the corresponding acyl chloride using excess of $SOCl_2$ at low temperature followed by the reaction with *o*-aminobenzophenone to afford the ligand (*S*)-**11** in 81 % yield. However, the use of almost 50 % excess of (*S*)-**17** on the amidation stage renders this procedure unattractive for large-scale preparation of the target Ni(II) complexes. An improved procedure, described by Soloshonok et al. included the in situ preparation of a mixed anhydride by addition of MsCl and *N*-MeIm to (*S*)-**17** in a CH_2Cl_2 solution. The reaction of thus prepared mixed anhydride with *o*-aminobenzophenone was completed at 40–50 °C affording higher than 90 % conversion of the phenone to the target ligand (*S*)-**11** which was isolated in 94 % yield (Ueki et al. 2003a). The ligand (*S*)-**11** can be purified by crystallization of the crude product from ethanol as well as by precipitation of the corresponding hydrochloride salt from a solution of the reaction mixture in acetone. Further formation of the Ni(II) complexes (*S*)-**9** and (*S*,*S*)-**18a–f** easily takes place on heating (*S*)-**11** in methanol in the presence of base, the corresponding α-amino acids and a source of Ni(II) ions (Belokon et al. 1988, 1998; Nádvorník and Popkov 2002; Ueki et al. 2003a; Soloshonok et al. 2008a; Nádvorník et al. 2008). Excess of aliphatic α-amino acids and $Ni(NO_3)_2{\cdot}6H_2O$ was used in a standard protocol in order to obtain Ni(II) complexes (*S*)-**9** and (*S*,*S*)-**18a–c** in >95 % yields. Using near stoichiometric amounts of nickel salt and aromatic α-amino acids led to lower yields of the Ni(II) complexes (*S*,*S*)-**18d–f**. In the case of the Ni(II) complex (*S*,*S*)-**18a** the use of enantiomerically pure (*S*)- or racemic (*R*/*S*)-alanine had no influence on the final diastereomeric purity (>90 %) of the isolated complex. Since the complex was synthesized in highly alkaline media at elevated temperatures, racemization of the amino acid, via enolate formation, proceeds fast and the ratio of the diastereomeric complexes reflects the thermodynamic equilibrium between them. The Ni(II) complexes (*S*,*S*)-**18b**,**c** containing bulkier substituents were obtained in diastereomerically pure form while the diastereomeric excess of (*S*,*S*)-**18d–f** in all cases was >95 %. It should be noted that the *N*-atom of the proline residue is chiral; however, it creates no problem in terms of possible diastereomers formation as the absolute configuration of the *N*-stereogenic center is completely controlled by the proline's *C*-chirality.

These methods were also successfully used for preparing Ni complexes **19–27** (De and Thomas 1997; Ueki et al. 2003a; Belokon et al. 2002; Saghiyan et al. 2006, 2010; Popkov et al. 2002), containing ligands with various substituents on the *o*-amino-benzo/aceto-phenone moiety as well as the proline chiral auxiliary (Fig. 4).

Ni(II) glycine-derived achiral complexes **12** and **13** as well as alanine-derived racemic complex **30** were prepared by condensation of the acid chloride derived from picolinic acid **28** with *o*-amino-benzo/aceto-phenones followed by heating ligands **29** with glycine or (*S*/*R*)-alanine and $Ni(NO_3)_2$ in the presence of KOH or MeONa in methanol (Belokon et al. 1997, 2001, 2003a) (Scheme 4). The structures of complexes **12**, **13** and **30** were confirmed by X-ray analysis. It should be noted that application of excess of $SOCl_2$ for the preparation of the acid chloride of **28** led to substantial formation of byproducts and laborious purification of ligands **29**. On the other hand, when activation of **28** was carried out by the mixed anhydride method using ethyl chloroformate, complete conversion of *o*-aminobenzophenone as well as *o*-aminoacetophenone was observed during the condensation step. The amidation proceeded smoothly giving rise, in quantitative chemical yield, to the target ligands **29**, which could be used without any additional purification for preparing the corresponding Ni(II) complexes **12**, **13** and **30** (Ellis et al. 2003a; Ueki et al. 2003b).



Scheme 3 Synthesis of Ni(II) complexes of Schiff bases derived from 2-[*N*-(*N*′-benzylprolyl)amino]benzophenone (*S*)-**11** and α-amino acids

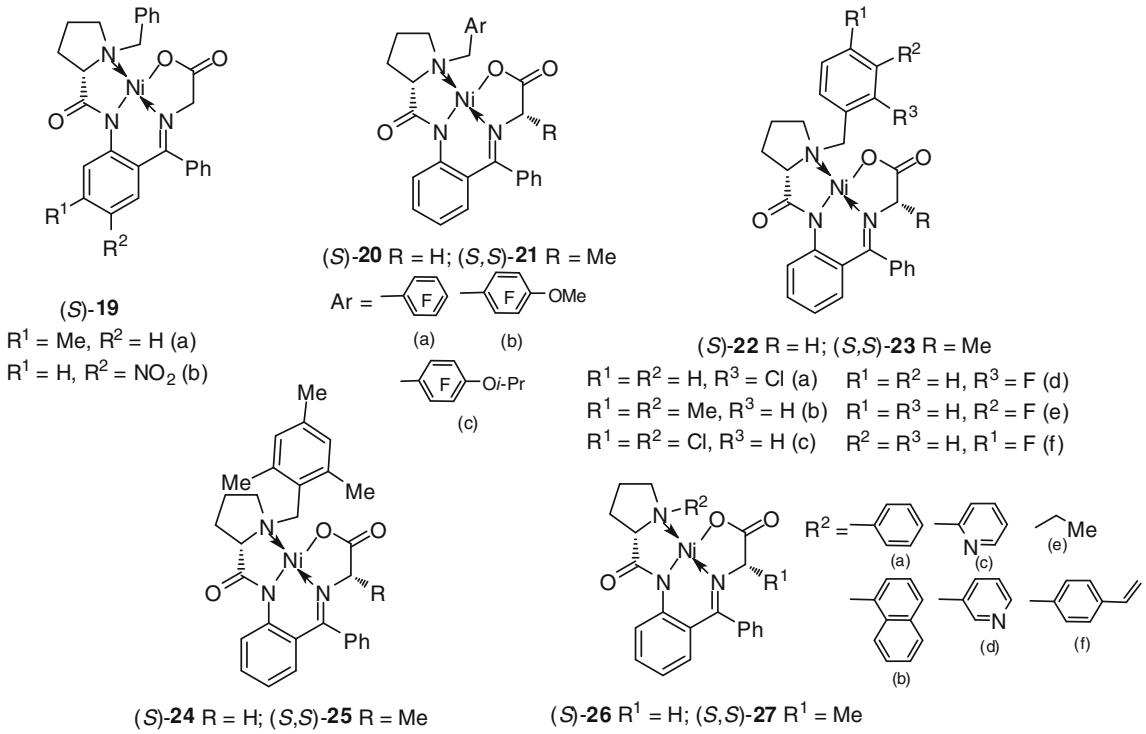
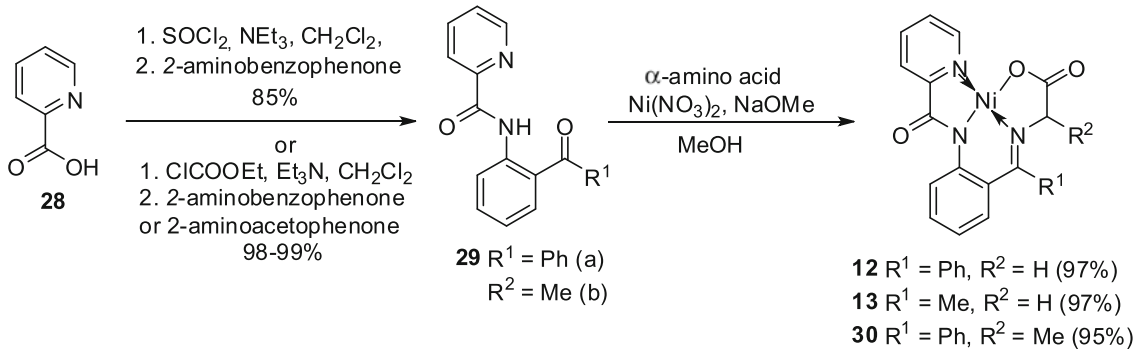


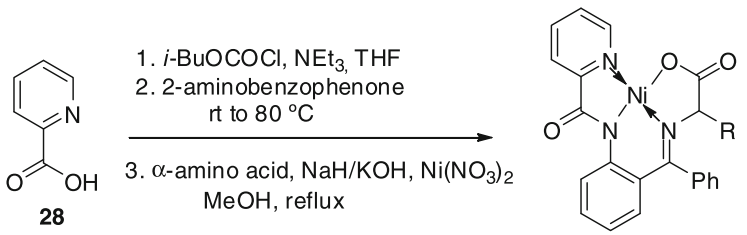
Fig. 4 Modified chiral Ni(II) complexes of Schiff bases of α-amino acids

On the basis of the mixed anhydride method, a one-pot, two-step protocol, which did not require isolation of ligand **29a** as a separate step, has been developed for preparation of Ni(II) complexes derived from picolinic acid (Deng et al. 2007). Optimization of the one-pot procedure conditions using sterically hindered isobutyl chloroformate,



Scheme 4 Synthesis of the Ni(II)-complexes of glycine and alanine Schiff bases with 2-[*N*-(α-picolyl)amino]aceto/benzophenones

Scheme 5 One-pot synthesis of Ni(II) complexes derived from picolinic acid



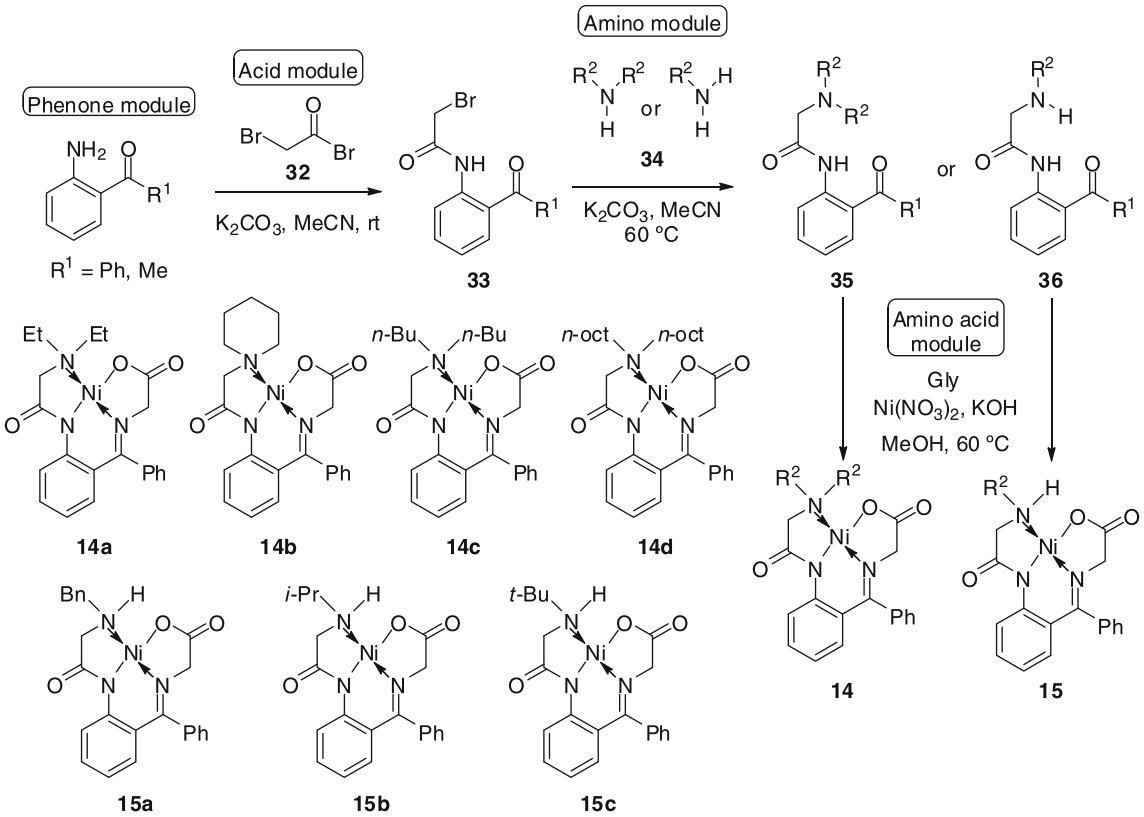
mixed bases NaH/KOH and THF as solvent allowed to obtain the Ni(II) complexes **12**, **30** and **31** in 84–98 % yield (Scheme 5).

Most recently, the need for a more flexible methodology and inexpensive achiral Ni(II) complexes led to the development of the new generation of achiral glycine equivalents **14** (Ellis and Soloshonok 2006; Ellis et al. 2006) and **15** (Scheme 6). The synthesis of glycine derivatives **14** and **15** is based on the combination of three different modules: phenone module, acid module **32**, and amine module **34**. The nature of these modules allowed for a rational control of geometry, physical properties and reactivity of derivatives **14** and **15**. Further advantage of this new generation of ligands/Ni(II)-complexes is that the reaction of phenones and commercially available bromoacetyl bromide **32** was usually accomplished in MeCN solution in the presence of K_2CO_3 furnishing acetamide intermediate **33** with high chemical purity. Next, the reaction of **33** with secondary or primary amines **34** afforded ligands **35** and **36**. This reaction was also accomplished in MeCN solution with K_2CO_3. Formation of the Ni(II) complexes **14** and **15** readily took place on moderate heating of MeOH solution of ligands **35** and **36**, glycine and Ni(II) in the presence of KOH. Potassium hydroxide was utilized to catalyze the imine formation as well as to neutralize the corresponding acid formed from the reaction. All three synthetic steps usually proceeded with excellent yields (>95 %) and purification of the intermediate products was not required. This new generation approach has a very attractive cost structure as the average cost of these complexes is less than $1 per gram. To illustrate how easily the physicochemical properties, in particular solubility, of the corresponding Ni(II) complexes can be rationally controlled one can consider a series of derivatives **14a–d**. Thus, the complex **14a** is soluble in DMF or chlorinated solvents such as $CHCl_3$ and CH_2Cl_2. Piperidine-derived **14b** can be dissolved in acetone or methanol, while the *N*,*N*-di-*n*-butylamine derivative **14c** can be used for phase-transfer reactions using benzene and toluene. Finally, *N*,*N*-di-*n*-octylamine containing complex **14d** is soluble in *n*-hexane. In principle, this approach allows preparation of the corresponding Ni(II) complexes soluble in virtually any known solvents including water or a perfluorinated (fluorous) phase.

Besides the synthesis of amino acids via homologation of the corresponding glycine derivatives, this type of new generation of glycine equivalents, containing residues of chiral amines, can also be used for deracemization and (*S*) to (*R*) interconversion of higher amino acids (Soloshonok et al. 2009c; Sorochinsky et al. 2013).

Alkylation of the Ni(II) complexes of the Schiff bases of (*S*)-2-[*N*-(*N*′-benzylprolyl)-amino]benzophenone and α-amino acids

The diastereoselective α-alkylation of chiral Ni(II) complex (*S*)-**9** with alkyl halides is based on the high acidity of the α-protons. In this context, the corresponding enolate can undergo alkylation reactions under different

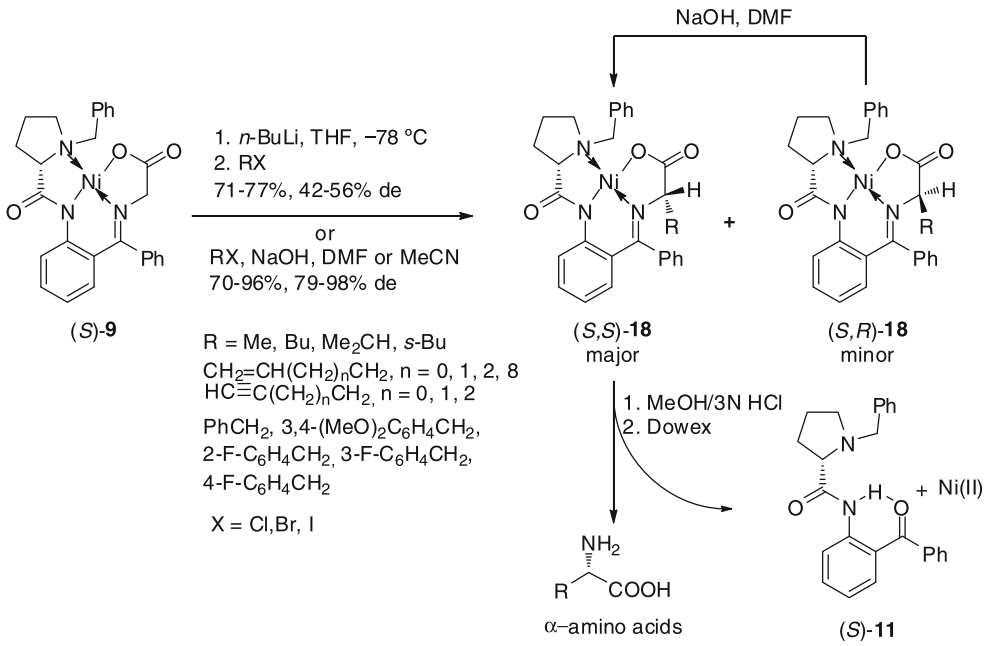


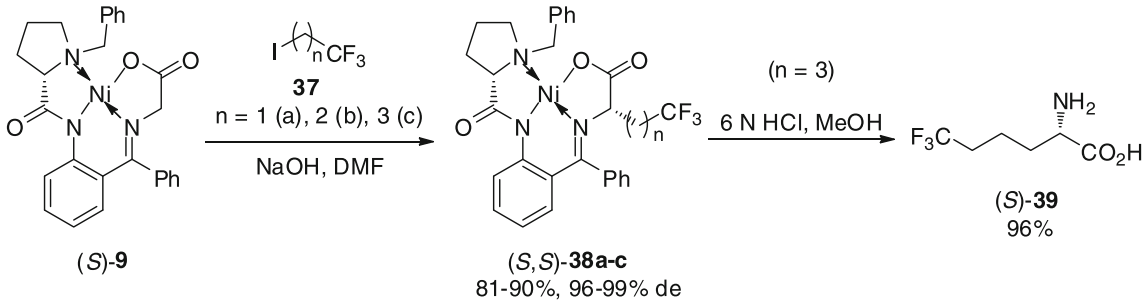
Scheme 6 Synthesis of new generation of nucleophilic glycine equivalents

operationally convenient basic conditions and in high chemical yields. When the enolate was generated using *n*-BuLi in THF at −70 °C followed by treatment with alkyl halides under kinetically controlled conditions the alkylation reactions afforded the corresponding diastereomeric Ni(II) complexes **18** with good chemical yields and 41–42 % diastereoisomeric excess (Belokon et al. 1988) (Scheme 7). Thus, the kinetic stereoselectivity for the monoalkylation is not very high and in the case of sterically small electrophiles is not favored at all. The (*S*) absolute configuration of the *N*-benzylproline residue in (*S*)-**9** induced the (*S*) stereochemistry of the newly formed stereogenic center in the major diastereomers. Alkylation of Ni(II) complex (*S*)-**9** is usually conducted in aprotic solvents such as DMF or MeCN in the presence of NaOH at ambient temperature affording diastereomeric alkylation products which under the experimental conditions undergo α-epimerization leading to thermodynamic control. Thus, in the presence of 2.5 equivalents of NaOH all alkyl halides tested gave thermodynamically favored monoalkylated complex with (*S*)-amino acid residue in up to 98 % de and with yields in the 70–96 % range (Belokon et al. 1988; Collet et al. 1998, 2000; Gu et al. 2002; Le Chevalier Isaad et al. 2008; Kawamoto et al. 2012). While activated benzyl, allyl and propargyl halides can be used as both bromides and chlorides, introduction of non-activated alkyl groups required application of the corresponding bromides or iodides. In order to avoid dialkylation, all active halides were used in slightly less than 1 equiv. Enantiomerically pure α-amino acids with different side chains can be obtained after separation of alkylated diastereoisomeric complexes by fractional recrystallization or column chromatography on SiO_2. Disassembly of the diastereomerically pure alkylation products is usually conducted via hydrolysis with aqueous HCl in MeOH and isolation of the target amino acids by ion-exchange chromatography. The Ni(II) ions remain on the column and can be regenerated with 1 N HCl solution. This procedure also allowed recovery of the chiral ligand (*S*)-**11** which can be reused for the preparation of starting glycine complex (*S*)-**9**.

Successful application of asymmetric alkylation reactions between the glycine equivalent (*S*)-**9** and ω-trifluoromethyl alkyl iodides **37** allowed for an efficient access to enantiomerically pure, linear ω-(trifluoromethyl)-containing α-amino acids (Wang et al. 2011b) (Scheme 8). After optimization of bases, solvents and reaction temperature, the alkylation was performed in the presence of NaOH at ambient temperature in DMF for half an hour to afford the alkylation adducts (*S*,*S*)-**38** with high diastereoselectivity. However, the chemical yields of Ni(II) complexes

Scheme 7 Alkylation of the glycine Ni(II) complex (*S*)-**9**



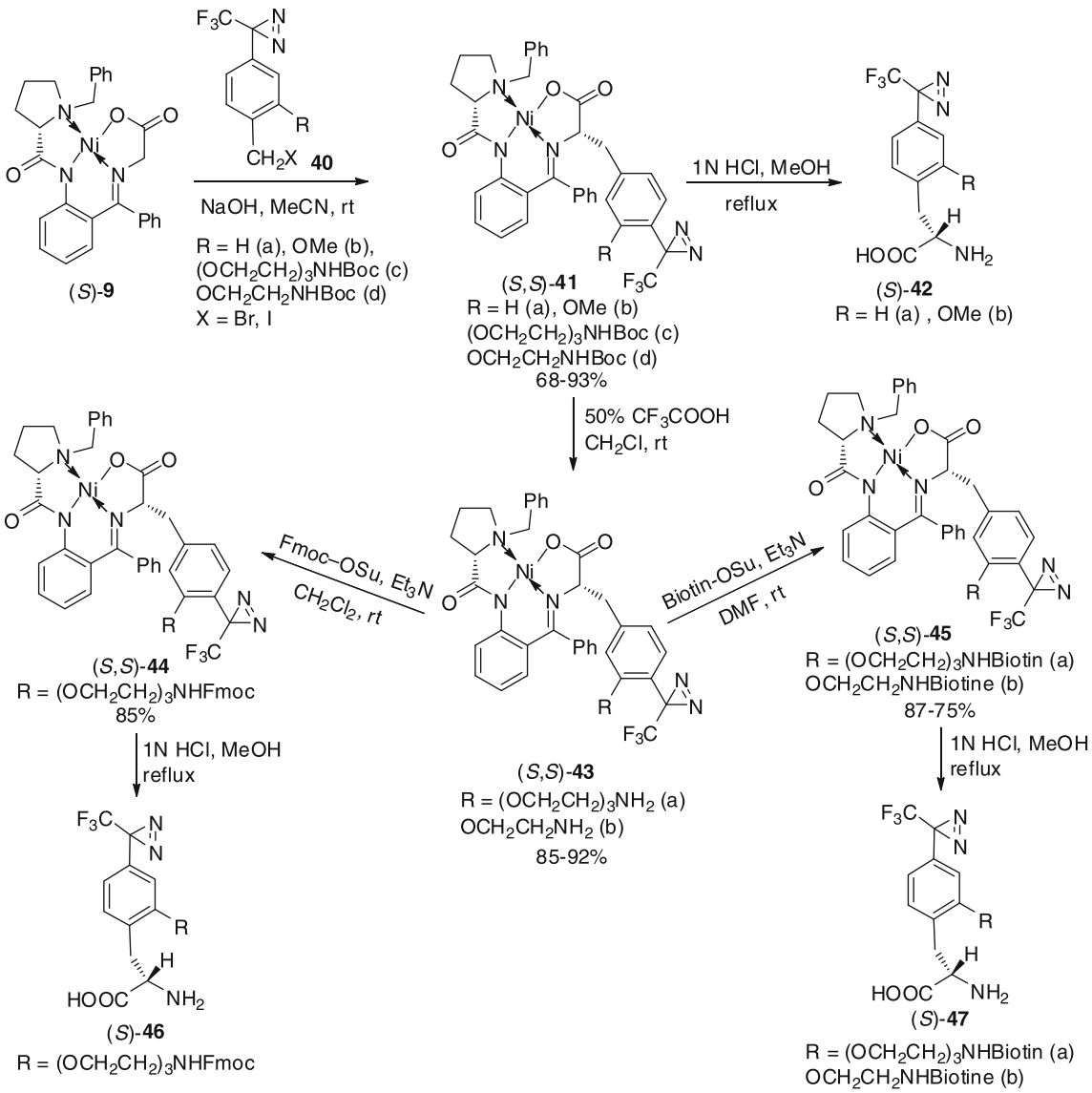


Scheme 8 Alkylation of the glycine Ni(II) complex (*S*)-**9** with ω-trifluoromethyl alkyl iodides **37**

gradually decreased with the alkyl chain length, indicating the increasing electronic effect of the trifluoromethyl group (Soloshonok et al. 1994a, b). The standard procedure for hydrolysis was performed by heating (*S*,*S*)-**38c** in methanol/6 N HCl to afford 2-amino-6,6,6-trifluorohexanoic acid (*S*)-**39** in 96 % yield.

Alkylation of chiral glycine equivalent (*S*)-**9** with (3-trifluoromethyl)phenyldiazirinyl bromides **40** has been developed for efficient synthesis of photoreactive L-phenylalanine derivatives (Fishwick et al. 1994; Hashimoto et al. 2002) (Scheme 9). The reactions proceeded in the presence of powdered NaOH in MeCN at room temperature with virtually complete diastereoselectivity to afford alkylated Ni(II) complexes (*S*,*S*)-**41** in high yield. Hydrolysis of the Ni(II) complexes (*S*,*S*)-**41a**,**b** occurred rapidly in refluxing HCl/MeOH, without destruction of the diazirine ring, to give the amino acids (*S*)-**42** after cation-exchange chromatography. On the other hand treatment of the Ni(II) complexes (*S*,*S*)-**41c**,**d** with 50 % TFA–CH_2Cl_2 at room temperature selectively deprotected the *N*-Boc groups affording the amino containing Ni(II) complexes (*S*,*S*)-**43**. Subsequent reactions of (*S*,*S*)-**43** with FmocOSu and biotin *N*-hydroxysuccinimide under standard conditions afforded *N*-protected Ni(II) complexes (*S*,*S*)-**44** and (*S*,*S*)-**45**. Finally, acidic hydrolysis allowed quantitative disassembly of the Ni(II) complexes (*S*,*S*)-**44** and (*S*,*S*)-**45** giving rise to Fmoc-protected and biotinylated amino acid derivatives (*S*)-**46** and (*S*)-**47**, respectively. These amino acids are suitably protected for incorporation into bioactive peptides to investigate their properties and functions.

An approach to 3-(*trans*-2-nitrocyclopropyl)alanine (2*S*,1′*R*,2′*S*)-**50** was developed based on the alkylation of the Ni(II) complex (*S*)-**9** with enantiomerically enriched *trans* 1-(iodomethyl)-2-nitrocyclopropane (1*S*,2*S*)-**48**. The fast and highly diastereoselective alkylation of (*S*)-**9** in a DMF/MeCN mixture using NaH as a base yielded the alkylation product (*S*,*S*)-**49** as a single diastereomer (Larionov et al. 2003; Zlatopolskiy et al. 2004) (Scheme 10). Only trace amounts of other diastereomers of **49** were observed by ^{1}H NMR analysis of the reaction mixture. The

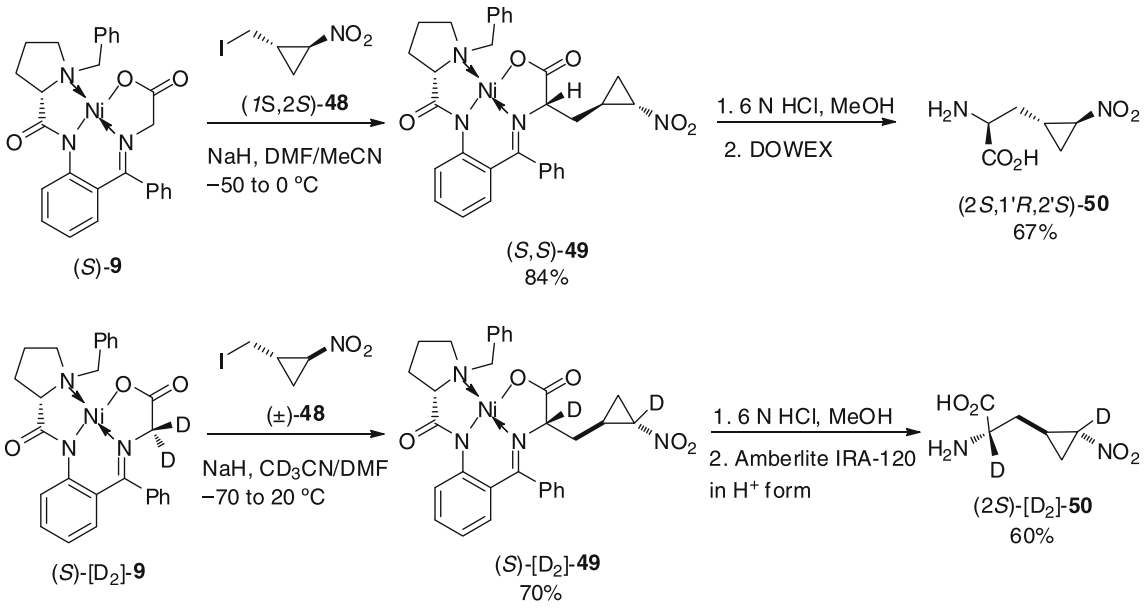


Scheme 9 Synthesis of 3-(trifluoromethyl)phenyldiazirine based alanine derivatives

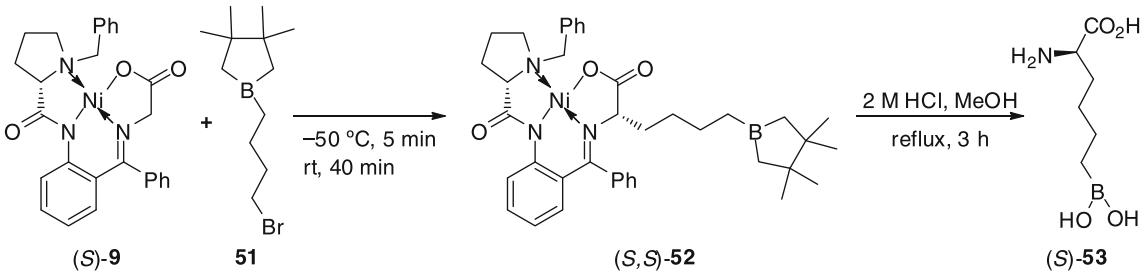
Ni(II) complex (*S*,*S*)-**49** was decomposed by treatment with 6 N HCl to give the amino acid (2*S*,1′*R*,2′*S*)-**50** with 95 % ee and 67 % yield after ion-exchange chromatography and crystallization. Following this protocol the deuterated compound (*S*)-$[D]_2$-**9**, which was prepared by a hydrogen/deuterium exchange with a very high degree of deuteration (>97 % of the incorporation of two deuterium atoms per molecule), was alkylated with the racemic iodide **48** in a mixture of CD_3CN and DMF to give deuterated Ni(II) complex (*S*)-$[D_2]$-**49** in 70 % yield. The subsequent hydrolysis of the Ni(II) complex (*S*)-$[D_2]$-**49** gave the corresponding deuterated amino acid (2*S*)-$[D_2]$-**50** isolated in 60 % yield by ion-exchange chromatography.

A simple synthesis of the potent arginase inhibitor 2-amino-6-boronohexanoic acid (*S*)-**53** included alkylation of the Ni(II) complex (*S*)-**9** with pinacol 4-bromobutylboronate **51** (Vadon-Legoff et al. 2005) (Scheme 11). When the reaction was performed using 3.0 equiv of *t*-BuOK as a base in THF at room temperature alkylated Ni(II) complex (*S*,*S*)-**52** was formed with 80 % de and 83 % yield. Application of other solvents or bases resulted in lower yields and stereochemical outcome of alkylated Ni(II) complex (*S*,*S*)-**52**. Further recrystallization and hydrolysis of the alkylated Ni(II) complex (*S*,*S*)-**52** by heating in HCl/MeOH with simultaneous deprotection of the boronic acid led to 2-amino-6-boronohexanoic acid (*S*)-**53** with 97 % ee.

Taking into account the biological importance of phosphorus-functionalized amino acids (Kukhar et al. 1994), a highly selective procedure for the synthesis of ω-phosphino- and phosphono-α-amino acids through the alkylation of the Ni(II) complex (*S*)-**9** has been developed.



Scheme 10 Synthesis of 3-(trans-2-nitrocyclopropyl)alanine (2*S*,1′*R*,2′*S*)-**50** and the corresponding deuterated amino acid (2*S*)-[D_2]-**50**

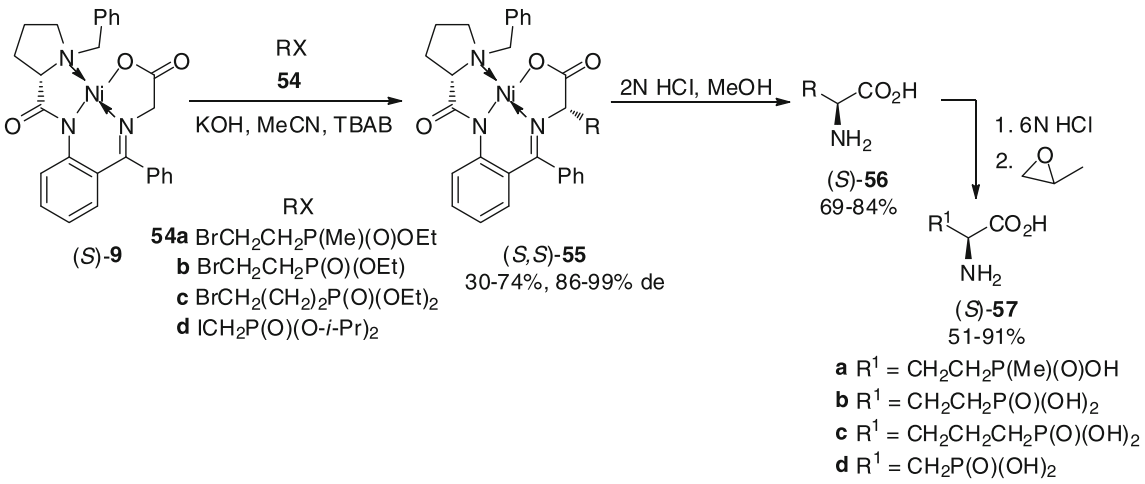


Scheme 11 Synthesis of 2-amino-6-boronohexanoic acid (*S*)-**53**

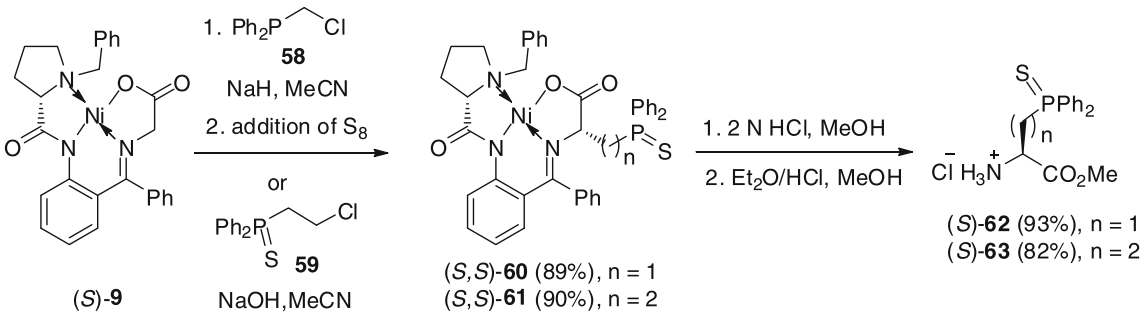
Alkylation of (*S*)-**9** with the halogenoalkylphosphinate **54a** and halogenoalkylphosphonates **54b**,**c** in MeCN solution at ambient temperature in the presence of powdered KOH favored the formation of (*S*,*S*)-diastereoisomers **55a–c** in a 86–90 % de (Soloshonok et al. 1992a, b) (Scheme 12). On the other hand alkylation of the Ni(II) complex (*S*)-**9** with diisopropyl iodomethylphosphonate **54d** gave the corresponding diastereoisomerically pure complex (*S*,*S*)-**55d**. Decomposition of complexes (*S*,*S*)-**55** under mild conditions with 2 N HCl furnished amino acids (*S*)-**56**, which had free carboxyl groups and esterified phosphinic and phosphonic groups. Enantiomerically pure α-amino-ω-phosphinic and -phosphonic acids (*S*)-**57** can be obtained from the corresponding esters after hydrolysis with HCl under reflux and treatment with propylene oxide.

Alkylation of the Ni(II) complex (*S*)-**9** with the phosphine-containing reagents **58** and **59**, followed by sulfurization in the case of **55**, afforded alkylated Ni(II) complexes (*S*,*S*)-**60** and (*S*,*S*)-**61** as single diastereomers (Burck et al. 2009) (Scheme 13). After column chromatography the complexes (*S*,*S*)-**60** and (*S*,*S*)-**61** were isolated as red powders in yields of about 90 %. The (*S*) configuration at the α-carbon atom of the glycine fragment was confirmed for both products by X-ray analysis. Ni(II) complexes (*S*,*S*)-**60** and (*S*,*S*)-**61** were hydrolyzed by heating in a mixture of MeOH and 2 M HCl and after simple work-up, including the recovery of the free ligand (*S*)-**11**, methyl esters (*S*)-**62** and (*S*)-**63** were isolated in 93 and 82 % yield, respectively.

Alkylation of the Ni(II) complex (*S*)-**9** conducted under thermodynamically controlled conditions at room temperature in the presence of KOH or NaOH was efficiently carried out with sterically hindered 2′,2′-dimethylbenzyl halides **64** (Tang et al. 2000; Soloshonok, et al. 2001a). The benzylation occurred at temperature from 25 to 50 °C furnishing products (*S*,*S*)-**65** in 95 % chemical yield and 94 % de (Scheme 14). Investigation of the chiroptical properties of major complexes allowed assigning the absolute configuration of the α-stereogenic carbons as (*S*). It could be mentioned that the corresponding dibenzylation of Ni(II) complex (*S*)-**9** did not take place in these cases at all. After isolation via column chromatography



Scheme 12 Synthesis of α-amino-ω-phosphinic- and phosphonic acids (*S*)-**57**

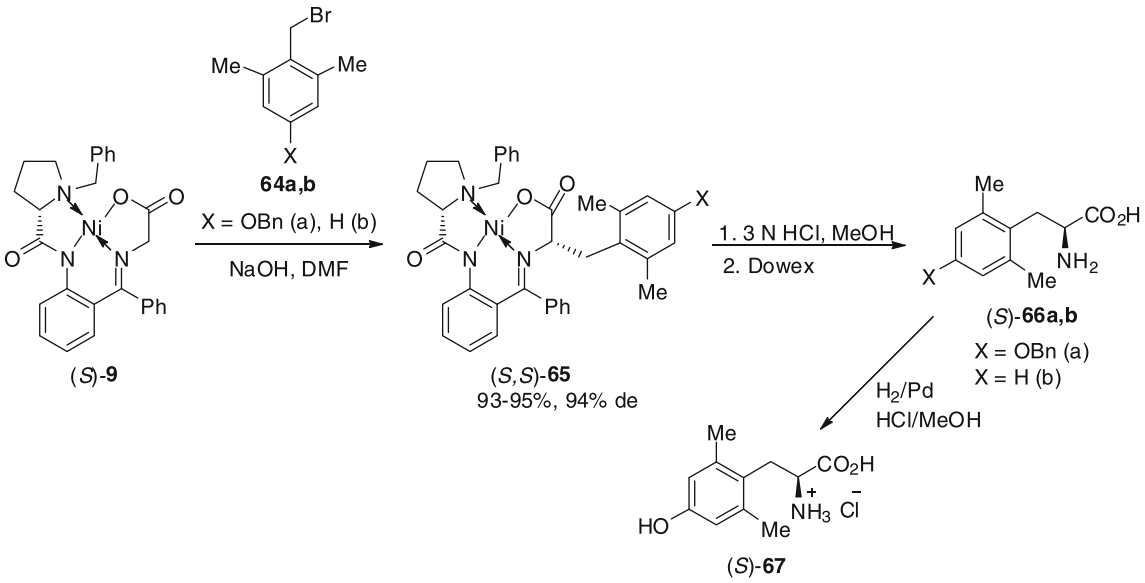


Scheme 13 Synthesis of phosphine substituted amino acid derivatives (*S*)-**62** and (*S*)-**63**

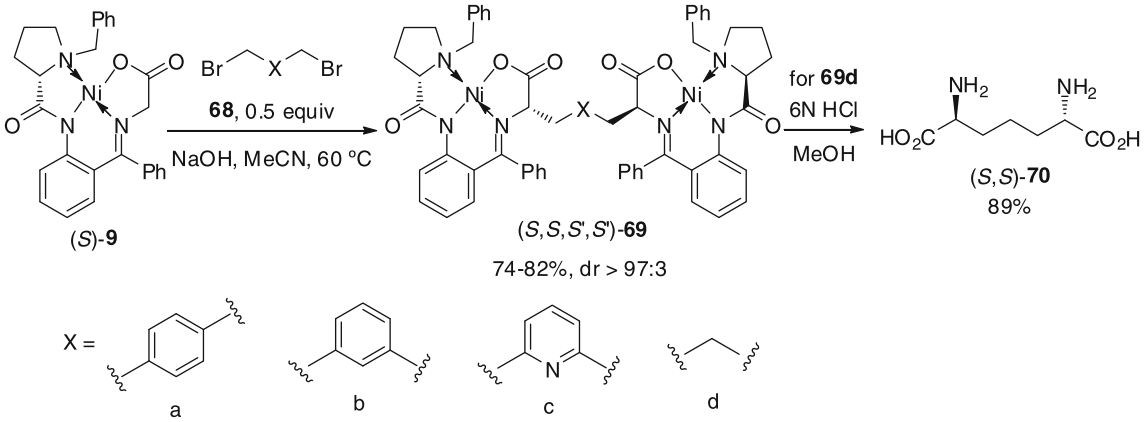
diastereomerically pure complexes (*S*,*S*)-**65** were decomposed following the standard procedure to afford free amino acids (*S*)-**66** which were isolated in high chemical yield by cation-exchange chromatography along with quantitative recovery of the chiral ligand (*S*)-**11**. Hydrogenation of benzyl ethers (*S*)-**66a** in a solution of conc. HCl/MeOH afforded enantiomerically pure 2′,6′-dimethyltyrosine (*S*)-**67** which is used as a key structural unit in the design of numerous bioactive peptides, some of which have potential medicinal applications.

The Ni(II) complex (*S*)-**9** has been effectively alkylated with α,ω-dibromide reagents under homogeneous conditions (Wang et al. 2013). Optimized protocol using NaOH as base in MeCN at 60 °C and 0.5 equiv of dihalogenated reagents such as *para*- and *meta*-bis(bromomethyl)benzenes **68a** and **68b** produced the corresponding bis-alkylated products **69a**–**b** in 79–82 % yield (Scheme 15). It is worth mentioning that this bis-alkylation proceeded with excellent diastereoselectivity, as only the (*S*,*S*,*S*′,*S*′)-diastereomers were observed by NMR analysis of the crude reactions mixtures. Similarly, *meta*-substituted pyridine **68c** led to the corresponding bis-alkylation product **69c** in about 68 % yield. The method also enabled to use non-activated alkyl dibromides, and the reaction of (*S*)-**9** with 1,3-dibromopropane **68d** produced **69d** in similar yield to those obtained with benzylic reagents. All bis-alkylation reactions demonstrated complete stereochemical control giving rise to diastereomerically pure products **69**. The disassembly of the Ni(II) complex **69d** was carried out using standard conditions (6 N HCl, MeOH) and was followed by isolation of free (2*S*,6*S*)-diaminopimelic acid **70** using a cation-exchange resin.

Depending on the reaction conditions the alkylation of the Ni(II) complex (*S*)-**9** with α,α'-dibromo-*o*-xylene **71** allowed to obtain both mono- and bis-alkylation complexes **72** and **73** (Belokon et al. 2003b) (Scheme 16). Monoalkylation product (*S*,*S*)-**72** was formed under standard alkylation conditions at ambient temperature with ratio of reagents 1:1 in 72 % yield. Decrease of the quantity of the alkylating agent **71** up to 0.5 equiv and heating of the reaction mixture to 50 °C resulted in producing bis-alkylated complex (*S*,*S*,*S*′,*S*′)-**73** in 62 % yield. The decomposition of complex (*S*,*S*,*S*′,*S*′)-**73** by aqueous HCl gave bis-amino acid (*S*,*S*′)-**75**. On the other hand decomposition of monomeric complex (*S*,*S*)-**72** with aqueous HCl led to the intramolecular alkylation of the free amino group with the formation of cyclic amino acid (*S*)-**74**.



Scheme 14 Synthesis of 2′,6′-dimethyltyrosine (*S*)-**67**

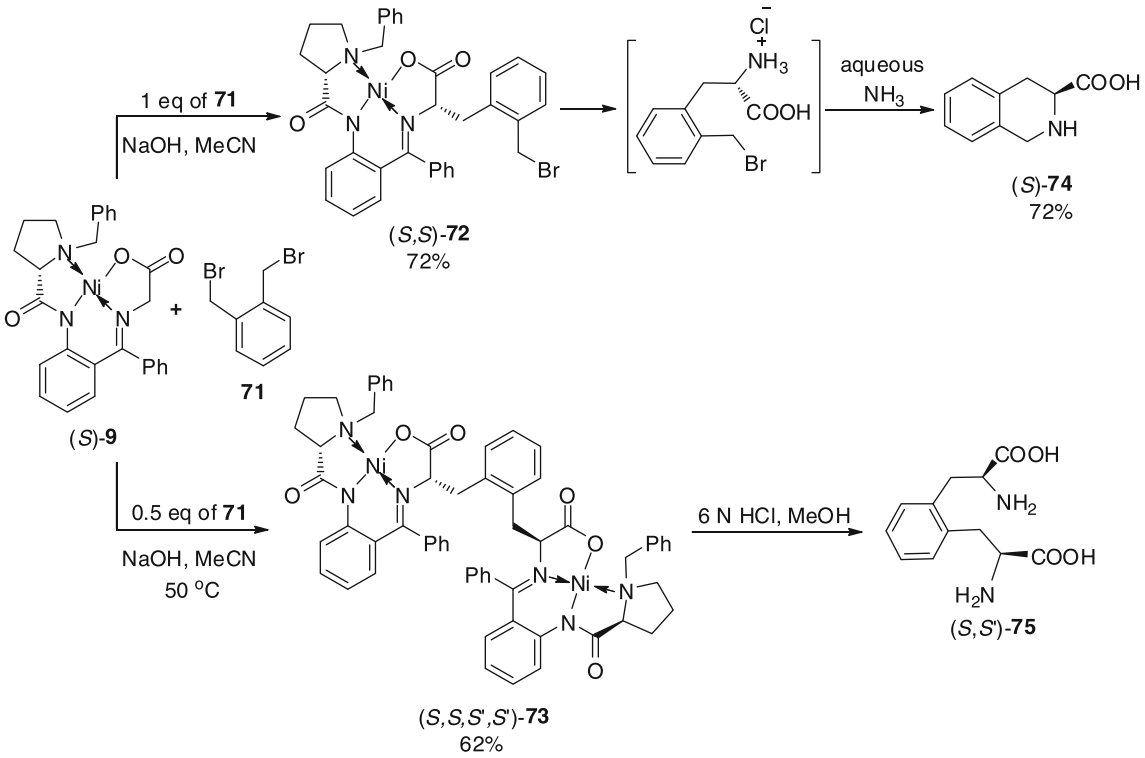


Scheme 15 Alkylation of the Ni(II) complex (*S*)-**9** with α,ω-dibromide reagents. Synthesis of diaminopimelic acid (2*S*,6*S*)-**70**

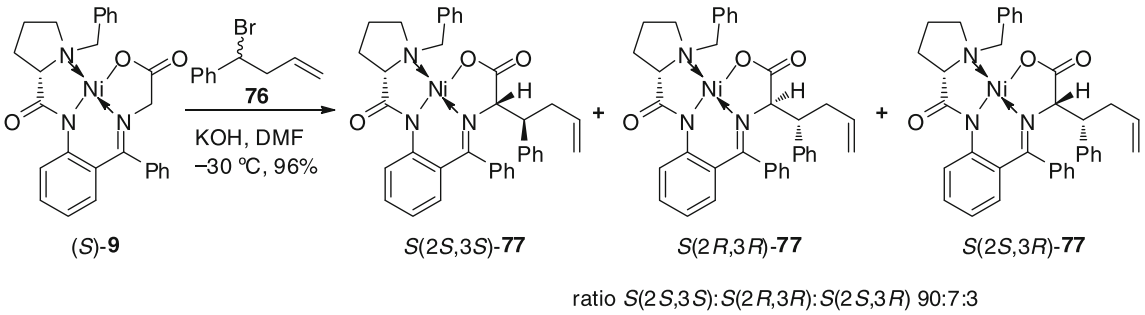
Of particular interest is the preparation of enantiomerically pure α,β-dialkyl substituted α-amino acids via alkylation of the Ni(II) complex (*S*)-**9** with racemic *sec*-alkyl bromide **76**. The reaction, conducted in DMF in the presence of KOH, generated a mixture of three diastereomers **77**, out of four theoretically possible products (Gu et al. 2003, 2004) (Scheme 17). The reaction was conducted at low temperatures and the corresponding alkylation products were obtained in good combined yield (96 %) and diastereomeric purity (80 % de) of the major product. Relative stereochemistry of the products **77** was confirmed by X-ray crystallography. While the major product *S*(2*S*,3*S*)-**77** was kinetically controlled, the authors could not explain the origin of this relatively high *S*(2*S*,3*S*)-**77**/*S*(2*S*,3*R*)-**77** selectivity.

Further investigation of reactions between the Ni(II) complex (*S*)-**9** and racemic *sec*-alkyl bromide **78a** under standard conditions using DMF as a solvent and powdered NaOH as a base has shown that lowering the temperature in this case decreased the rate of alkylation but not markedly improved the diastereoselectivity. For example, reaction conducted at − 15 °C resulted in formation of diastereomers (*S*)(2*S*,3*R*)-**79** and (*S*)(2*S*,3*S*)-**79** in a ratio of 1.9:1 and combined yield 89 % (Soloshonok et al. 2008a) (Scheme 18). Complex (*S*)(2*S*,3*R*)-**79** was isolated in diastereomerically pure form by column chromatography on silica gel and disassembled to afford enantiomerically pure β-methylphenylalanine (2*S*,3*R*)-**80**. To explain the stereochemical outcome of this reaction, theoretically possible transition states representing the interactions between the *si*-face of the enolate derived from the Ni(II) complex (*S*)-**9** and the (*S*)- and (*R*)-enantiomers of the *sec*-alkyl bromide **78a** have been discussed.

The synthetic approach based on the alkylation of glycine equivalent (*S*)-**9** was applied for the preparation of



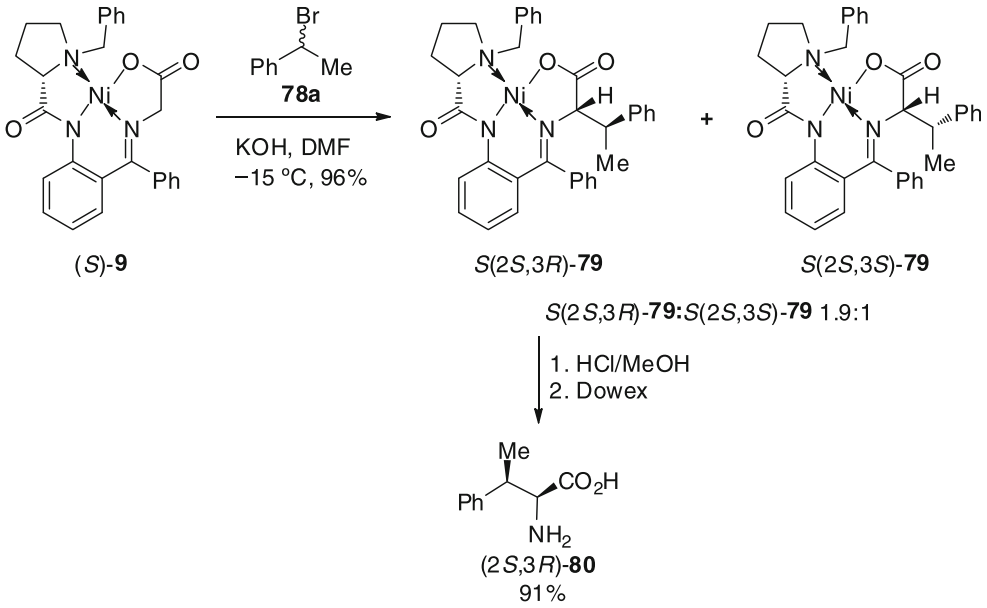
Scheme 16 Alkylation of the Ni(II) complex (*S*)-**9** with α,α′-dibromo-*o*-xylene **71**

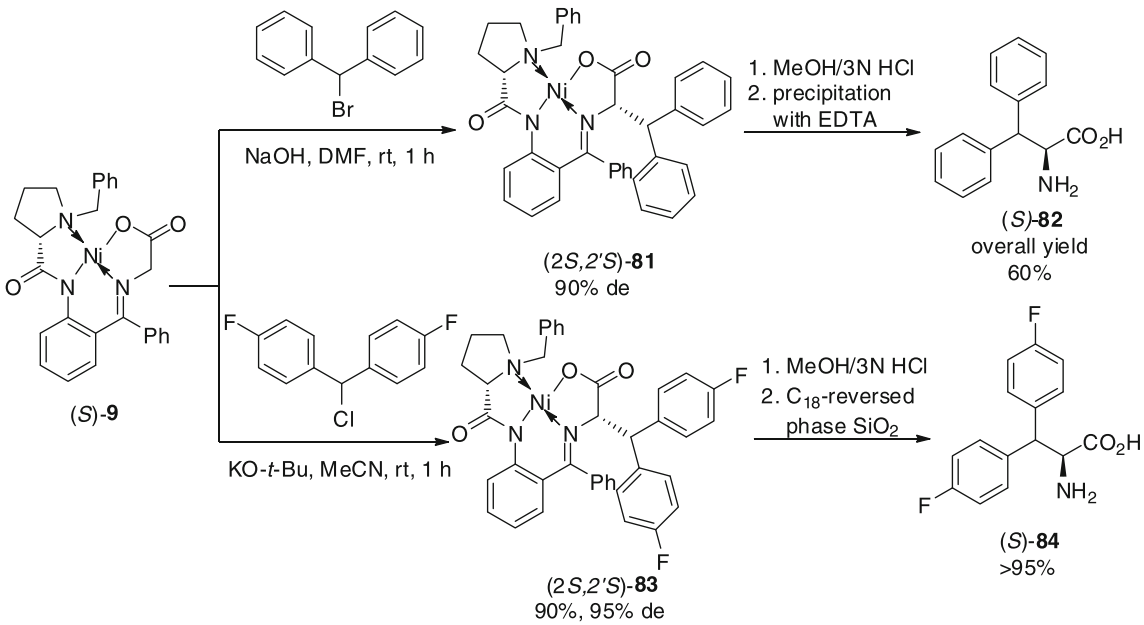


Scheme 17 Alkylation of the Ni(II) complex (*S*)-**9** with racemic *sec*-alkyl bromide **76**

β,β-diphenylalanine and its fluorinated analog (*S*)-2-amino-3,3-bis-(4-fluorophenyl)propanoic acid as key intermediates for the synthesis of dipeptidyl peptidase IV inhibitors (Scheme 19). Fast alkylation of Ni(II) complex (*S*)-**9** with Ph_2CHBr in DMF using sodium hydroxide as a base led to formation of two diastereomeric complexes in ratio 58:42 and 95:5 after 5 and 60 min, respectively (Tararov et al. 1997). The initial ratio of the diastereomers reflected the kinetic diastereoselectivity of the reaction. When thermodynamic equilibrium was established after 1 h the major diastereomer (*S*,*S*)-**81** was isolated from the reaction mixture by crystallization. β,β-Diphenylalanine (*S*)-**82** was obtained in enantiomerically pure form after hydrolysis of Ni(II) complex (*S*,*S*)-**81** and precipitation with ethylene diamine tetraacetic acid (EDTA) in 60 % overall yield. Diphenylalanine (*R*)-**82** was successfully synthesized according to the same synthetic protocol starting from Ni(II) complex (*R*)-**9**. On the other hand, alkylation of Ni(II) complex (*S*)-**9** with chlorides Ph_2CHCl and $(4\text{-F-}C_6H_4)_2CHCl$ in the presence of NaOH or KOH as a base led to relatively slow reaction rates and formation of undesired byproducts. Careful study of the reaction with $(4\text{-F-}C_6H_4)_2CHCl$ including solvent, base and temperature has shown that alkylation runs smoothly with 3 equiv of NaH as a base, DMF as a solvent at −20 °C for 2.5 h yielding the diastereoisomeric complex (*S*)-**83** in 86 % yield and excellent diastereoselectivity (Deng et al. 2008). More recently, an operationally convenient procedure for the alkylation of Ni(II) complex (*S*)-**9** with $(4\text{-F-}C_6H_4)_2CHCl$ employing well-soluble in MeCN potassium

Scheme 18 Synthesis of β-methylphenylalanine (2*S*,3*R*)-**80**





Scheme 19 Synthesis of β,β-diphenylalanine (*S*)-**82** and its fluorinated analog (*S*)-**84**

tert-butoxide as a base provided nearly quantitative yield of product (2*S*,2′*S*)-**83** with excellent stereochemical outcomes (>95 % de) (Soloshonok and Ono 2009). Diastereomerically pure product (2*S*,2′*S*)-**83** was obtained by column chromatography and hydrolyzed by standard procedure. The target amino acid (*S*)-**84** was isolated as hydrochloric salt by reversed-phase chromatography in high isolated yield (>95 %).

Although alkylations of glycine Ni(II) complex (*S*)-**9** are typically carried out under homogeneous conditions to achieve the best stereoselectivity of the corresponding homologated products, heterogeneous phase-transfer catalysis (PTC) conditions are usually milder and never lead to formation of double alkylation products. It should be mentioned that quite low solubility of (*S*)-**9** in usual PTC solvents such as benzene or toluene limited the synthetic potential of these reactions. Thus, in early experiments on phase-transfer benzylation and allylation of glycine Ni(II) complex (*S*)-**9** CH_2Cl_2 was used as organic solvent affording products with low stereochemical outcome (Belokon et al. 1988). However, it was recently demonstrated that CH_2Cl_2 could be used as a practical reagent for the methylene dimerization of Ni(II) complexes under PTC producing diastereoisomeric dimers. The first

asymmetric version of "methylene dimerization" was reported by Belokon et al. by treatment of Ni(II) complex (*S*)-**9** with 0.5 equiv of CH_2Br_2 and powdered NaOH in dry MeCN resulting in the formation of Ni(II) complex (*S*,*S*,*S*′,*S*′)-**85** as a major product, which was converted into 4-aminoglutamic acid (2*S*,4*S*)-**86** (Belokon et al. 1987) (Scheme 20). The main disadvantages of these reaction conditions were the formation of the diastereomeric product as well as substantial amount of decomposition products. As a result the Ni(II) complex (*S*,*S*,*S*′,*S*′)-**85** could be obtained in about 50 % yield after painstaking column purification. Optimization of the reaction conditions for methylene dimerization of Ni(II) complex (*S*)-**9** by screening various bases, solvents, phase-transfer catalysts, and concentration of the reagents showed that application of tetra-*n*-butylammonium bromide (TBAB), aqueous NaOH, and a solution of Ni(II) complex (*S*)-**9** in CH_2Cl_2 gave within 1 h the best outcome of products (*S*,*S*,*S*′,*S*′)-**85** and (*S*,*S*,*S*′,*R*′)-**85** in a ratio of 1:1 and 95 % combined yield (Taylor et al. 2004; Soloshonok et al. 2006c). The initial 1:1 ratio of the two products was gradually changed under the thermodynamic control, leading to complete disappearance of the complex (*S*,*S*,*S*′,*R*′)-**85** after 24 h, leaving complex (*S*,*S*,*S*′,*S*′)-**85** as a sole diastereomer. This result suggested that (*S*,*S*,*S*′,*S*′)-**85** was the thermodynamically controlled product and (*S*,*S*,*S*′,*R*′)-**85** was the kinetically controlled product. Fast epimerization for 1 h of diastereomer (*S*,*S*,*S*′,*R*′)-**85** to diastereomer (*S*,*S*,*S*′,*S*′)-**85** was achieved by treatment of the corresponding 1:1 mixture with strong bases such as guanidine, producing Ni(II) complex (*S*,*S*,*S*′,*S*′)-**85** as a sole product in 80 % isolated yield. Thus, prepared product (*S*,*S*,*S*′,*S*′)-**85** without any chromatographic purification was disassembled under the standard conditions to give 4-aminoglutamic acid (2*S*,4*S*)-**86**.

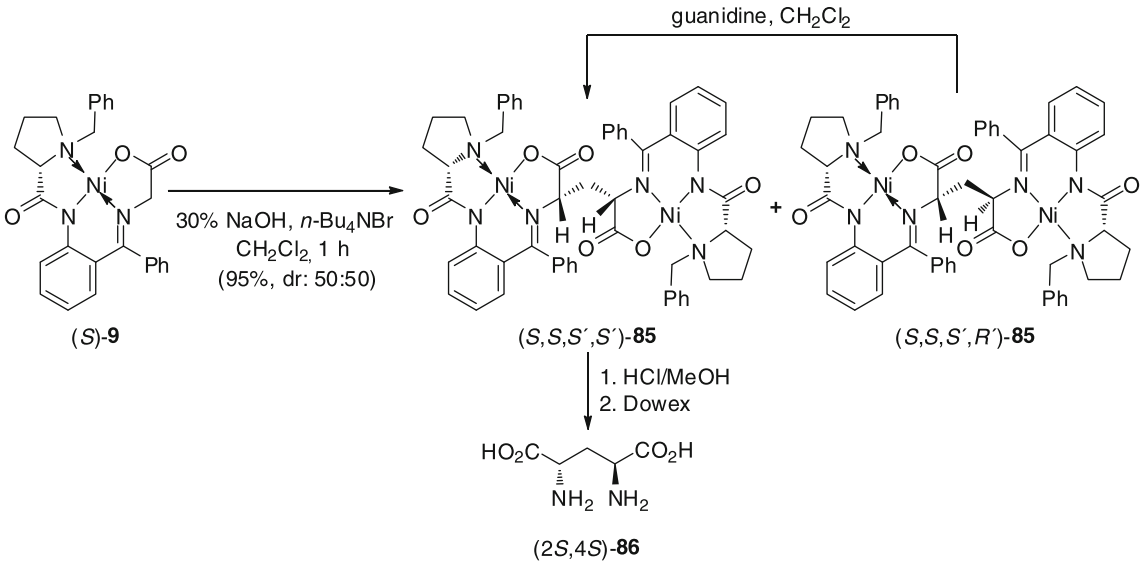
The reaction most likely proceeds through the formation of an intermediate mono-alkylated Ni(II) complex **87**, which can undergo dehydrohalogenation, leading to the formation of an unsaturated Ni(II) complex **88** (Scheme 21). This intermediate complex can react as Michael acceptor with the starting glycine complex (*S*)-**9** furnishing the reaction products (*S*,*S*,*S*′,*S*′)-**85** and (*S*,*S*,*S*′,*R*′)-**85**. The intermediate Michael acceptor **88** was isolated in a reaction conducted in benzene with CH_2Br_2 as an alkylating reagent. The Michael addition between complexes **88** and (*S*)-**9** under the standard PTC conditions successfully gave rise to a mixture of products (*S*,*S*,*S*′,*S*′)-**85** and (*S*,*S*,*S*′,*R*′)-**85** in a ratio similar to that observed in the direct methylene dimerization of (*S*)-**9** in CH_2Cl_2.

Further experiments with halogenated solvents have shown that benzylation of (*S*)-**9** in the presence of tetrabutylammonium iodide (TBAI) in a 1:1 mixture of $ClCH_2CH_2Cl$ and 30 % aqueous NaOH afforded diastereoisomeric complexes (*S*,*S*)-**89** and (*S*,*R*)-**89** in a 85:15 ratio and good overall yield without any trace of possible dimerization products (Houck et al. 2012) (Scheme 22). The minor isomers (*S*,*R*)-**89** could be epimerized to the most stable (*S*,*S*)-**89** by treatment with MeONa without purification of the initial mixture. In this manner the single isomer (*S*,*S*)-**89** was obtained in excellent overall yield. Reactions with substituted benzyl bromides, allyl bromides and propargyl bromides proceeded in good overall yields and diastereoselectivities after MeONa-mediated equilibration. Ethyl bromoacetate was also successfully used for alkylation. On the other hand, PTC alkylations of Ni(II) complex (*S*)-**9** with non-activated alkyl halides such as MeI and BuI were less successful and the reaction did not proceed at all with sterically demanding alkyl iodides.

Alkylation of alanine Ni(II) complex (*S*,*S*)-**18a** with benzyl and allyl halides was successfully carried out using 1.1–5 equiv. excess of the alkylating reagent producing the major diastereoisomer (*S*,*S*)-**90** in >80 % de (Belokon et al. 1985b, 1988) (Scheme 23). The ratio of the diastereoisomers was not influenced by the diastereoisomeric purity of the starting material and the experimental conditions. Since new complexes **90** contain no α-proton, the stereochemistry of the amino acid moiety is controlled kinetically. Sterically constrained α-methyl-α-amino acids can be prepared in enantiomerically pure form by chromatography separation of the corresponding diastereomeric Ni(II) complexes followed by their hydrolytic disassembly and isolation of the target amino acid.

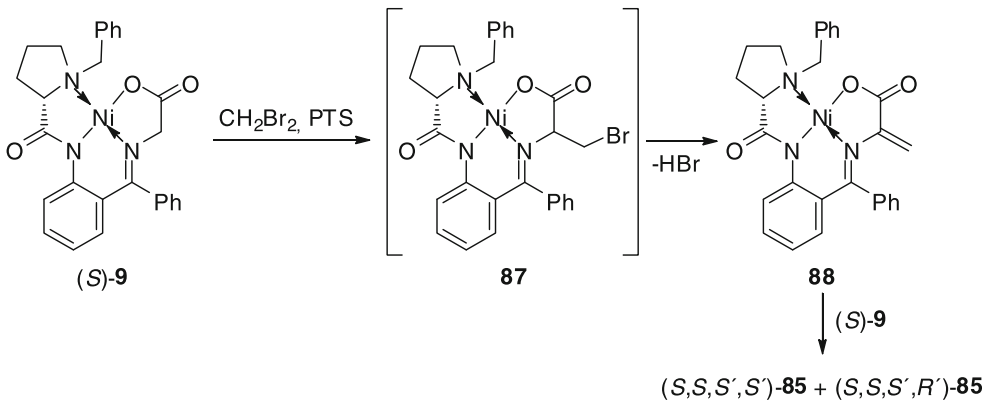
It is interesting to note that alkylation of alanine Ni(II) complex (*S*,*S*)-**18a** with *trans*-cinnamyl bromide (Qiu et al. 2000) or fluorine-containing benzyl chlorides (Soloshonok et al. 1990; Kukhar et al. 1993) and KOH as a base afforded the corresponding products (*S*,*S*)-**91** and (*S*,*S*)-**92** in high chemical yields, and the diastereoselectivity of these reactions (>90 % de) was better than the usually observed for the benzylation or allylation of alanine Ni(II) complex (*S*,*S*)-**18a** (Scheme 24). After separation of the alkylated diastereomers on silica gel, decomposition of products (*S*,*S*)-**91** and (*S*,*S*)-**92** led to enantiomerically pure α-*trans*-cinnamyl-α-alanine (*S*)-**93** and α-methyl (fluorophenyl)alanines (*S*)-**94**, respectively, in good overall yields.

Application of NaOH as a base in DMF at ambient temperature for the alkylation of the alanine Ni(II) complex (*S*,*S*)-**18a** with 1,1,1-trifluoro-4-iodobutane **37c** did not result in formation of any desirable product. In this case the alkylation could be successfully performed using *t*-BuOK as a strong and non-nucleophilic base affording the product (*S*,*S*)-**95** in 74 % yield and with complete diastereoselectivity (Wang et al. 2011b) (Scheme 25). Unfortunately, application of 1,1,1-trifluoro-3-iodopropane **37b** and 1,1,1-trifluoro-2-iodoethane **37a**, containing a shorter alkyl chain, did not allow for preparation of the corresponding products, indicating limitations of this method. Disassembly of the

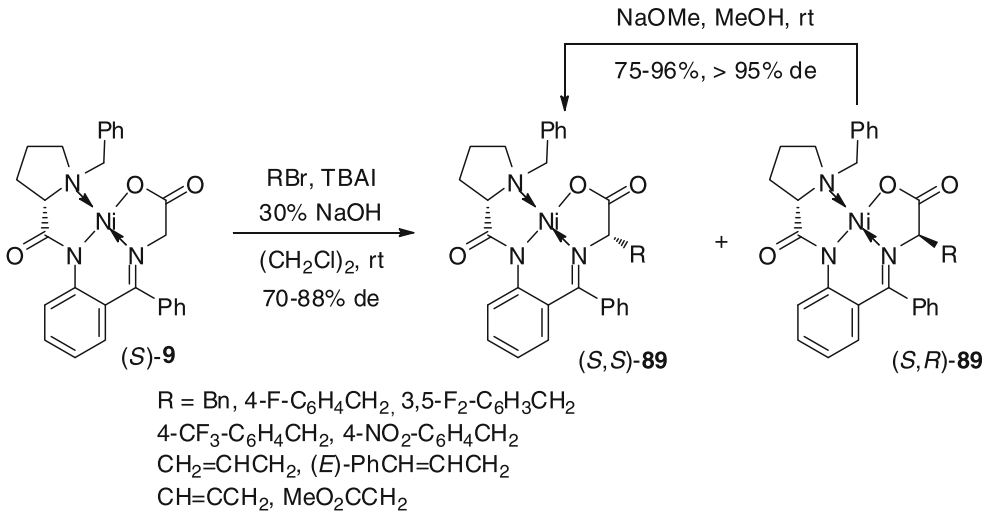


Scheme 20 Methylene dimerization of Ni(II) complex (*S*)-**9** under phase-transfer conditions

Scheme 21 Synthesis of intermediate Michael acceptor **88**

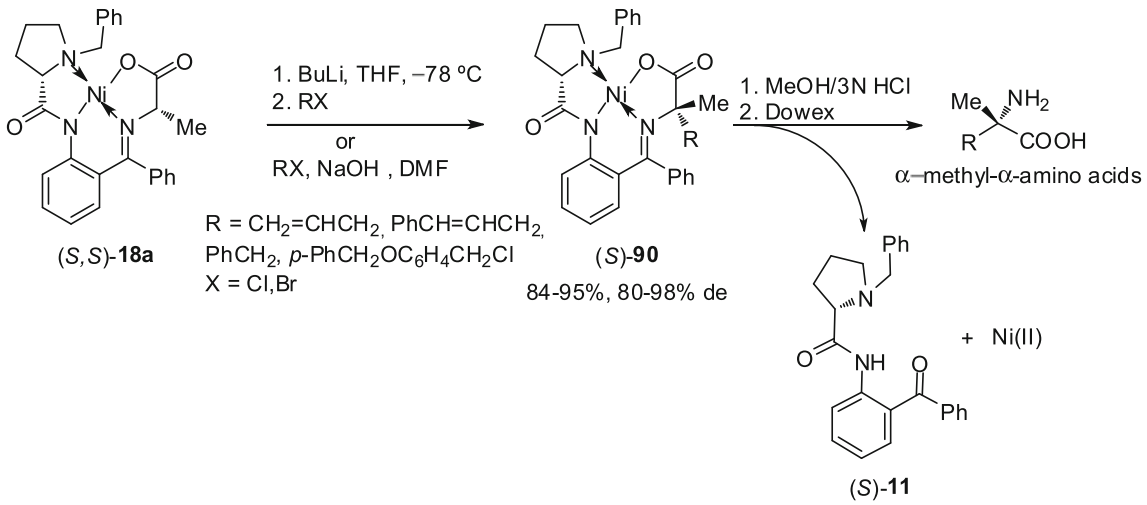


Scheme 22 Alkylation of glycine Ni(II) complex (*S*)-**9** under phase-transfer conditions

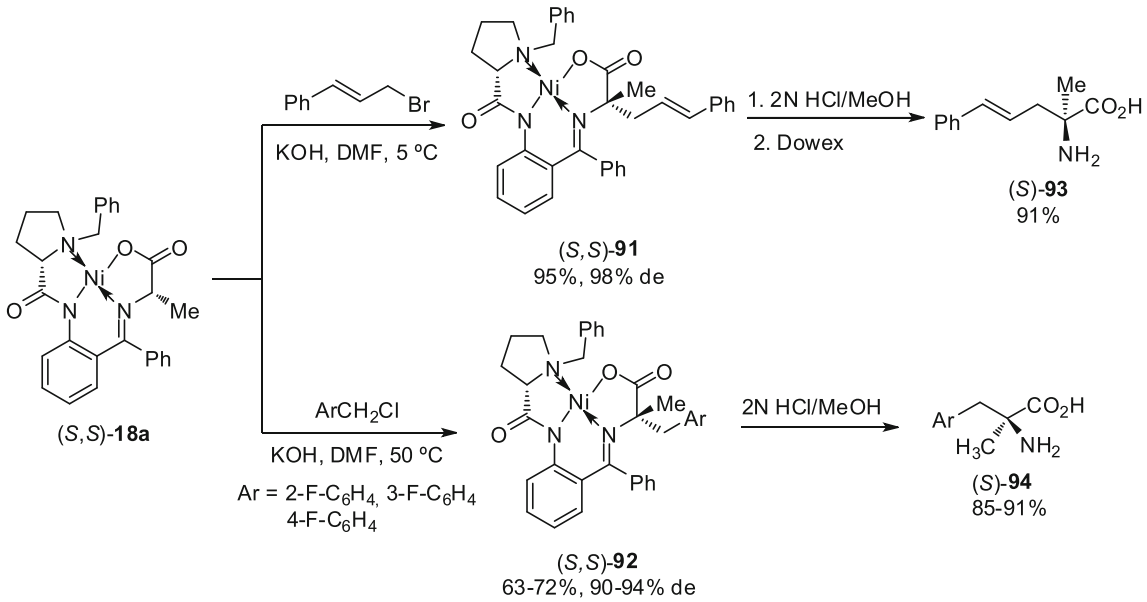


diastereomerically pure complex (*S*,*S*)-**95** under the standard conditions afforded the target 2-amino-6,6,6-trifluoro-2-methylhexanoic acid (*S*)-**96** in 96 % yield.

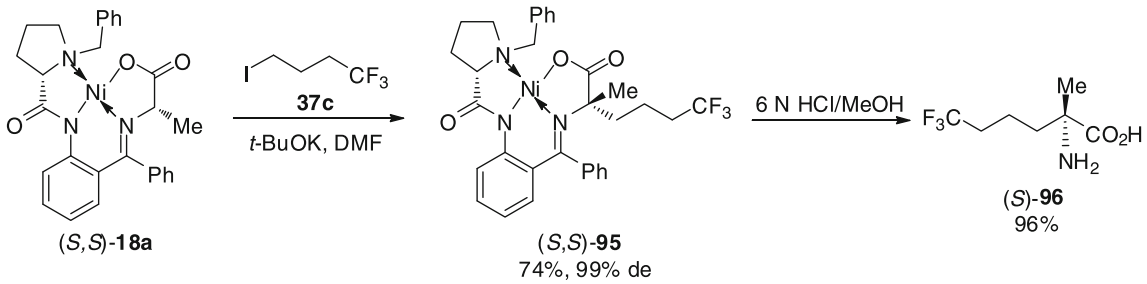
The reactions between alanine Ni(II) complex (*S*,*S*)-**18a** and sterically constrained benzyl bromides **66** in DMF using powdered NaOH as base were studied under different



Scheme 23 Alkylation of the alanine Ni(II) complex (*S*,*S*)-**18a**

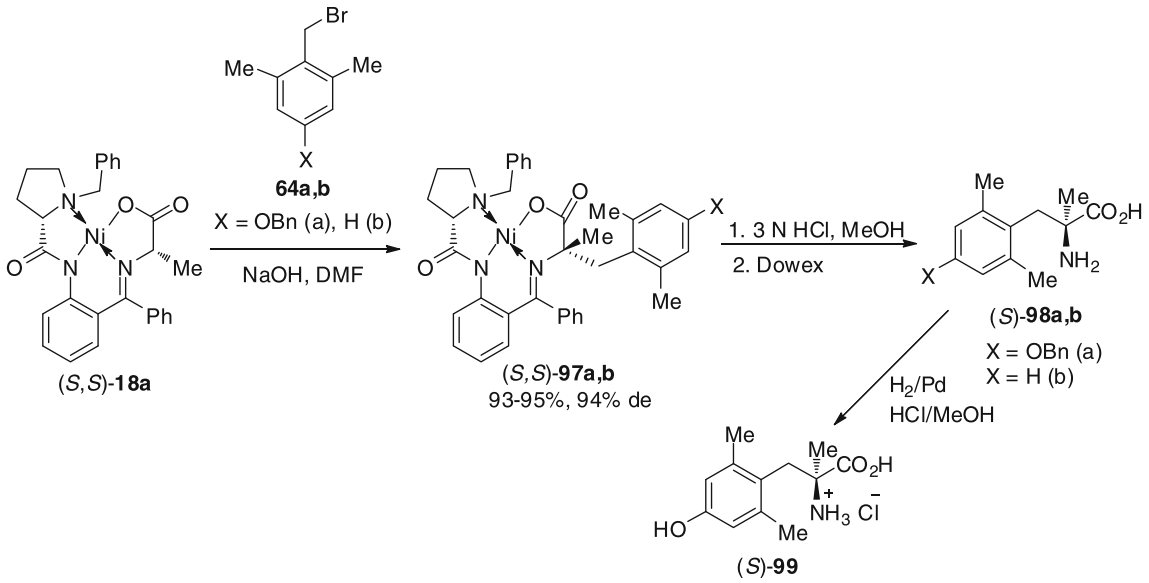


Scheme 24 Benzylation and allylation of alanine Ni(II) complex (*S*,*S*)-**18a**

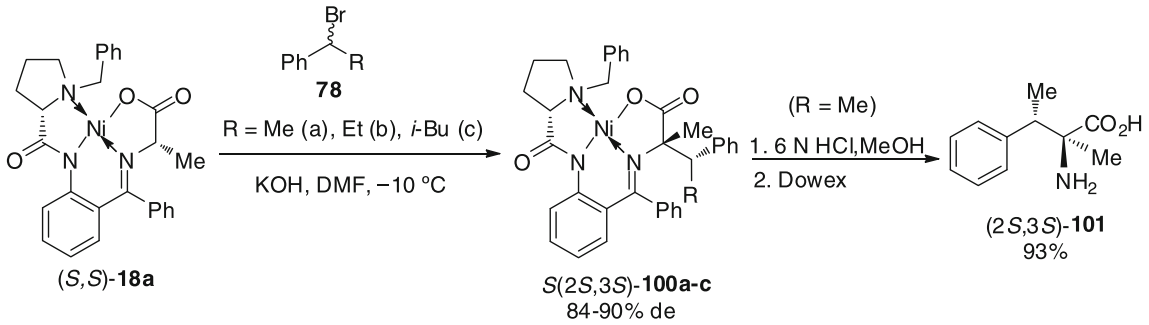


Scheme 25 Synthesis of 2-amino-6,6,6-trifluoro-2-methylhexanoic acid (*S*)-**96**

temperatures. It turned out that regardless of the reaction temperature the benzylation occurred with diastereoselectivities in range 70–74 % de affording Ni(II) complexes (*S*,*S*)-**97** as major reactions products (Soloshonok et al. 2001a) (Scheme 26). This is in good agreement with the kinetically controlled stereochemical outcome of the



Scheme 26 Synthesis of α,2′,6′-trimethyltyrosine (*S*)-**99**



Scheme 27 Alkylation of the alanine Ni(II) complex (*S*,*S*)-**18a** with racemic *sec*-alkyl bromides **78**

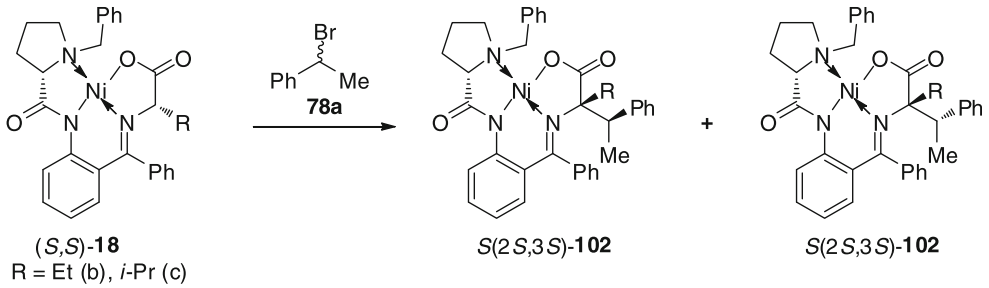
reactions of alanine Ni(II) complex (*S*,*S*)-**18a** with benzyl bromides. Products (*S*,*S*)-**97** were easily isolated by column chromatography in diastereomerically pure form and their decomposition gave α-amino acids (*S*)-**98** isolated by ion-exchange chromatography. *O*-benzyl protected α-amino acid (*S*)-**98a** was hydrogenated under standard conditions to afford enantiomerically pure α,2′,6′-trimethyltyrosine (*S*)-**99**.

The alkylation of the alanine Ni(II) complex (*S*,*S*)-**18a** with racemic *sec*-alkyl bromides **78a-c**, in contrast to the corresponding reactions of the glycine Ni(II) complex (*S*)-**9**, occurred under standard conditions at −15 °C with high stereochemical outcome of >84 % allowing isolation of the major products (*S*)(2*S*,3*S*)-**100a–c** in good chemical yield (Soloshonok et al. 2001b, 2008a) (Scheme 27). Further decomposition of the complex (*S*)(2*S*,3*S*)-**100a** afforded the enantiomerically pure α,β-dimethylphenylalanine (2*S*,3*S*)-**101**. Because of the simplicity of the experimental procedure and high chemical and stereochemical outcome, this direct alkylation of alanine Ni(II) complex (*S*,*S*)-**18a** with racemic **78** is a synthetically useful approach for preparing α,β-dialkyl-substituted α-amino acids.

Surprisingly, the alkylation of the ethyl-containing Ni(II) complex (*S*,*S*)-**18b** with **78a** occurred at a noticeably slower rate at ambient temperature giving rise to a mixture of (*S*)(2*S*,3*R*)-**102** and (*S*)(2*S*,3*S*)-**102** in a low ratio of 1:1.6 (Scheme 28). Attempts to improve the stereochemical outcome by lowering the reaction temperature were unsuccessful. Thus, the reaction conducted at −10 °C was too sluggish to produce reliable amounts of product. Even slower reaction rates and the same stereochemical outcome were observed in the alkylation of the leucine-derived complex (*S*,*S*)-**18c** indicating that an increase in the steric bulk of the amino acid residue interferes with the reactivity of the Ni(II) complexes and stereoselectivity of the alkylation.

Several attempts have been made to increase the diastereoselectivity of the alkylation reactions using derivatives of Ni(II) complex (*S*)-**9** with various substituents on the benzyl group of the proline chiral auxiliary. For

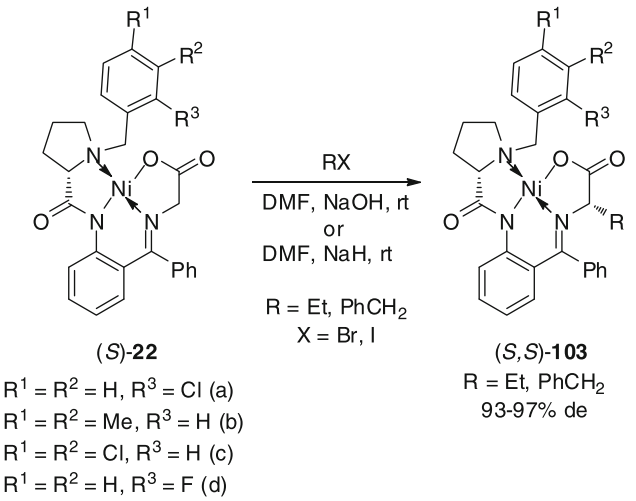
Scheme 28 Alkylation of the Ni(II) complexes (*S*,*S*)-**18b,c** with (1-bromoethyl)benzene **78a**



(*S*,*S*)-**18**
R = Et (b), *i*-Pr (c)

S(2*S*,3*S*)-**102**

S(2*S*,3*S*)-**102**



(*S*)-**22**
$R^1 = R^2 = H$, $R^3 = Cl$ (a)
$R^1 = R^2 = Me$, $R^3 = H$ (b)
$R^1 = R^2 = Cl$, $R^3 = H$ (c)
$R^1 = R^2 = H$, $R^3 = F$ (d)

(*S*,*S*)-**103**
R = Et, $PhCH_2$
93-97% de

Scheme 29 Alkylation of modified glycine Ni(II) complexes (*S*)-**22**

example, Saghiyan et al. reported that 2-chloro-, 3,4-dimethyl-, 3,4-dichloro- and 2-fluoro-substituted glycine Ni(II) complexes (*S*)-**22a**–**d** gave better diastereoselectivity of alkylation with BnBr and MeI conducted in DMF and NaOH or NaH as a base at ambient temperature than the original Ni(II) complex (*S*)-**9** (Belokon et al. 2002; Saghiyan et al. 2006, 2010) (Scheme 29). The best results both in terms of stereoselectivities and the rate of reactions were obtained for 2-chloro-, 3,4-dichloro- and 2-fluoro-substituted Ni(II) complexes (*S*)-**22a**, (*S*)-**22c** and (*S*)-**22d** affording the alkylated products (*S*,*S*)-**103** in 95–97 % de. The 3,4-dimethyl-substituted Ni(II) complex (*S*)-**22b** was less efficient with the 93 % de of alkylated product (*S*,*S*)-**103**. In these cases the stereochemical outcome of the alkylation reactions reflected the position of thermodynamic equilibrium between the diastereoisomeric complexes (*S*,*R*)/(*S*,*S*).

The best kinetic stereoselectivity of alkylation of alanine-derived Ni(II) complexes with allyl and benzyl bromides was observed in the case of 2-chloro- and 2-fluoro-substituted complexes (*S*,*S*)-**23a** and (*S*,*S*)-**23d** ranging from 94 to 99 % de (Scheme 30). In general, modified Ni(II) complexes (*S*,*S*)-**23a**,**d** were found efficient for highly stereoselective syntheses of α-methyl-α-amino acids with high enantiomeric purity (ee > 95 %).

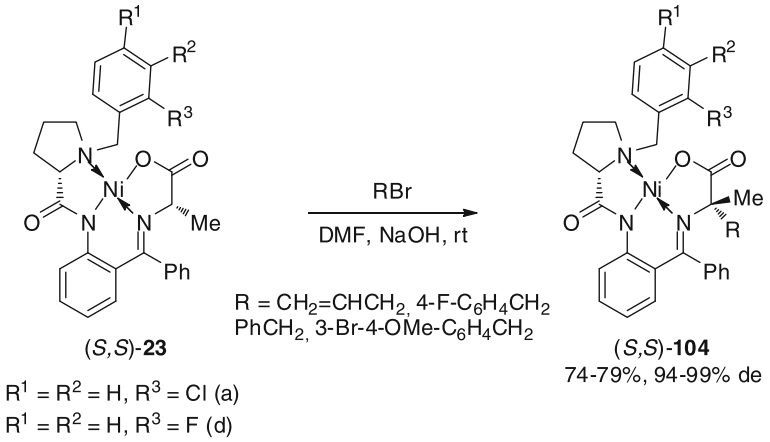
In contrast to the above discussed results, the methylation of alanine-derived Ni(II) complex (*S*,*S*)-**25**, containing *ortho*- and *para*-methyl groups which provide both steric hindrance and supposedly donation of the electron density to nickel orbitals, with $^{13}CH_3I$ led to the corresponding Ni(II) complex (*S*,*S*)-**105** in only 66 % de (Popkov et al. 2002) (Scheme 31). After chromatographic purification on silica gel, which did not affect the ratio of the diastereomers, complex (*S*,*S*)-**105** was used for preparation of [^{13}C]-α-aminoisobutyric acid **106**.

Due to the generality and simplicity of the experimental procedures as well as high stereochemical outcome of the alkylation reactions of the Ni(II) complexes of the Schiff bases of glycine and alanine, derived from (*S*)- or (*R*)-BPB, this approach has been used to provide fast access to isotopically enriched valine **107** (Chaykovski et al. 2003), δ-silanediol amino acid **108** (Kim and Sieburth 2012), linear backbone of (2*S*,4*R*)-4-methylpipecolic acid **109** (Hung et al. 2010) as well as pyrenylalanine **110** (Alves et al. 2004; Chen et al. 2012) (Fig. 5).

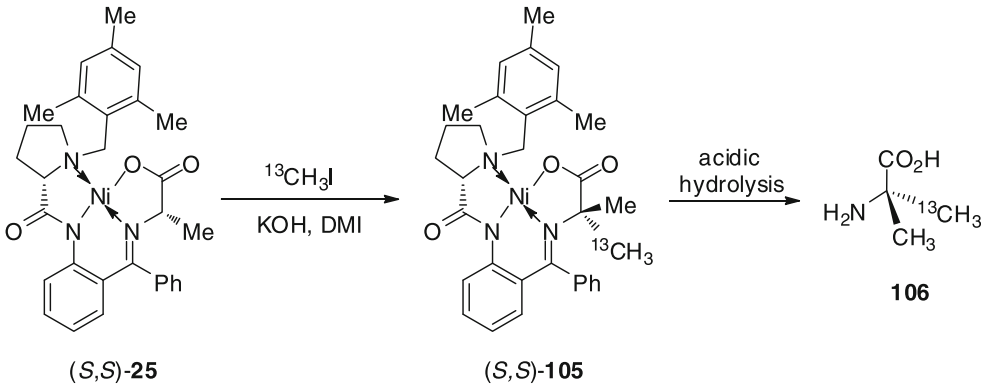
Alkylation of the Ni(II)-complexes of glycine Schiff bases of 2-[*N*-(α-picolyl)-amino]benzophenone

The achiral Ni(II) complex of glycine Schiff base of 2-[*N*-(α-picolyl)-amino]benzophenone **12** was found to a be stable yet highly reactive nucleophilic glycine equivalent and its alkylation could be carried out at ambient temperature without inert atmosphere or dried and degassed solvent. The corresponding acetophenone-derived complex **13**, useful for Michael addition reactions (Ellis et al. 2009), was rather unsuitable for the alkylation reactions due to the relatively high C–H acidity of the methyl group. On the other hand, the reactions of Ni(II)-complex **12** with an excess of alkyl halides, conducted under homogeneous conditions in DMF resulted in complete (>99 %) α,α-dialkylation offering a convenient method for preparation of *sym*-α,α-AAs **112** (Ellis et al. 2003a, b) (Scheme 32). Generation of the corresponding enolate from Ni(II)-complex **12** could be effectively achieved using simple sodium and potassium hydroxides or alkoxides. However, NaO-*t*-Bu was significantly more efficient than KOH as a base

Scheme 30 Alkylation of modified alanine Ni(II) complexes (*S*,*S*)-**23**



Scheme 31 Methylation of alanine Ni(II) complex (*S*,*S*)-**25**



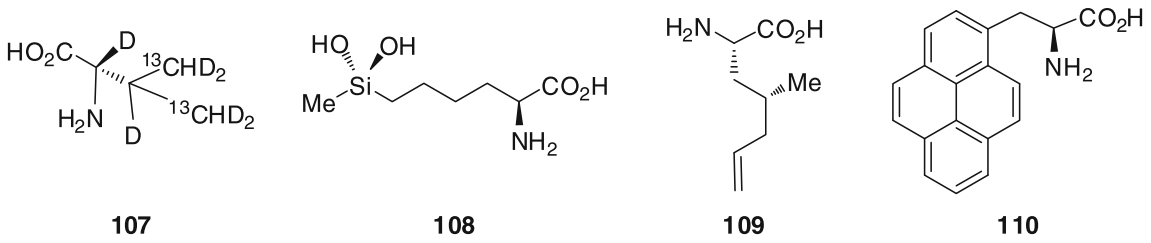
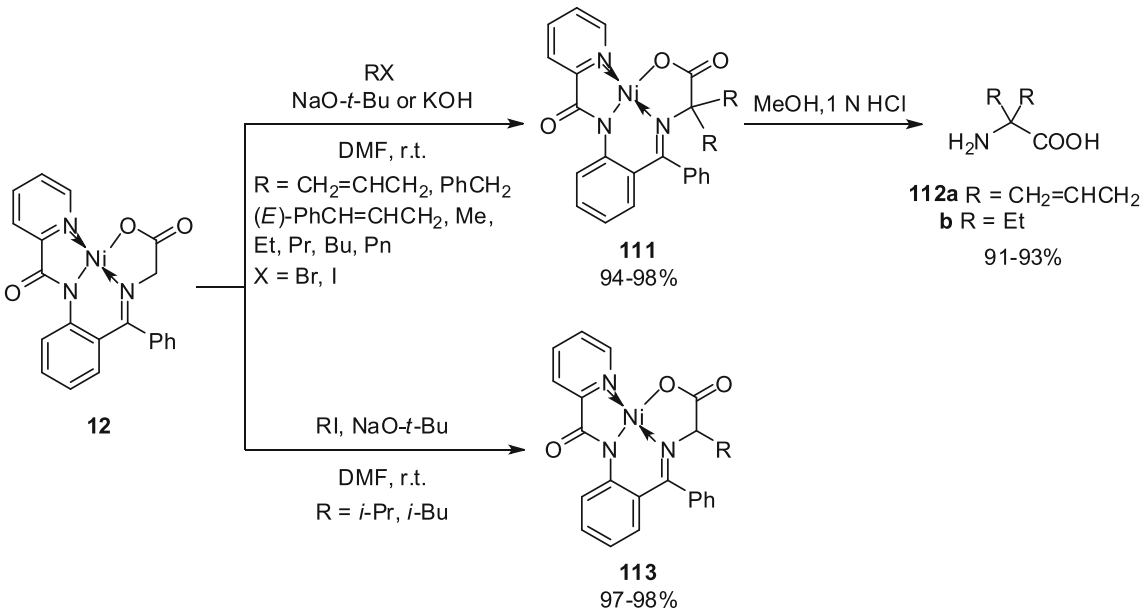


Fig. 5 α-Amino acids prepared by alkylation of the chiral glycine and alanine Ni(II) complexes

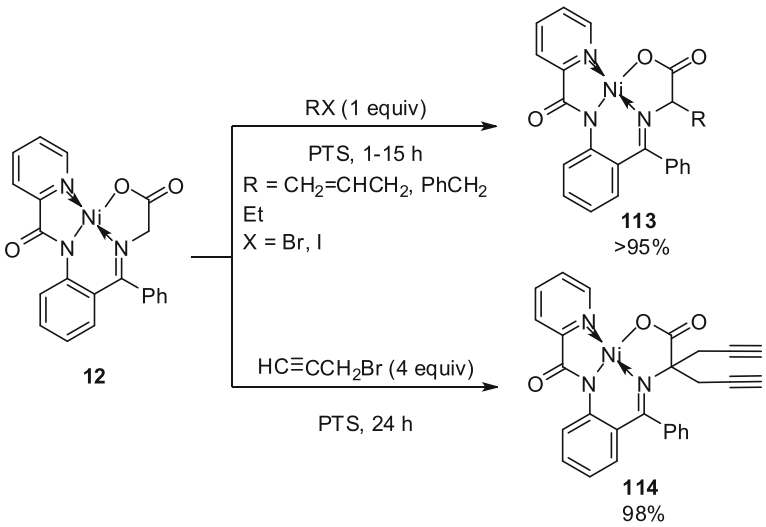
allowing conducting the reactions under homogeneous conditions as only 3.5 equivalents of base was required to complete the dialkylation process. Activated alkyl halides, such as allyl, benzyl and cinnamyl, could be used as bromides, while introduction of usual alkyl groups required application of the corresponding iodides. It should be noted that use of only 3.5 equivalents of alkyl halide was enough for complete, fast, and clean dialkylation of **12** to afford compounds **111** in high isolated yields. By contrast, alkylation of complex **12** with *iso*-propyl and *iso*-butyl bromides or iodides, even under high temperatures and long reaction times resulted in quantitative formation of only monoalkylated products **113**. Dialkylation products **112** were isolated simply by pouring the reaction mixture into ice water followed by filtration of the precipitate. Procedure for isolation of the target symmetrically α,α-disubstituted α-amino acids **112** included heating of the corresponding products **111** in methanol in the presence of 1 *N* hydrochloric acid followed by neutralization of the resultant mixture with aqueous ammonia. The ligand can be extracted and recycled to produce back the glycine complex **12** and symmetrically α,α-disubstituted α-amino acids **112a** and **112b** were isolated in free form in 91 and 93 % yield using cation-exchange resin.

Achiral Ni(II) complex **12** was found to undergo alkylation with alkyl halides under phase-transfer conditions in the presence of benzyltriethylammonium bromide as catalyst and 30 % aqueous NaOH as the base. The reactions were extremely fast and clean, proceeding to completion with an equimolar ratio (1:1) of substrate and alkylating agent to give the mono-alkylated products **113** quantitatively (Belokon et al. 2003a) (Scheme 33). When



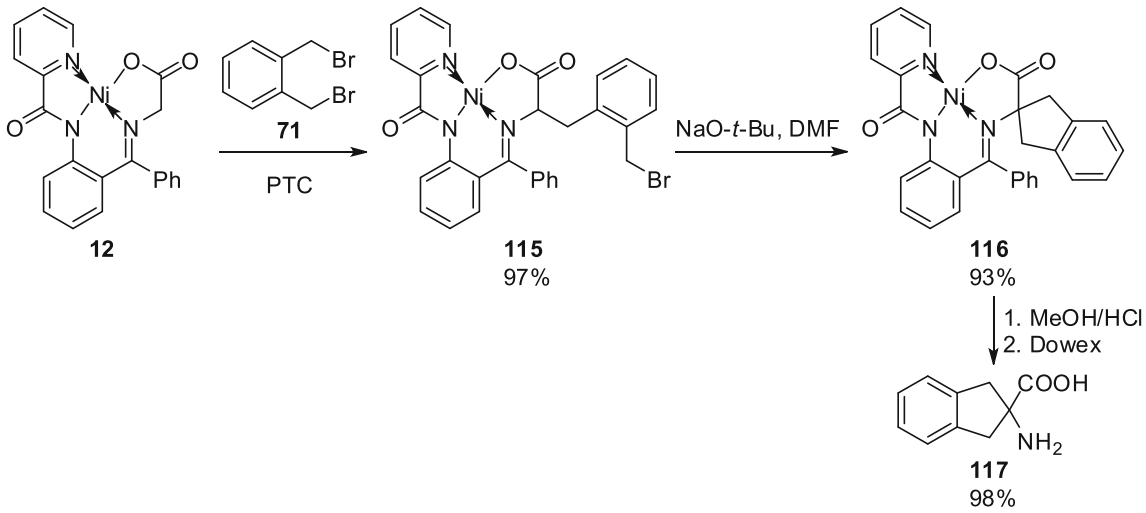
Scheme 32 Alkylation of the glycine Ni(II)-complex **12** under homogeneous conditions

Scheme 33 Alkylation of the glycine Ni(II)-complex **12** under phase-transfer conditions



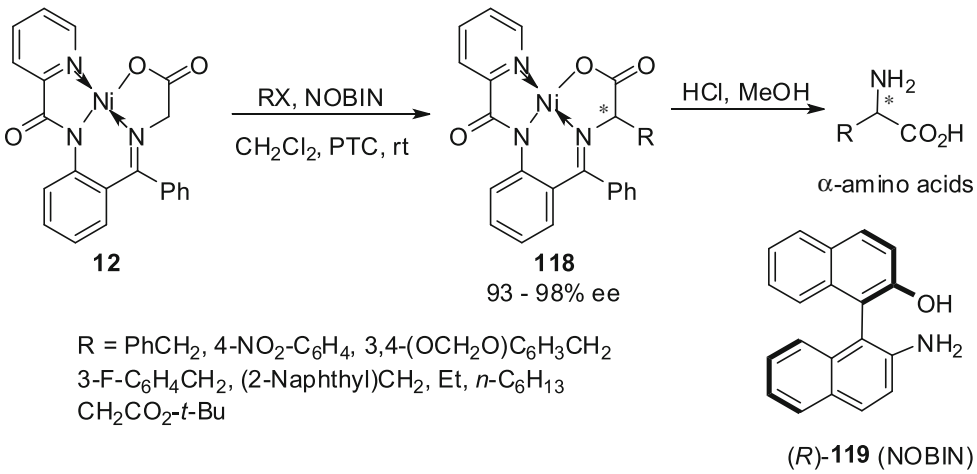
the reaction of Ni(II) complex **12** was carried out using 4 equiv of propargyl bromide at room temperature under phase-transfer conditions in dichloromethane in the presence of tetrapropylammonium iodide, quantitative conversion of Ni(II) complex **12** to the mono-substituted product was observed within 45 min with further clean conversion of **113** to the target disubstituted complex **114** in >98 % yield after running the reaction overnight.

Application of glycine Ni(II) complex **12** for preparation of cyclic amino acids was also demonstrated. For example, a method for preparing 2-aminoindane-2-carboxylic acid **117** included a two-step alkylation of Ni(II)-complex **12** with *o*-dibromoxylylene **71** (Ellis et al. 2003c) (Scheme 34). The first step, monoalkylation of **12** with **71**, conducted under the phase-transfer conditions, gave the corresponding complex **115** in excellent chemical yield. Without any purification the intermediate **115** was cyclized under homogeneous conditions in DMF with NaO-*t*-Bu as a base to give the product **116** in high chemical yield. Finally, decomposition of Ni(II) complex **116** was conducted under standard conditions by heating in methanol/3 N HCl. The target amino acid **117** was isolated by ion-exchange chromatography in greater than 95 % purity. It should be mentioned that the reaction between complex **12** and *o*-dibromoxylylene conducted under standard conditions for dialkylation with NaO-*t*-Bu in DMF was complicated by the formation of undesired byproducts and afforded Ni(II) complex **115** in 70 % yield.



Scheme 34 Synthesis of 2-aminoindane-2-carboxylic acid **117**

Scheme 35 Catalytic asymmetric alkylation of Ni(II) complex **12** under phase-transfer conditions

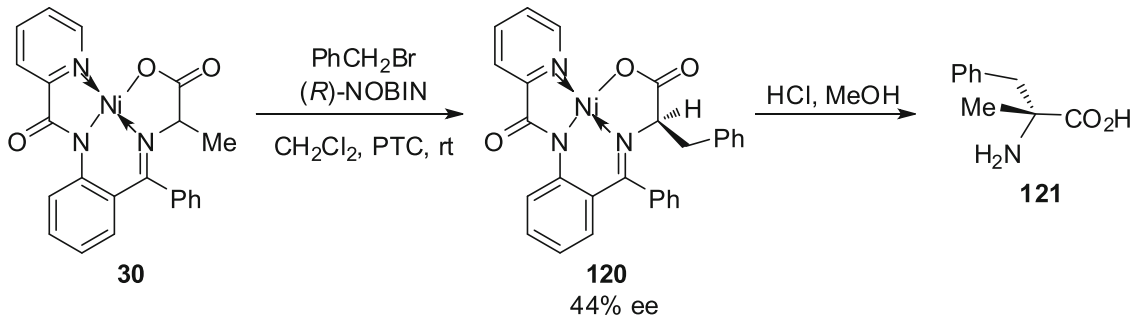


Asymmetric alkylation of Ni(II) complex **12** in CH_2Cl_2 catalyzed by (*S*) or (*R*) 2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) **119** with activated alkyl halides, conducted at room temperature, gave monoalkylated Ni(II) complexes **118** in good chemical yields and up to 93–98 % enantiomerical purity (Belokon et al. 2001, 2003a) (Scheme 35). Relatively low yields of the alkylated products were obtained with unactivated alkyl halides, although the enantiomeric purity of the resulting amino acids was reasonably high. Increasing the polarity of the solvent resulted in lower enantioselectivities, down from 96 % in CH_2Cl_2 to 17 % in MeCN. Attempts of using BINOL or 2,2′-diamino-1,1′-binaphtyl as catalysts resulted in both low enantioselectivity and chemical yields of the alkylation products. The enantiomeric purity of isolated amino acids could be further improved by crystallization of the intermediate alkylated Ni(II) complexes. The target amino acids could be easily obtained by hydrolysis of the alkylation products with aqueous HCl in MeOH followed by ion-exchange chromatography.

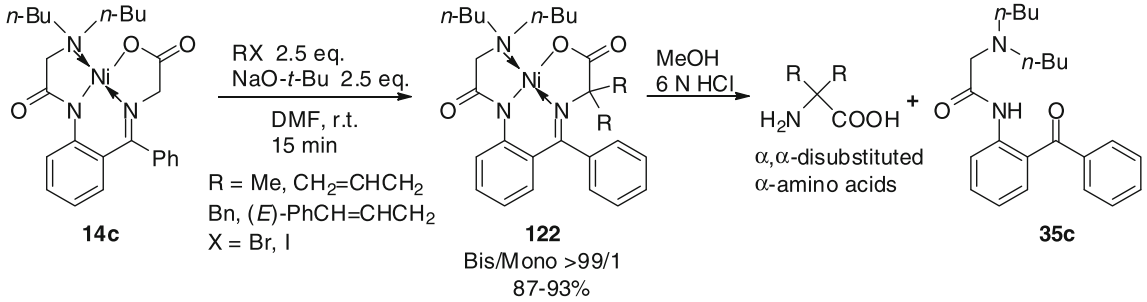
On the other hand, catalysis by (*R*)-NOBIN of the benzylation of Ni(II) complex **30** derived from alanine proved to be very slow and gave resulting amino acid **121** in only 44 % ee (Scheme 36).

Alkylation of new generation of Ni(II)-complexes

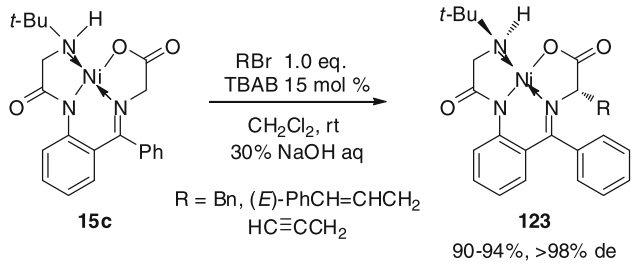
Achiral Ni(II) complex **14c** incorporating a dibutylamine moiety (Soloshonok et al. 2009b) was found to be efficient in dialkylation reactions which were conducted under homogeneous conditions in DMF at ambient temperature with only 2.5 equivalents of NaO-*t*-Bu and benzyl, allyl or cinnamyl bromide (Ellis et al. 2006) (Scheme 37). Most of the reactions were completed in about 15 min giving rise to α,α-dialkylation products **122** in high chemical yields (Soloshonok et al. 2008b). No alkylation products on the *N*,*N*-di-*n*-butyl glycine methylene moiety were observed in the crude reaction mixtures. Introduction of two



Scheme 36 Catalytic asymmetric benzylation of Ni(II) complex **30** under phase-transfer conditions



Scheme 37 Dialkylation of achiral Ni(II) complex **14c** under homogeneous conditions



Scheme 38 Alkylation of Ni(II) complex **15c** under phase-transfer conditions

unactivated alkyl groups could also be accomplished using the more reactive methyl iodide. Isolation of the free α,α-disubstituted α-amino acids was conducted by standard procedure along with recovery of ligand **35c**. Operationally convenient experimental procedures, mild reaction conditions, as well as high chemical yields render this method practical for preparing α,α-disubstituted α-amino acids and their analogs.

Unusual chemoselectivity was demonstrated during the alkylation reactions of Ni(II) complex **15c** containing a secondary amino group. For example, the alkylation of *t*-butylamine-derived NH–Ni(II) complex with one equivalent of benzyl, cinnamyl or propargyl bromides under phase-transfer conditions produced the corresponding homologated products **123** in 90–94 % yield and in diastereomerically pure form (Ellis and Soloshonok 2006) (Scheme 38). The complete C–H chemoselectivity observed in these reactions suggested that coordination of nitrogen to a metal has a significant synthetic potential as protecting a group without the need of introducing a transient N–C substituent.

Conclusions

The data discussed in this Review, clearly suggest that alkylation of the Ni(II) complexes (*S*)-**9**, **12**–**15** is a mature methodology for preparation of natural as well as various unnatural amino acids. In particular, asymmetric synthesis via homologation of glycine and alanine-derived complexes (*S*)-**9** and (*S*,*S*)-**18a**, respectively, provides a reliable and synthetically attractive approach for preparation of the target amino acids in enantiomerically pure form. It would be beneficial for the readers, to emphasize in this section the major features of this methodology which make it markedly different from other numerous literature approaches. First of all, these Ni(II) complexes, including the chiral (*S*)-**9**, are very inexpensive and can be easily prepared on large scale. Second, the alkylation reactions of glycine and alanine complexes can be conducted under operationally convenient conditions without recourse to specially dry solvents, moisture/air-sensitive bases, like *n*-BuLi, or extreme low temperatures. Third, the corresponding alkylation products are highly crystalline compounds and can be further purified to diastereomerically pure form simply by crystallization. Fourth, glycine (*S*)-**9** and alanine (*S*,*S*)-**18a**-derived complexes can be alkylated

by chiral (racemic) secondary alkyl halides with appreciable kinetic resolution providing the most direct approach to extremely valuable sterically constrained β-substituted amino acids. Fifth, in most of cases, the alkylation reactions occur at high reaction rates rendering this approach as a method of choice for time-sensitive projects such as preparation of radioactive amino acid derivatives for positron-emitting tomography (PET). Finally, the alkylation reactions can be conducted under variety of conditions, such as phase-transfer and homogeneous, to accommodate various functional groups on the alkylation reagents. Furthermore, recently developed bis-alkylation procedure allows for straightforward preparation of bis-amino acids, relatively unexplored class of compounds. Here, we also should mention some drawbacks of this approach. Probably the most important one is incomplete diastereoselectivity, in particular under the kinetically controlled condition, necessitating the additional purification step. Also, relatively large molecular weight of these Ni(II) complexes provides for some inconvenience. Thus, only about 20 % of the total weight of an alkylated product carry the target amino acid and the rest is the ligand and Ni(II), requiring to use large quantities of solvents per gram of the target amino acid. Nevertheless, all these drawbacks play rather minor role as compared to the synthetic advantages provided by this methodology. It should also be stated that this approach attracts an increasing attention of chemists as the most simple and reliable method for preparation of various amino acids.

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

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

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