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REVIEW ARTICLE

Asymmetric synthesis of α-amino acids via homologation of Ni(II) complexes of glycine Schiff bases. Part 3: Michael addition reactions and miscellaneous transformations

José Luis Aceña · Alexander E. Sorochinsky · Vadim Soloshonok

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Abstract The major goal of this review is a critical discussion of the literature data on asymmetric synthesis of α-amino acids via Michael addition reactions involving Ni(II)-complexes of amino acids. The material covered is divided into two conceptually different groups dealing with applications of: (a) Ni(II)-complexes of glycine as *C*-nucleophiles and (b) Ni(II)-complexes of dehydroalanine as Michael acceptors. The first group is significantly larger and consequently subdivided into four chapters based on the source of stereocontrolling element. Thus, a chiral auxiliary can be used as a part of nucleophilic glycine Ni(II) complex, Michael acceptor or both, leading to the conditions of matching vs. mismatching stereochemical preferences. The particular focus of the review is made on the practical aspects of the methodology under discussion and mechanistic considerations.

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

V. Soloshonok
e-mail: vadym.soloshonok@ehu.es

A. E. Sorochinsky · V. Soloshonok
IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain

A. E. Sorochinsky
Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, Murmanska 1, Kyiv 02660, Ukraine

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Introduction

This review article continues a comprehensive coverage of the chemistry of Ni(II)-complexes of amino acid Schiff bases as one of the most prolific methodologies in the area of asymmetric synthesis of α-amino acids (α-AAs) (Sorochinsky et al. 2013a, b). Some of the prominent features, distinguishing this methodology from other approaches for asymmetric synthesis of α-AAs (Ma 2003; Maruoka and Ooi 2003; Nájera and Sansano 2007), is its versatility and practicality. Thus, various α-AAs, in particular highly sterically constrained (Soloshonok et al. 2001, 2008; Ellis et al. 2003a), can be prepared on relatively large scale (Kukhar et al. 1993; Tang et al. 2000; Ellis et al. 2003b) using alkyl halide alkylations (Deng et al. 2008; Wang et al. 2011a, 2013; Houck et al. 2012), aldol (Soloshonok et al. 1995, 1996a, b), Mannich (Soloshonok et al. 1997a; Wang et al. 2008a, 2010a, b) and Michael addition reactions. The former, alkylations, aldol and Mannich reactions were covered in the two preceding reviews, while Michael addition reactions is the subject of the current article.

The versatility of the Ni(II) complexes methodology is particularly emphasized by its applications in asymmetric Michael addition reactions. Hence, there are two conceptually different cases using Ni(II) complexes in these additions. First, application of glycine Schiff base (*S*)-**1** (Belokon et al. 1998a; Ueki et al. 2003a) as a nucleophilic partner in the reactions with various Michael acceptors (Fig. 1). In the second case Ni(II)-complex of dehydroalanine (*S*)-**2** (Belokon et al. 1988a) is used as an

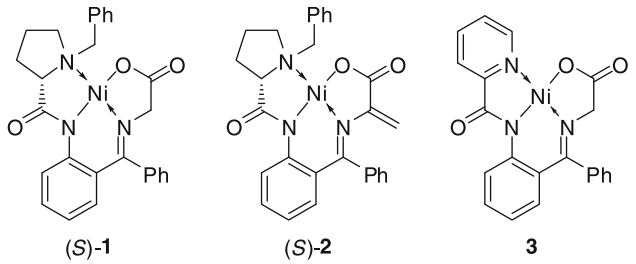


Fig. 1 Structures of Ni(II) complexes **1**–**3**

electrophilic unsaturated kind in the Michael additions with a range of nucleophiles. Furthermore, the former case itself can be performed in a variety of ways in terms of the position of a chiral auxiliary or using a chiral catalyst. For example, the stereocontrolling element can be located on glycine complex (*S*)-**1**, Michael acceptor of both. All these variations, their advantages and shortcomings are critically discussed as separate chapters.

Of particular interest are reactions of achiral Ni(II)-complex **3** (Ueki et al. 2003b; Deng et al. 2007) with chiral β-substituted Michael acceptors resulting in the formation of the corresponding glutamic acid derivatives possessing two consecutive stereogenic centers (Soloshonok 2002). These β-substituted glutamic acids can be further elaborated to various, so-called, χ-constrained α-AAs founding growing application in the de novo peptide design and synthesis of conformationally constrained reverse β-turn dipeptide mimetics (Qiu et al. 2001).

Considering that the goal of these three-review series was originally set as a comprehensive treatment of the chemistry and applications of Ni(II)-complexes of α-AAs, we added a special last chapter of miscellaneous transformations in which we included all examples that for some reasons were not described in the previous reviews or do not fall in any group defined as alkylations, aldol, Mannich or Michael addition reactions. Still, if any of the publications were left out, we will be grateful to the readers for kindly alerting our attention.

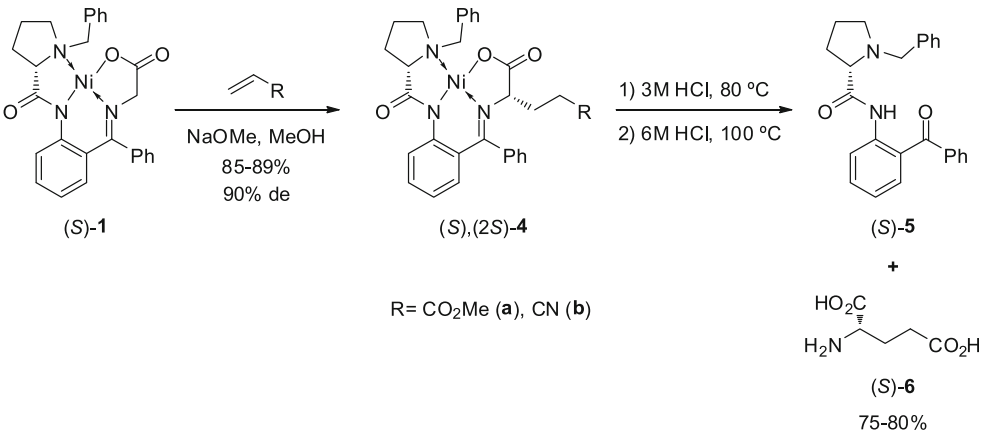
Additions of Ni(II) complexes to Michael acceptors

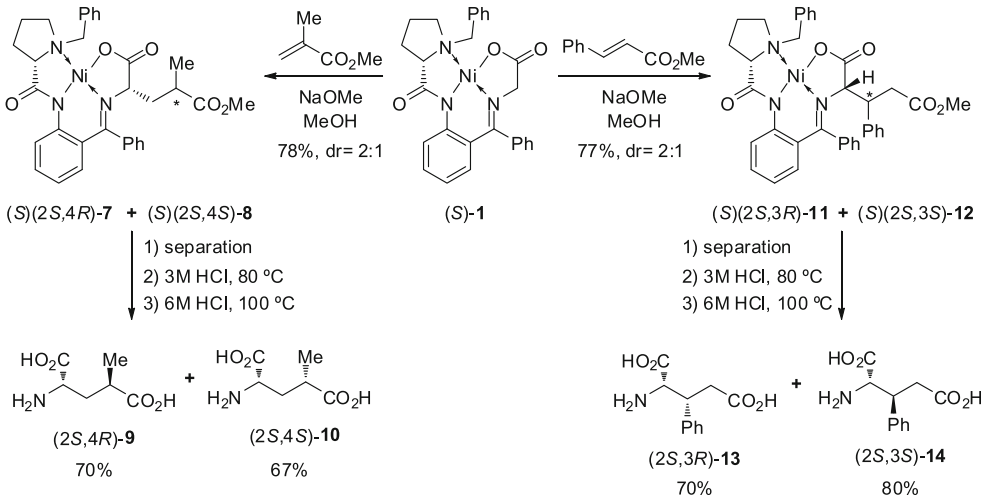
Additions of BPB-Ni-Gly complex (S)-1

Michael additions using chiral Ni(II) complex (*S*)-**1** as nucleophile and conducted under thermodynamically controlled conditions usually display the same high level of diastereoselectivity at the newly generated stereogenic α-carbon as in the other types of homologation reactions. The first example reported in the literature involved the addition of glycine complex (*S*)-**1** to either methyl acrylate or acrylonitrile using NaOMe as base to afford the corresponding adducts (*S*)(2*S*)-**4a** and (*S*)(2*S*)-**4b**, respectively, in high yield and diastereoselectivity (90 % de) (Belokon et al. 1986) (Scheme 1). It should be mentioned that secondary cyclization reactions arising from the attack of the carbanion intermediate to the C=N double bond are circumvented due to the steric hindrance provided by the phenyl ring. Compounds (*S*)(2*S*)-**4a**, **b** were disassembled by acidic treatment with recovery of the chiral ligand (*S*)-**5**, and further hydrolysis of the ester or cyano groups under stronger acidic conditions led to glutamic acid (*S*)-**6**.

The use of other acrylate derivatives bearing substituents on the double bond was also investigated (Belokon et al. 1986). Although the observed level of diastereoselectivity at the α-carbon was in the usual range of 90 % de, the stereocontrol at the newly formed stereocenter in the γ-position of the amino acid side chain was rather low. Thus, a mixture of diastereomers (*S*)(2*S*,4*R*)-**7** and (*S*)(2*S*,4*S*)-**8** was obtained in 2:1 ratio from the reaction of complex (*S*)-**1** with methyl methacrylate (Scheme 2). After chromatographic separation, each diastereomer was transformed into the corresponding 4-methylglutamic acid (2*S*,4*R*)-**9** and (2*S*,4*S*)-**10** under the acidic hydrolytic conditions. In a similar fashion, Michael addition of (*S*)-**1** to methyl cinnamate yielded (*S*)(2*S*,3*R*)-**11** and (*S*)(2*S*,3*S*)-**12** also in 2:1 ratio, which were further transformed into 3-phenylglutamic acids (2*S*,3*R*)-**13** and (2*S*,3*S*)-**14**, respectively.

Scheme 1 Michael additions of complex (*S*)-**1** to methyl acrylate and acrylonitrile





Scheme 2 Michael additions of complex (*S*)-**1** to methyl methacrylate and methyl cinnamate

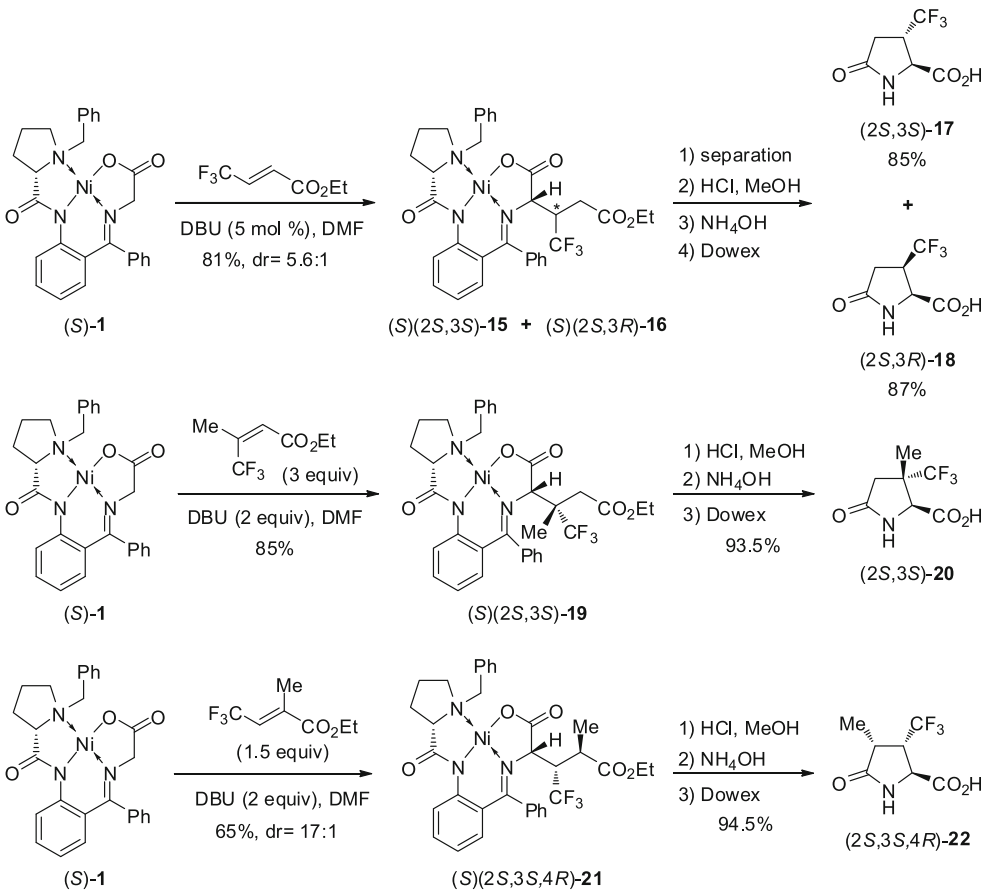
Much higher diastereoselectivities were achieved by installing a trifluoromethyl group at the β position of the Michael acceptor, probably due to electrostatic attractive interactions between the CF_3 moiety and the Ni atom in the most energetically favorable transition states leading to the major diastereomers. For example, addition of Ni(II) complex (*S*)-**1** to ethyl 4,4,4-trifluorocrotonate employed only catalytic amounts of DBU as base and led to the corresponding pair of diastereomers (*S*)(2*S*,3*S*)-**15** and (*S*)(2*S*,3*R*)-**16** in 5.6:1 ratio (Soloshonok et al. 1997b, 1999a) (Scheme 3). After separation, both complexes were disassembled with HCl and cyclised under basic conditions to afford pyroglutamic acid derivatives (2*S*,3*S*)-**17** and (2*S*,3*R*)-**18**, respectively. Most notably, ethyl 3-(trifluoromethyl)crotonate furnished a single Michael adduct (*S*)(2*S*,3*S*)-**19** upon its reaction with complex (*S*)-**1**, whereas the addition to ethyl 2-methyl-4,4,4-trifluorocrotonate also proceeded in good diastereomeric ratio (17:1) (Soloshonok et al. 1999b). However, both processes necessitated the use of excess of DBU as well as of the Michael acceptor due to their higher steric hindrance. Using the same hydrolytic conditions, two new fluorinated glutamic acids (2*S*,3*S*)-**20** and (2*S*,3*S*,4*R*)-**22** were prepared from complexes (*S*)(2*S*,3*S*)-**19** and (*S*)(2*S*,3*S*,4*R*)-**21**, respectively.

More recently, α-bromo- or α-fluoroacrylates were also employed as Michael acceptors in the reaction with complex (*S*)-**1**, although the choice of base led to different results (Belokon et al. 2005, 2010). Thus, DBU-catalyzed addition of (*S*)-**1** to ethyl α-bromoacrylate furnished an equimolecular mixture of cyclopropyl derivatives (*S*)(2*S*,3*R*)-**23** and (*S*)(2*S*,3*S*)-**24**, along with a small amount (7 %) of the (2*R*)-diastereomers (Scheme 4). Changing the base to the more hindered *i*-Pr_2NH prevented the intramolecular displacement of the bromine atom, thus allowing the isolation of the expected Michael adducts (*S*)(2*S*,4*R*)-**25a** and (*S*)(2*S*,4*S*)-**26a** but, again, in low diastereomeric ratio (2:1). The mechanistic pathway was demonstrated by the reaction of Michael adduct (*S*)(2*S*,4*R*)-**25a** with DBU affording almost quantitatively the corresponding cyclopropyl derivative (*S*)(2*S*,3*R*)-**23**. However, the disassembly of complexes **23**–**24**, **25a**–**26a** did not produce any desired amino acid, as only undefined mixtures of products were obtained. On the other hand, addition of (*S*)-**1** to methyl α-fluoroacrylate also proceeded with low diastereoselectivity, but after separation the resulting adducts (*S*)(2*S*,4*R*)-**25b** and (*S*)(2*S*,4*S*)-**26b** could be successfully transformed into the corresponding 4-fluoroglutamic acids (2*S*,4*R*)-**27** and (2*S*,4*S*)-**28**, respectively.

Acrylate derivatives **29**, bearing an allylic acetoxy moiety, readily reacted with complex (*S*)-**1** to produce adducts (*S*)(2*R*)-**30** after the in situ elimination of the AcO group (Wang et al. 2009) (Scheme 5). The process took place with excellent diastereoselectivity, but it should be mentioned that the (2*R*)-diastereomer was formed predominantly, in clear contrast to the previously shown similar reactions with other derivatives of acrylic acid. Furthermore, only the *E*-olefin was formed. A variety of aromatic and heteroaromatic substituents were tolerated and this method can be used for the synthesis of 4-alkylidene glutamic acids, as exemplified in the preparation of 4-nitrophenyl substituted derivative (*R*)-**31**.

The 1,4-addition of (*S*)-**1** to di-*tert*-butyl methylenemalonate in the presence of DBU led to the corresponding adduct (*S*)(2*S*)-**36** with moderate diastereoselectivity (Smith et al. 2011) (Scheme 6; Table 1, entry 1). Further work revealed that derivatives of (*S*)-**1** suitably substituted at the benzyl group with either a chlorine atom, (*S*)-**32**, or a thiomethyl moiety, (*S*)-**33**, improved the diastereoselectivity under the same reaction conditions as a result of the distortion of the square-planar geometry in the starting Ni(II) complexes (entries 2–3). An important decrease in

Scheme 3 Additions of complex (*S*)-**1** to fluorinated Michael acceptors



Scheme 4 Michael additions of complex (*S*)-**1** to methyl α-bromo- and α-fluoroacrylates

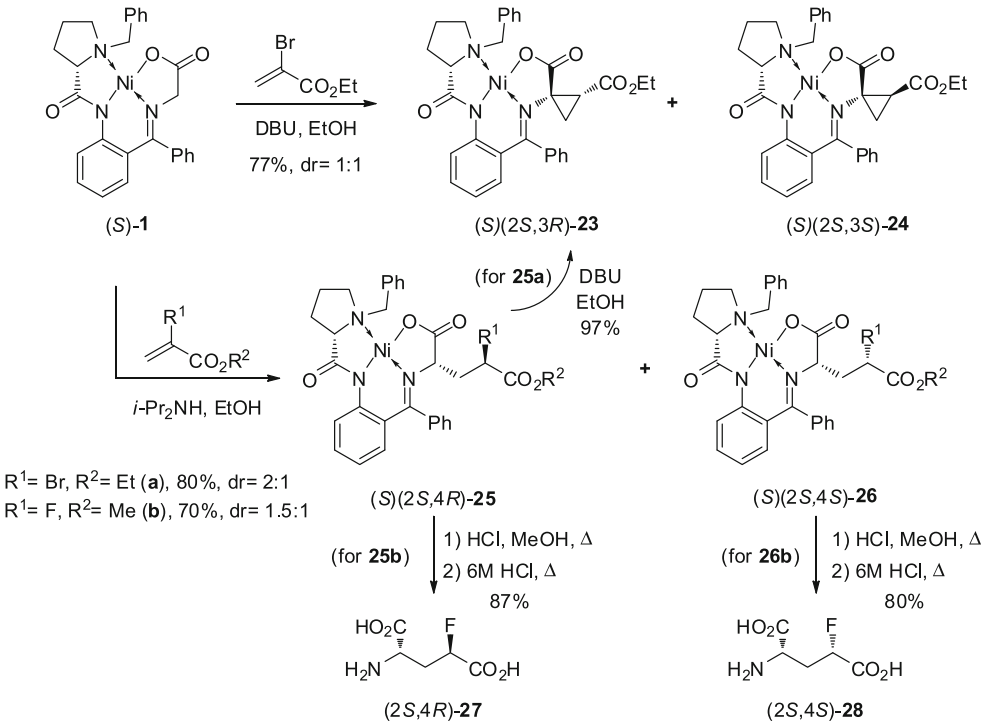


Table 1 Michael additions of Ni(II) and Cu(II) complexes **1**, **32–35** to di-*tert*-butyl methylenemalonate

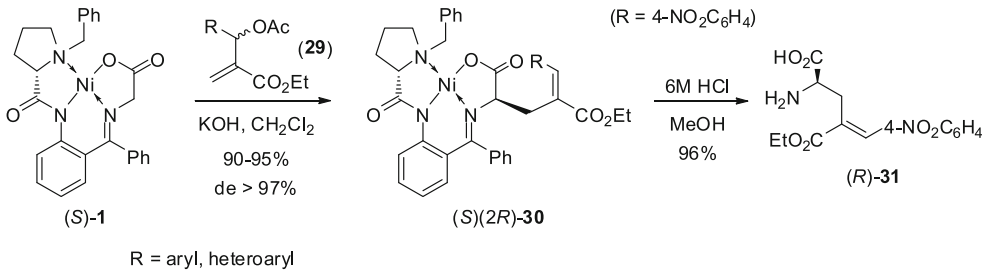
Entry	Ni(II) and Cu(II) complexes **1**, **32–35**	M	R	Michael adducts **36–40**	Yield (%)[a]	de (%)
1	(*S*)-**1**	Ni	H	(*S*)(2*S*)-**36**	75	82
2	(*S*)-**32**	Ni	Cl	(*S*)(2*S*)-**37**	94	85
3	(*S*)-**33**	Ni	SMe	(*S*)(2*S*)-**38**	81	90
4	(*S*)-**34**	Cu	H	(*S*)(2*S*)-**39**	64	49
5	(*S*)-**35**	Cu	SMe	(*S*)(2*S*)-**40**	70	93

[a] Overall yield of isolated products

the diastereomeric ratio was observed on the corresponding unsubstituted Cu(II) complex (*S*)-**34** (entry 4), but MeS-substituted analogue (*S*)-**35** was the most efficient on these series in terms of diastereoselectivity, this time as a consequence of apical coordination of the sulfur atom to the copper (entry 5). Hydrolytic treatment of the resulting adduct (*S*)(2*S*)-**40** followed by amino group protection afforded the γ-carboxyglutamic acid derivative (*S*)-**41**.

α,β-Unsaturated carbonyl compounds were efficiently used as Michael acceptors in the reaction with complex (*S*)-**1**, and hence various proline derivatives could be prepared upon disassembly of the resulting adducts (Belokon et al. 1988b) and the sequence of cyclization and reduction of the C=N bond (Scheme 7). Thus, addition of (*S*)-**1** to acrolein proceeded with good diastereoselectivity and the major product (*S*)(2*S*)-**42** was further transformed into (*S*)-proline **49** by acidic treatment followed by reduction of the 1-pyrroline intermediate with $NaBH_3CN$ (Table 2, entry 1). The analogous reaction with methacrolein resulted in a mixture of diastereomeric adducts (*S*)(2*S*,4*R*)-**43** and (*S*)(2*S*,4*S*)-**44** as the major products in 2.1:1 ratio, but after disassembly of the Ni(II) complexes the corresponding pyrroline intermediates were prone to racemization at the

Scheme 5 Michael addition of complex (*S*)-**1** to acrylates **29**



Scheme 6 Michael additions of complexes (*S*)-**1**, **32–35** to di-tert-butyl methylenemalonate

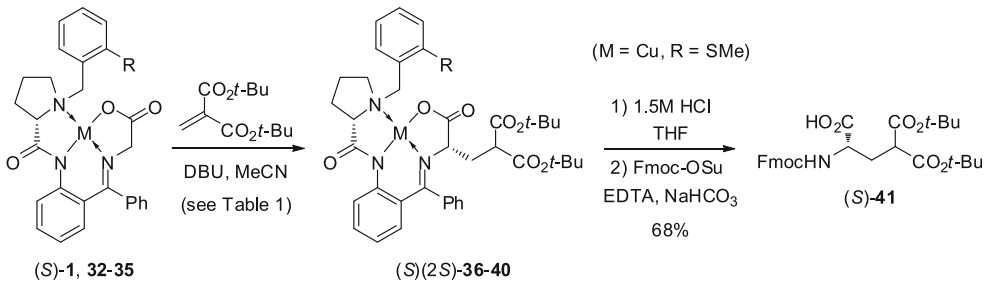


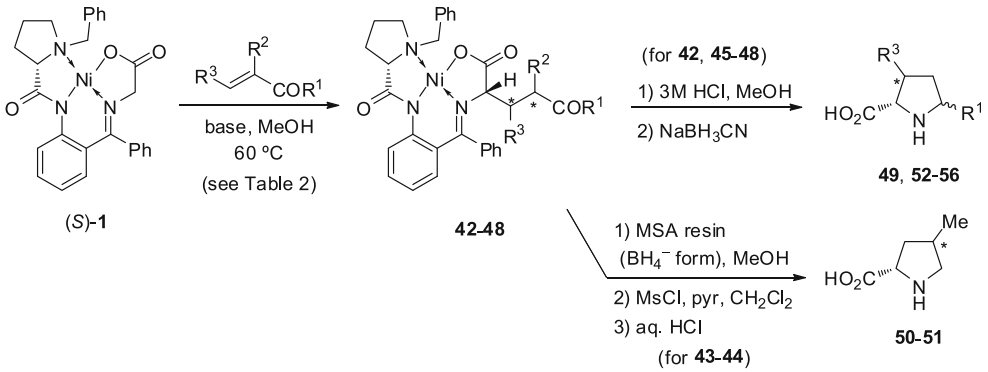
Table 2 Michael additions of Ni(II) complex **1** to α,β-unsaturated carbonyl compounds

Entry	R^1	R^2	R^3	Base	Michael adducts **42–48**	Yield (%)[a]	dr	Prolines **49–56**	Yield (%)
1	H	H	H	Et_3N	(*S*)(2*S*)-**42**	73	N/A	(*S*)-**49**	73
2	H	Me	H	Et_3N	(*S*)(2*S*,4*R*)-**43**	98	2.1:1	(2*S*,4*S*)-**50**	74
					(*S*)(2*S*,4*S*)-**44**			(2*S*,4*R*)-**51**	70
3	H	H	Me	Et_3N	(*S*)(2*S*,3*S*)-**45**	96	1:0	(2*S*,3*S*)-**52**	70
4	H	H	Ph	Et_3N	(*S*)(2*S*,3*R*)-**46**	100	8.2:1	(2*S*,3*R*)-**53**	75
					(*S*)(2*S*,3*S*)-**47**			(2*S*,3*S*)-**54**	71
5	Me	H	H	NaOMe	(*S*)(2*S*)-**48**	100	N/A	(2*S*,5*R*)-**55** + (2*S*,5*S*)-**56**[b]	69

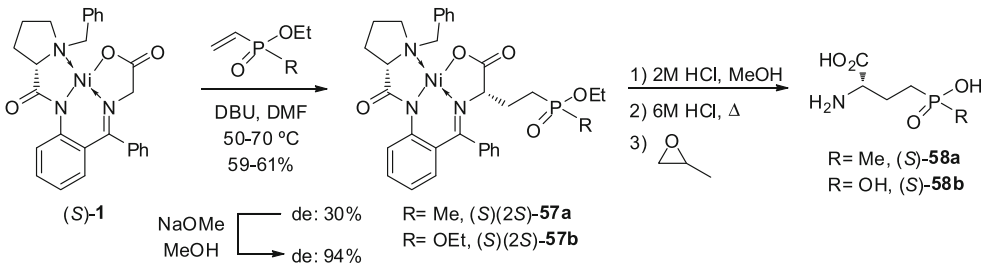
[a] Overall yield of isolated products; includes 4–8 % of the corresponding (2*R*)-isomers

[b] A 1:1 mixture of epimeric prolines **55** and **56** was obtained after the reduction step

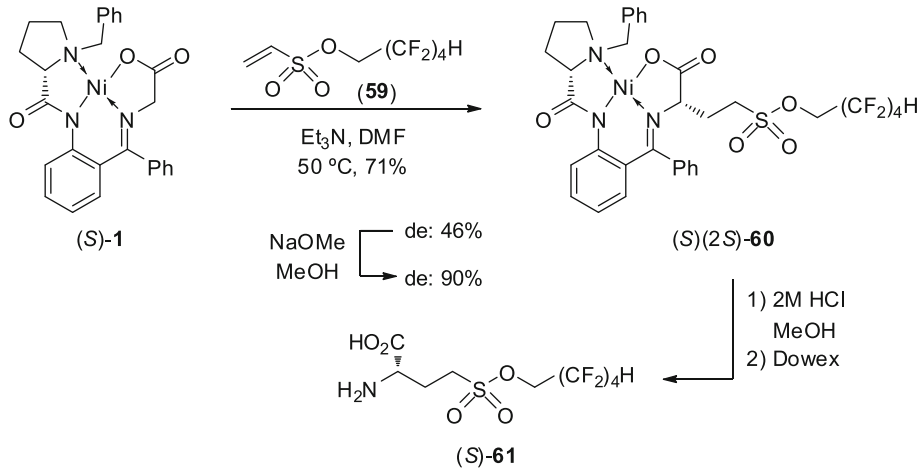
Scheme 7 Michael additions of complex (*S*)-**1** to α,β-carbonyls



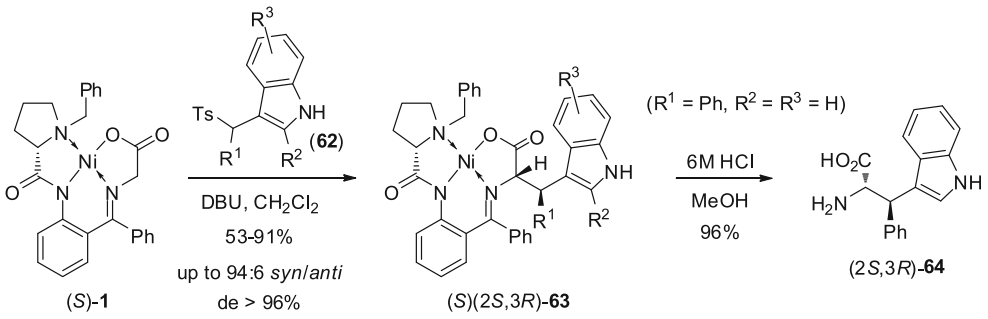
Scheme 8 Michael additions of complex (*S*)-**1** to vinylphosphonates and phosphinates



Scheme 9 Michael addition of complex (*S*)-**1** to vinylsulfonic acid **59**

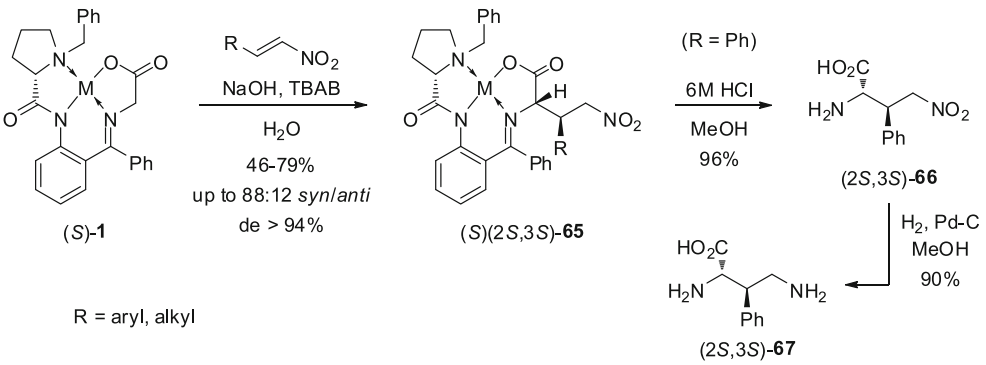


Scheme 10 Michael additions of complex (*S*)-**1** to sulfonylindoles

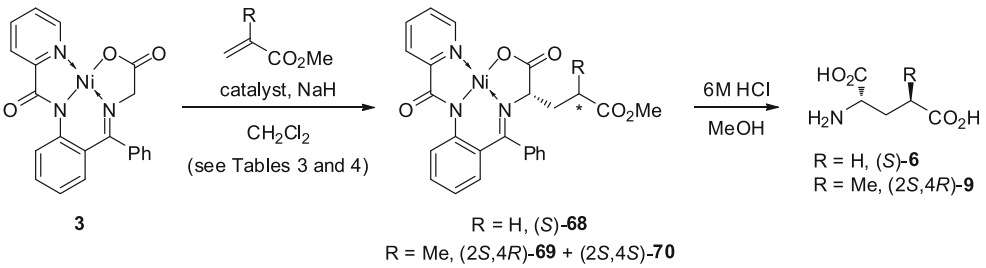


R^1 = aryl, heteroaryl
R^2 = H, Me
R^3 = H, 4-Me, 5-Me, 5-Cl, 7-Me

Scheme 11 Michael additions of complex (*S*)-**1** to nitroalkenes



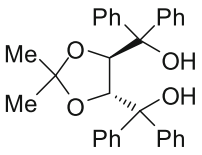
Scheme 12 Michael additions of complex **3** to methyl acrylate and methyl methacrylate



methyl group prior to reduction of the C=N double bond. Therefore, an alternative procedure was pursued consisting in reduction and mesylation of the resulting hydroxyl group, followed by cyclization under the hydrolytic treatment (entry 2). As a result, the desired 4-methylprolines (2*S*,4*S*)-**50** and (2*S*,4*R*)-**51** underwent an inversion of the configuration at the methyl group. On the contrary, the addition of (*S*)-**1** to crotonaldehyde and cinnamaldehyde was much more selective, and a single (2*S*)-configured product (*S*)(2*S*,3*S*)-**45** was observed in the former case (entries 3 and 4). This protocol can be used for the synthesis of 3-substituted prolines **52**–**54**, but it has been applied as well to the preparation of the naturally occurring amino acid (*S*)-pyrrolysine (Hao et al. 2004). Finally, the process was also suitable for the addition to methyl vinyl ketone, although it was unavoidable to get a 1:1 mixture of the target 5-methylprolines (2*S*,5*R*)-**55** and (2*S*,5*S*)-**56** (entry 5).

Vinylphosphonates and phosphinates are other type of Michael acceptors suitable for reacting with Ni(II) complex (*S*)-**1**, as a key step for the convenient access to phosphorous-containing amino acids (Soloshonok et al. 1992). In terms of chemical yield, the best choice of base was DBU, but resulted in low levels of kinetic diastereocontrol in the corresponding adducts **57a**, **b** (Scheme 8). However, the selectivity could be much improved by epimerization of the initially formed diastereomeric mixture by treatment with NaOMe. Disassembly of compounds **57** under standard acidic conditions followed by hydrolysis of the phosphinate or phosphonate ester functionalities afforded amino acids **58a** and **58b**, respectively, the former being the naturally occurring herbicide agent phosphinothricin.

Fig. 2 Structure of TADDOL **71**



71

Table 3 Michael additions of Ni(II) complex **3** to methyl acrylate or methyl methacrylate catalyzed by TADDOL **71**

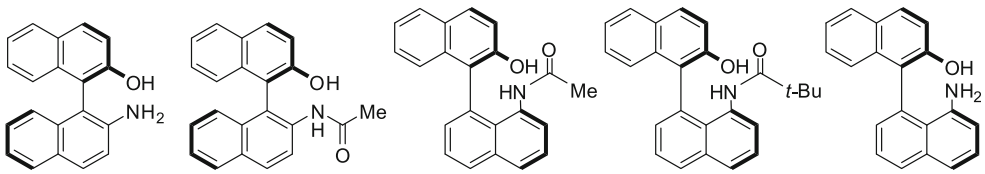
Entry	R	Mol % of **71**	Temp. (°C)	Reaction time (min)	Yield (%)[a]	de (%)	ee (%)[b]
1	H	100	25	5	76	N/A	18
2	H	100	−20	30	48	N/A	45
3	Me	100	25	15	51	38	28
4	Me	100	−20	90	12	80	9
5	Me	10	25	40	56	56	20

[a] Overall yield of isolated products

[b] Measured on the corresponding free amino acid (*S*)-**6** or (2*S*,4*R*)-**9**

In a similar fashion, the conjugate addition of (*S*)-**1** to fluorinated ester of vinylsulfonic acid **59** using Et_3N as base proceeded in good diastereoselectivity after NaOMe-mediated epimerization to give adduct (*S*)(2*S*)-**60** (Soloshonok et al. 1993) (Scheme 9). It should be noted that a one-pot process carried out in the presence of NaOMe as base afforded a much lower yield of compound **60**. Acidic treatment followed by Dowex purification furnished the fluorinated ester of (*S*)-homocysteic acid, (*S*)-**61**.

Fig. 3 Structures of NOBIN and *iso*-NOBIN catalysts **72–76**



72 **73** **74** **75** **76**

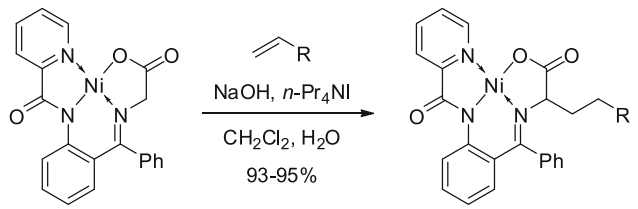
Table 4 Michael additions of Ni(II) complex **3** to methyl acrylate or methyl methacrylate catalyzed by NOBIN or *iso*-NOBIN derivatives **72–76**

Entry	R	Catalyst (15 mol %)	Yield (%)[a]	de (%)	ee (%)[b]
1	H	**72**	40	N/A	26
2	H	**73**	50	N/A	55
3	H	**74**	70	N/A	90–94
4	H	**75**	80	N/A	96
5	H	**76**	50	N/A	13
6	Me	**74**	60	75	61[c]

[a] Overall yield of isolated products

[b] Measured on the corresponding free amino acid (*S*)-**6** or (2*S*,4*R*)-**9**

[c] % ee of the minor isomer (2*S*,4*S*)-**70** was 54 %



3

R= CN, **77a**
R =CO_2Et, **77b**

Scheme 13 Michael additions of complex **3** under PTC

Sulfonylindoles **62** may act as surrogates of Michael acceptors through their derived iminium species as an expedient procedure for the synthesis of β-substituted tryptophans (Wang et al. 2011b) (Scheme 10). Thus, Ni(II) complex (*S*)-**1** reacted with various substituted sulfonylindoles **62** in the presence of DBU to afford compounds **63** with excellent diastereoselectivity at the α-carbon and acceptable syn/anti ratio in both newly formed stereogenic centers. Tryptophan **64** was easily obtained after disassembly of the corresponding Ni(II) complex.

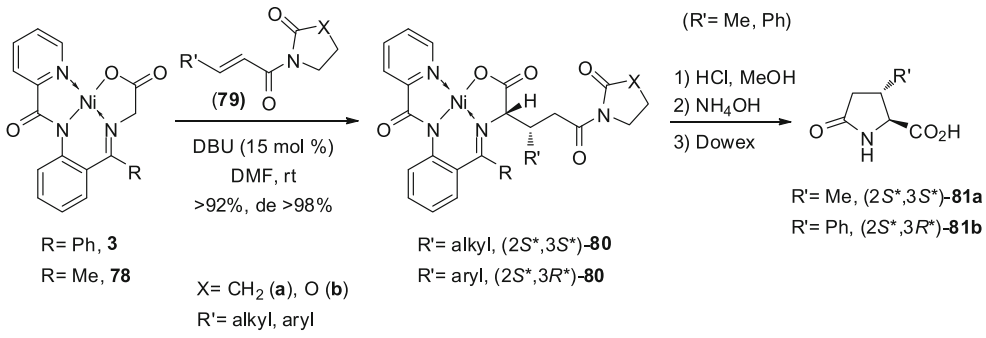
Recently, nitroalkenes were successfully employed as Michael acceptors in water as solvent (Wang et al. 2012). Thus, addition of (*S*)-**1** to 2-aryl- or 2-alkyl-1-nitroalkenes, using NaOH as base in the presence of tetra-*n*-butylammonium bromide (TBAB), furnished adducts (*S*)(2*S*,3*S*)-**65** in moderate-to-fair yields, acceptable *syn*/*anti* ratio and very good diastereoselectivities at the α-carbon (Scheme 11). The phenyl-derived Ni(II) complex (R = Ph) was disassembled to render γ-nitro-α-amino acid (2*S*,3*S*)-**66**, which could also be transformed into β-phenyl-α,γ-diaminobutyric acid (2*S*,3*S*)-**67**.

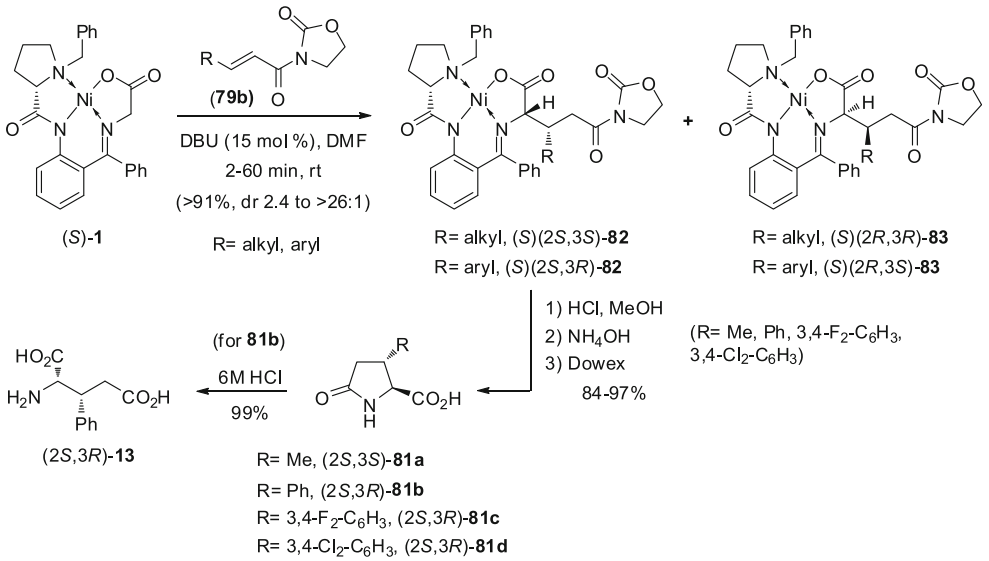
Additions of PABP-Ni-Gly complex **3**

Achiral Ni(II) complex **3** derived from picolinic acid, 2-aminobenzophenone and glycine has been used in enantioselective Michael additions in the presence of chiral promoters/catalysts. As a model reaction, the addition of **3** to either methyl acrylate or methyl methacrylate was tested by using a variety of chiral alcohols, diols and amino alcohols in the presence of NaH as base, although only moderate enantioselectivities were initially achieved (Belokon et al. 1997, 1998b) (Scheme 12). The in situ formed sodium dialkoxide derived from (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol (TADDOL) **71** (Fig. 2) provided the best results and, for instance, the addition of **3** to methyl acrylate using an stoichiometric amount of **71** at room temperature led to compound (*S*)-**68** with 18 % ee (Table 3, entry 1) which was improved to 45 % at lower temperatures (entry 2). The analogous reaction with methyl methacrylate afforded a mixture of diastereomers (*S*)(2*S*,4*R*)-**69** and (*S*)(2*S*,4*S*)-**70**, from which the major one had 28 % ee (entry 3). The diastereoselectivity was improved at low temperature, however, this was accompanied by a decrease in the enantiomeric excess (entry 4). Finally, catalytic amounts of **71** produced similar results compared to the stoichiometric examples (entry 5). In all cases, the enantioselectivity was measured after disassembly of the addition products to give the corresponding free amino acids, namely, glutamic acid (*S*)-**6** and 4-methylglutamic acid (2*S*,4*R*)-**9**.

A survey for more efficient catalysts was next conducted, eventually leading to 1,1′-binaphtyl derivatives (Fig. 3) as promising candidates for performing the enantioselective 1,4-addition of complex **3** to methyl acrylate (Vyskočil et al. 2002; Belokon et al. 2003). The first catalyst evaluated within this family was (*R*)-(2-amino-2′-hydroxy-1,1′-binaphthyl) (NOBIN) **72** giving rise to a low enantiomeric excess (Table 4, entry 1). However, it was discovered that its derivative acetamide **73** improved the ee to a moderate level in the resulting adduct (*S*)-**68** (entry 2). As it turned out, the *iso*-NOBIN acetamide **74** truly

Scheme 14 Additions of complexes **3** and **78** to achiral Michael acceptors **79**





Scheme 15 Additions of complex (*S*)-**1** to achiral Michael acceptors **79b**

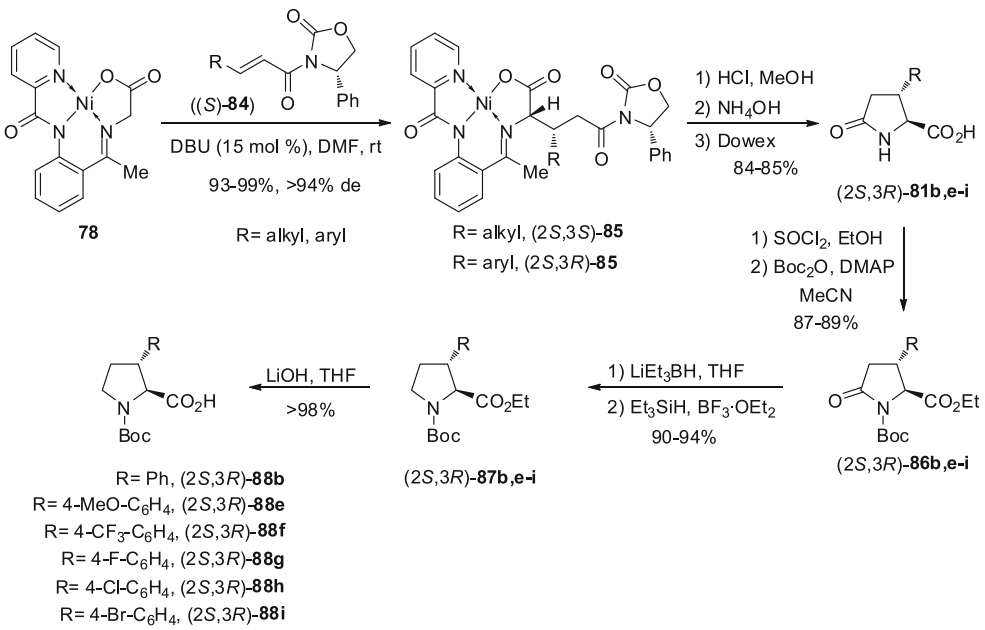
provided synthetically useful enantioselectivities (entry 3), and the best result (96 % ee) was achieved by introducing a larger amide moiety as in pivaloyl derivative **75** (entry 4). The presence of this amide residue proved to be essential because the parent unsubstituted *iso*-NOBIN catalyst **76** led to a significant drop in the observed ee (entry 5). Finally, the addition of **3** to methyl methacrylate catalyzed by acetamide **74** was also tested but resulted in a much less enantioselective outcome in both diastereomeric products (2*S*,4*R*)-**69** and (2*S*,4*S*)-**70** (entry 6).

Furthermore, the high reactivity of picolinic acid-derived complex **3** allowed its straightforward functionalization under phase-transfer catalysis conditions giving rise to products **77a** and **77b**, respectively (Ellis et al. 2003c) (Scheme 13).

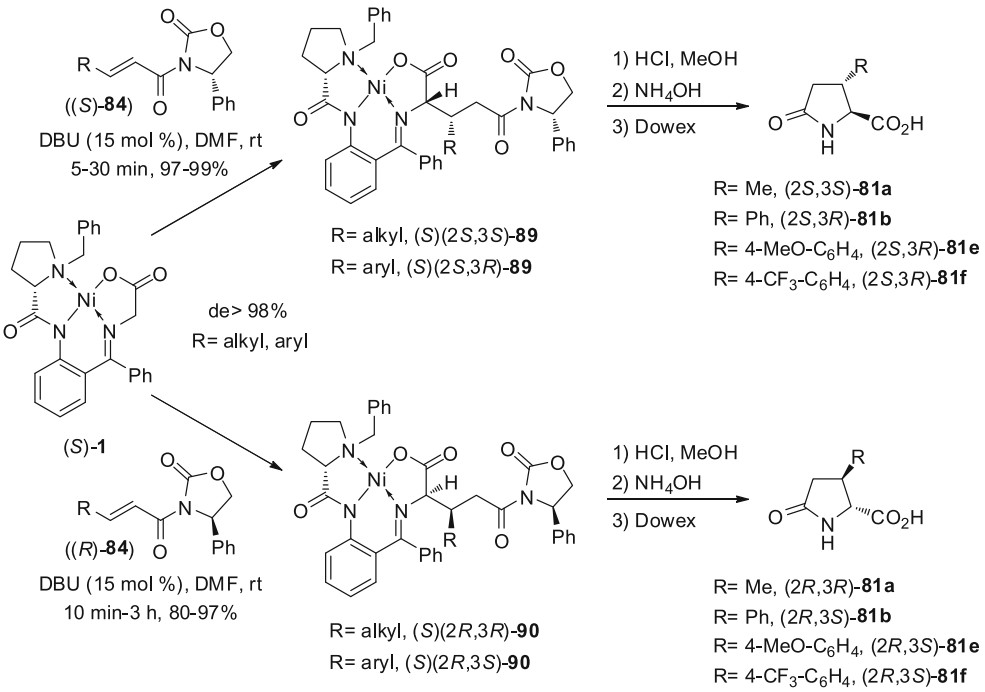
Additions of BPB-Ni-Gly complex (S)-1 and PABP-Ni-Gly complex 3 to trans-*N*-(enoyl)-1,3-oxazolidine-2-ones

In the absence of chelating ion metals, the diastereoselective outcome of the Michael addition reactions resulting in a formation of two adjacent stereogenic centers, normally depends on the geometric/conformational homogeneity of both reactants. Ni(II) complexes, such as (*S*)-**1** or **3** meet this requirement because the enolates derived from them can be generated only in (*E*)-configuration due to the cyclic structure of these nucleophilic glycine equivalents. However, in the examples shown thus far the employed Michael acceptors do not guarantee this criterion and therefore the diastereoselectivity is almost never complete. The first method that solved this drawback involved using *trans-N*-(enoyl)-pyrrolidin-2-ones **79a** or the corresponding 1,3-oxazolidine-2-ones **79b** as conformationally homogeneous Michael acceptors (Soloshonok et al. 2000a, b). These compounds are present exclusively in their *s-cis* conformers in order to minimize repulsive interactions between both carbonyl groups, and hence their reaction with picolinic acid-derived achiral Ni(II) complexes **3** or **78** proceeded in very high yields to furnish diastereomerically pure adducts **80** in racemic form (Scheme 14). The process took place in the presence of catalytic amounts of DBU, and the best combination of reagents in terms of reaction

Scheme 16 Additions of complex **78** to chiral Michael acceptors (*S*)-**84**



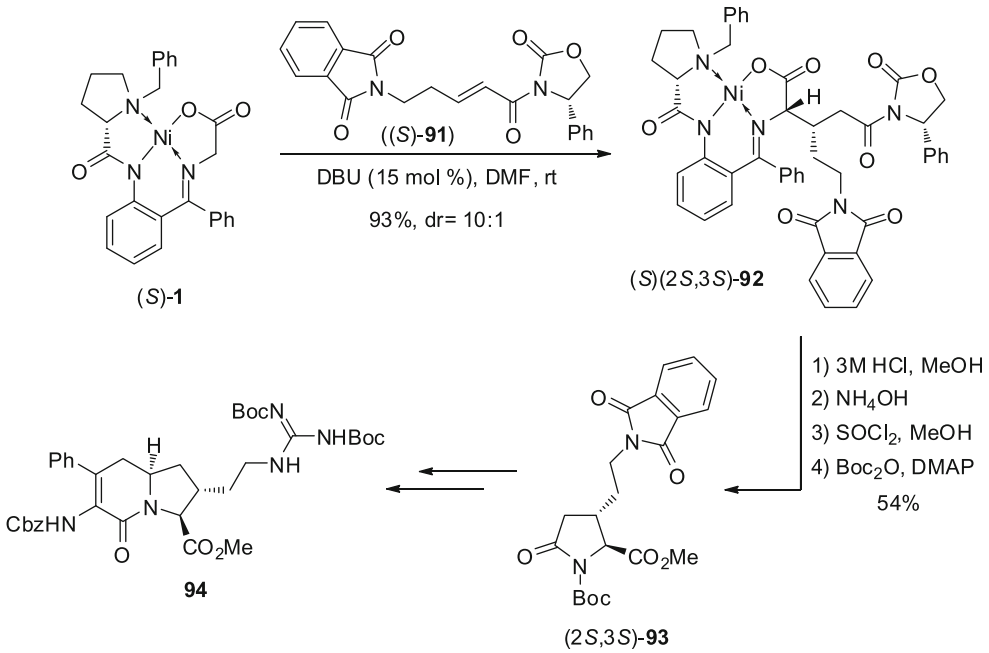
Scheme 17 Additions of complex (*S*)-**1** to chiral Michael acceptors (*S*)- and (*R*)-**84**

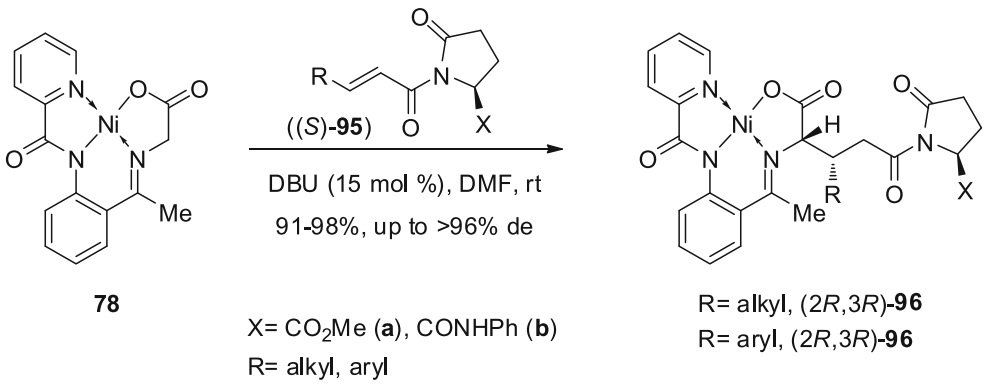


rate consisted in mixing oxazolidine-containing acrylamides **79b** with the acetophenone-derived complex **78** because of the less sterically demanding glycine moiety of the latter. Further treatment of compounds **80** (R′ = Me or Ph) with HCl led to disassembly of the Ni(II) complex followed by cyclization in basic media giving rise to pyroglutamic acids **81a**, **b**.

Synthesis of 3-substituted pyroglutamic acids in optically pure form by means of the above method first involved using the standard chiral Ni(II) complex (*S*)-**1** (Soloshonok et al. 1999c; Cai et al. 2001). Nevertheless, in most cases only moderate levels of diastereoselection were achieved in the corresponding adducts **82** and **83** as a result of incomplete facial selectivity at the α-carbon (Scheme 15). Thus, up to a 5.2:1 ratio was obtained in the case of alkyl-substituted oxazolidinones depending on the steric bulk of the R group, whereas in the aromatic series the best results were obtained when electron-withdrawing substituents (diastereomeric ratio >26:1 when R = C_6F_5) were present. Employing the usual hydrolytic treatment,

Scheme 18 Synthesis of β-turn mimic **94**





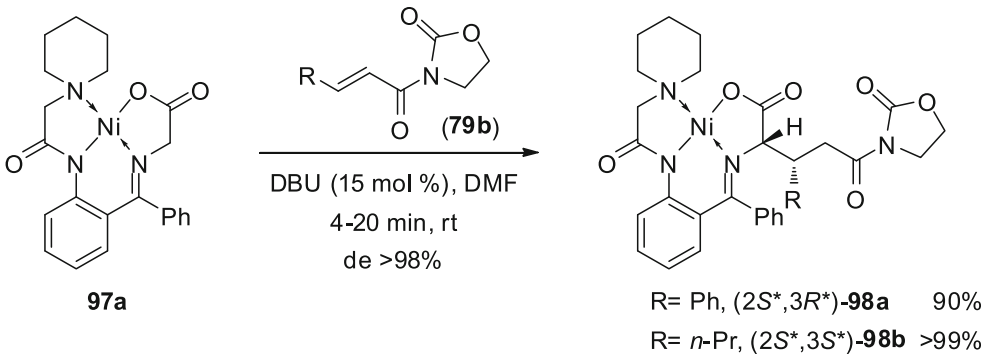
Scheme 19 Additions of complex **78** to chiral Michael acceptors (*S*)-**95**

enantiopure pyroglutamic acids **81a–d** as well as 3-phenylglutamic acid (2*S*, 3*R*)-**13** were prepared.

The obvious alternative procedure for accessing optically pure 3-substituted pyroglutamic acids was the introduction of a stereocontrolling element into the structure of oxazolidinone-derived acrylamides. It was envisaged that 4-phenyloxazolidin-2-ones (*S*)- or (*R*)-**84**, first introduced by Evans et al. (1988), would constitute outstanding chiral Michael acceptors in their reaction with achiral Ni(II) complexes such as **78** (Soloshonok et al. 2000c, 2004) (Scheme 16). Under standard DBU-catalyzed conditions, adducts **85** were obtained essentially as single diastereomers. Thus, not only simple diastereoselectivity was achieved as in the case of achiral *N*-(enoyl)oxazolidinones, but the enolate facial selectivity was also totally controlled by the chiral auxiliary attached to the acrylamide moiety by the virtue of a unique mode of steric interactions, regardless of the nature of the R substituents, that determine the transition state leading to the major diastereomer (Soloshonok et al. 2000d). Preparation of pyroglutamic acids **81** was complemented by their straightforward elaboration into *N*-protected, 3-substituted prolines **88** in the de novo peptide design (Cai et al. 2004a). It should also be mentioned that a suitable synthetic protocol for accessing these chiral Michael acceptors **84** was developed avoiding low-temperature procedures (Soloshonok et al. 2002), rendering this method fully amenable for high-scale applications.

Quite an interesting study involved the use of both chiral reacting partners, namely *N*-benzylproline-derived complex (*S*)-**1** and *N*-enoyloxazolidinones (*S*)- and (*R*)-**84** (Soloshonok et al. 2000e, 2005a). Thus, it was expected that there might be matched and mismatched pairs as a result of different stereodirecting preferences of each chiral

Scheme 20 Additions of complex **97a** to achiral Michael acceptors **79b**



Scheme 21 Additions of complexes **97a–f** to chiral Michael acceptor (*S*)-**99**

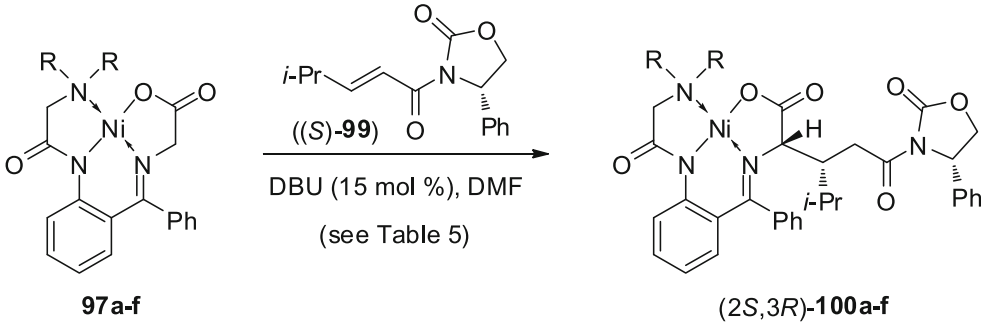


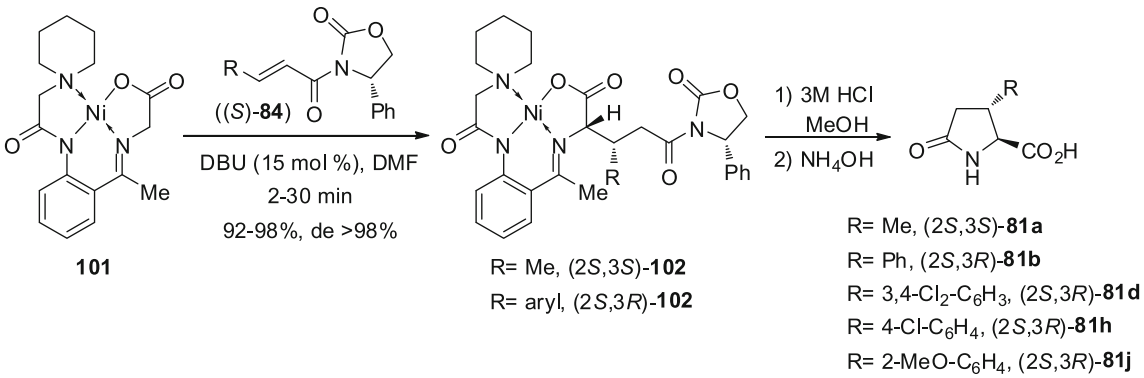
Table 5 Michael additions of Ni(II) complexes **97a–f** to *N*-(enoyl)-1,3-oxazolidine-2-one (*S*)-**99**

Entry	Ni(II) complex **97**	R_2N	Michael adduct **100**	Reaction time (h)	Conversion (%)	Yield (%)
1	**97a**	Piperidyl	**100a**	0.4	>99	>99
2	**97b**	Bn_2N	**100b**	26	88	86
3	**97c**	*n*-Bu_2N	**100c**	26	90	85
4	**97d**	Me_2N	**100d**	26	62	60
5	**97e**	Morpholyl	**100e**	18	>99	79
6	**97f**	2-Isoindolyl	**100f**	26	60	58

reagent. It was found that the glycine enolate facial selectivity in Ni(II) complex (*S*)-**1** was completely overwhelmed by the stereochemical preference of the Michael acceptors. Thus, addition of (*S*)-**1** to oxazolidinones (*S*)-**84** afforded compounds **89**, whereas the same reaction employing the (*R*)-configured Michael acceptors led to diastereomeric adducts **90** (Scheme 17). Both processes occurred in excellent yields with complete diastereoselectivity, and only in the mismatched case longer reaction times were needed. Nevertheless, the chemical reactivity of complex (*S*)-**1** was superior to the analogous Michael additions employing picolinic acid-derived complex **78** as substrate. The usefulness of this method allowed preparing enantiomerically pure 3-substituted pyroglutamic acids such as **81a–b**, **e–f** from a single enantiomer of the initial chiral Ni(II) complex.

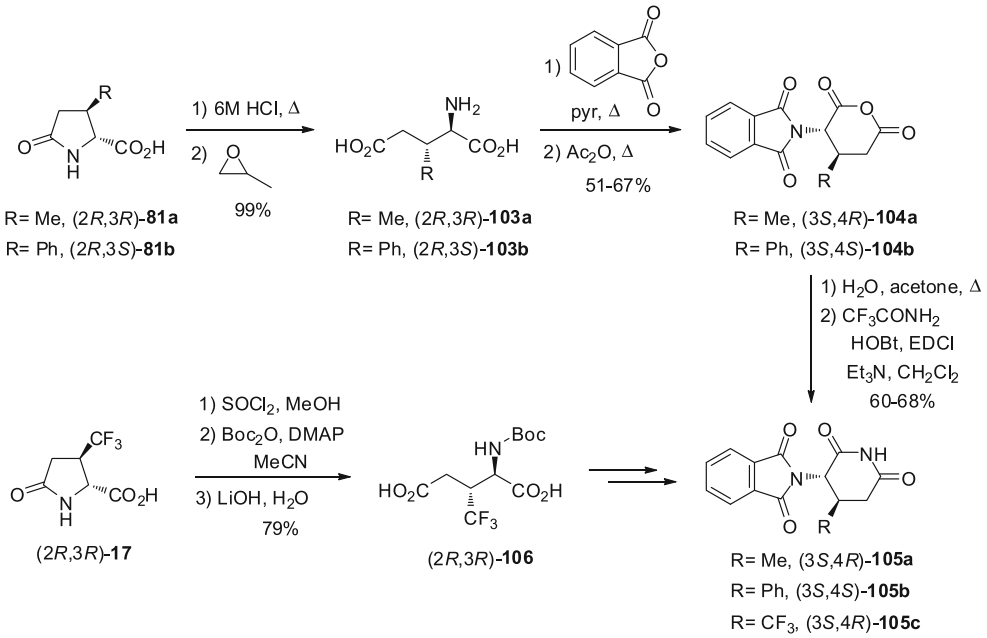
The above methodology could be applied to the synthesis of compounds of biological interest (Zhang et al. 2003). For instance, addition of (*S*)-**1** to oxazolidinone (*S*)-**91** bearing a β-(phthalimido)ethyl group proceeded with very good selectivity to render (*S*)(2*S*,3*S*)-**92**, which was next transformed into protected pyroglutamate (2*S*,3*S*)-**93** by means of standard procedures (Scheme 18). Compound **93** served as precursor for the synthesis of the β-turn mimic **94**.

In the context of designing similar Michael acceptors, other chiral scaffolds have been investigated (Cai et al. 2004b; Ellis et al. 2009). In particular, methyl *trans*-*N*-enoylpyroglutamates **95a** benefit from their cheaper commercial access in both enantiomeric forms compared to oxazolidinones **84**, and they have produced excellent results in terms of yield and diastereoselectivity in their reaction with picolinic acid-derived complex **78** (Scheme 19). The parent *N*-phenylamides **95b** turned out to be somewhat less reactive, and the corresponding adducts **96b** were more difficult to isolate due to their high solubility in DMF/H_2O mixtures.



Scheme 22 Additions of complex **101** to chiral Michael acceptors (*S*)-**84**

Scheme 23 Synthesis of thalidomide analogues **105a–c**

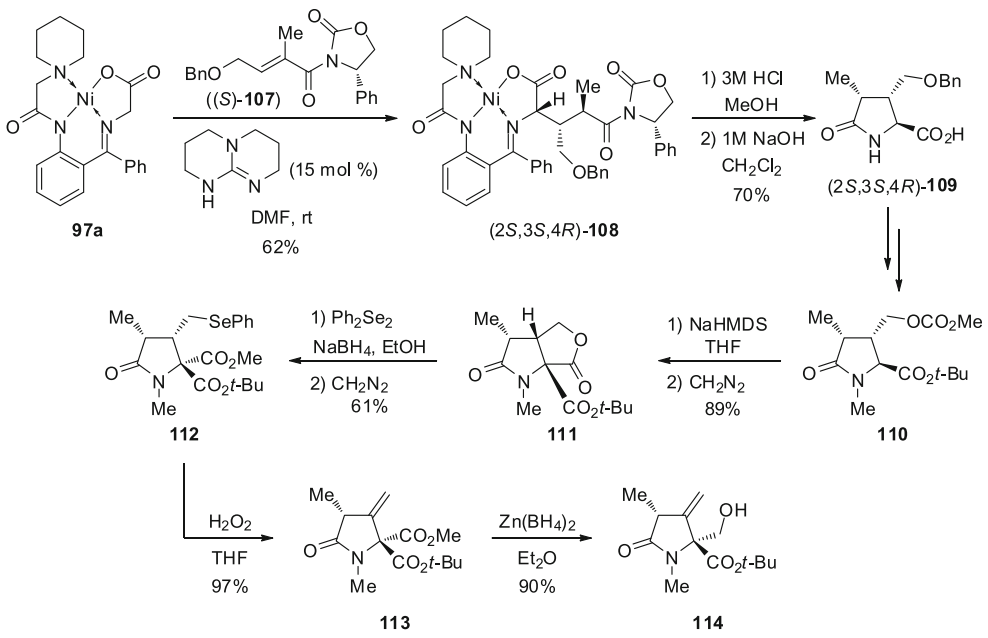


Additions of "new generation"-Ni-Gly complexes

Despite the great potential of Ni(II) complexes such as chiral (*S*)-**1** derived from *N*-benzylproline, as well as achiral **3** and **78** prepared from picolinic acid, all of them suffered some drawbacks as a result of their low solubility in common organic solvents, which is also the reason of the observed low reactivity in some cases. With the aim of improving these features, a "new generation" of achiral Ni(II) complexes was designed through a flexible modular assembly that allows the introduction of different secondary amines in order to fine-tune their physico-chemical properties (Soloshonok et al. 2009a). Moreover, the preparation of this new family of complexes resulted considerably easier employing readily available starting materials. Their synthetic value in the context of Michael addition reactions was also demonstrated. For instance, piperidine-derived complex **97a** was used effectively in the reaction with achiral oxazolidinones **79b** to render adducts **98a**, **b** as single diastereomers in racemic form (Soloshonok et al. 2005b) (Scheme 20).

A comparison study was next carried out in order to establish the most efficient substitution pattern on the amine moiety (Soloshonok et al. 2005c; Ellis et al. 2006). Thus, using the sterically demanding isopropyl-derived chiral oxazolidinone (*S*)-**99** as a model Michael acceptor, a variety of secondary amine-containing complexes **97a–e** were tested under the standard reaction conditions (Scheme 21; Table 5). Piperidyl complex **97a** readily reacted with (*S*)-**99** to produce adduct **100a** in quantitative yield and complete diastereoselectivity (entry 1). However, addition of complexes **97b–d**, although less sterically demanding in virtue of their acyclic secondary amine moieties, proceeded at a lower reaction rate and full

Scheme 24 Synthesis of the pyroglutamate moiety of oxazolomycin A and neooxazolomycin



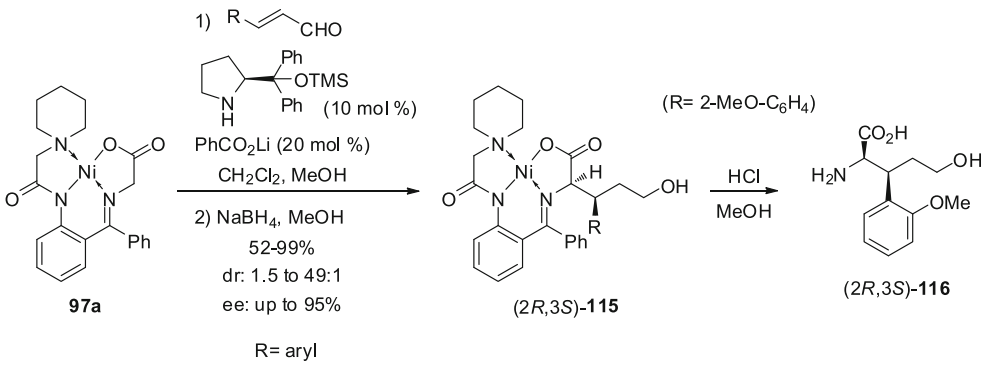
conversion was not achieved, most likely due to their somewhat lower solubility compared to **97a** (entries 2–4). Other cyclic amine derivatives such as **97e–f** were also less successful as a result of their different electronic or steric attributes (entries 5–6).

Piperidyl complex **97a** also demonstrated its usefulness in a series of Michael additions with a number of chiral oxazolidinones (*S*)-**84**, but its acetophenone-derived counterpart **101** proved to be even superior in terms of reactivity as the reactions proceeded at a much faster rate, being completed in a matter of a few minutes in most cases (Scheme 22). For instance, addition of **101** to a 2-(methoxy)phenyl-substituted oxazolidinone afforded compound **102** after 30 min in 94 % yield, whereas the analogous reaction with benzophenone-derived complex **97a** necessitated 1.75 h to bring the reaction to completion. Finally, disassembly of the new generation complexes took place under the usual acidic conditions to render, after cyclization in basic media, the target pyroglutamic acids **81a–b**, **d**, **h**, **j**.

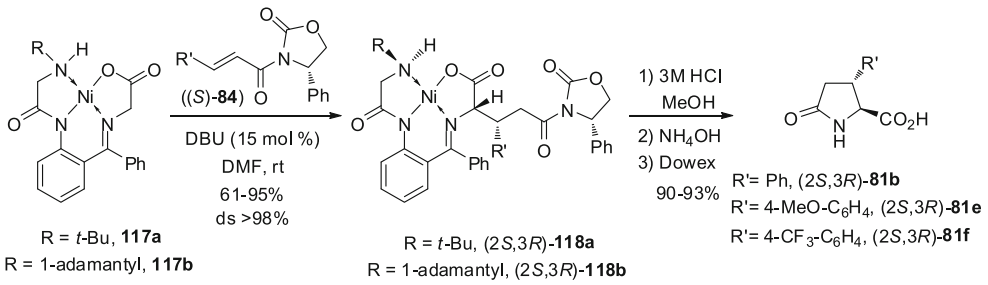
The search for non-epimerizable analogues of thalidomide is a research subject of prime interest in order to avoid the teratogenic properties associated to the (*S*)-enantiomer of the drug. In this context, a synthetic route towards 3,4-*trans*-substituted derivatives of thalidomide was envisioned starting from methyl- and phenyl-substituted pyroglutamic acids (2*R*,3*R*)-**81a** and (2*R*,3*S*)-**81b** (Yamada et al. 2006). Thus, hydrolysis of the lactam ring afforded the corresponding glutamic acids (2*R*,3*R*)-**103a** and (2*R*,3*S*)-**103b**, respectively, which were next converted into *N*-phthaloyl anhydrides (3*S*,4*R*)-**104a** and (3*S*,4*S*)-**104b** by reaction with phthalic anhydride followed by cyclization with Ac_2O (Scheme 23). Most notably, these compounds experimented epimerization at the C-4 position to produce the most stable *trans* diastereomer during the formation of the anhydride ring. The thalidomide analogues **105a** and **105b** were finally prepared by treatment with trifluoroacetamide. A similar synthetic approach to a trifluoromethyl-containing derivative of thalidomide **105c** was devised starting from fluorinated pyroglutamic acid (2*R*,3*R*)-**17** (Soloshonok et al. 2009b). Although the latter compound would be available by means of the conjugate addition of chiral complex (*R*)-**1** to ethyl 4,4,4-trifluorocrotonate (see Scheme 3), it was best prepared using a fully diastereoselective Michael addition of the new generation of Ni(II) complexes to the corresponding chiral oxazolidine. However, the free glutamic acid derived from (2*R*,3*R*)-**17** was not easily accessed because the CF_3 group reduced the basicity of the amino function (Soloshonok et al. 1988; Kobzev et al. 1989) in comparison to non-fluorinated pyroglutamic acids, and thus an equilibrium between open-chain and ring-closed forms always exists. Therefore, the *N*-Boc protected derivative (2*R*,3*R*)-**106** had to be obtained instead, and the rest of the synthetic route towards **105c** occurred in a similar manner as discussed before.

A Michael addition was also the key step in the synthesis of the pyroglutamate moiety of the antibiotics oxazolomycin A and neooxazolomycin (Yamada et al. 2008). Starting once again from piperidyl complex **97a**, the highly substituted chiral oxazolidine (*S*)-**107** was found unreactive employing DBU as catalyst, although the more basic 1,5,7-triazabicyclo[4,4,0]dec-5-ene proved efficient in building the Michael adduct (2*S*,3*S*,4*R*)-**108** as the major product of

Scheme 25 Organocatalyzed Michael additions of complex **97a** to α,β-unsaturated aldehydes



Scheme 26 Additions of complexes **117a–b** to chiral Michael acceptors (*S*)-**84**



a mixture of six diastereomers (Scheme 24). Transformation of **108** into pyroglutamic acid **109** proceeded smoothly, and this compound was next converted into **110** by standard functional group manipulations. Treatment of **110** with NaHMDS and subsequently with diazomethane afforded bicyclic lactone **111**, which was opened by reaction with diphenyl diselenide. After esterification, the PhSe group was eliminated in compound **112**, and final chemoselective ester reduction furnished the target pyroglutamate derivative **114**. It should be mentioned that a shorter route was envisaged from a serine-derived Ni(II) complex analogous to **97a** in order to access the corresponding Michael adduct bearing the required quaternary center, but this reaction proved unsuccessful due to the extreme steric interactions that occurred between both reactants.

The new generation of Ni(II) complexes were also suitable for enantioselective Michael additions using chiral catalysts (Luo et al. 2011). An appropriate protocol was developed for the reaction of complex **97a** to 3-aryl-substituted acroleins in the presence of Jørgensen–Hayashi catalyst, in order to afford compounds (2*R*,3*S*)-**115** in moderate-to-good yields after reduction of the initially formed 1,4-adduct with $NaBH_4$ (Scheme 25). The diastereomeric ratio was highly dependent on the nature of the aromatic R group, and electron-donating groups located in *ortho* or *para* positions provided the best *syn*/*anti* ratios. Nevertheless, a high enantioselectivity was observed in both diastereomers when additives such as lithium benzoate were employed. Ni(II) complexes bearing amino-moieties other than piperidine were less efficient in terms of diastereoselectivity. It should also be mentioned that halogen- or alkyl-substituted acroleins were not suitable for this method. An example of free amino acid, namely (2*R*,3*S*)-**116** having a 2-(methoxy)phenyl group was also described.

Finally, another type of "new generation" of Ni(II) complexes, referred to as "NH-type" are even easier to be synthesized using a primary amine in contrast to the secondary ones previously discussed (Ellis and Soloshonok 2006; Bergagnini et al. 2014). The resulting complexes possess a configurationally unstable stereogenic nitrogen atom, and their reactivity was also explored using chiral oxazolidinones (*S*)-**84** in the corresponding Michael addition reactions. Thus, it was found that bulky R groups on the amino moiety such as *tert*-butyl (**117a**) or 1-adamantyl (**117b**) displayed a complete level of diastereoselectivity in the corresponding products (2*R*,3*S*)-**118a** and **118b**, precursors of the pyroglutamic acid derivatives **81b**, **e**–**f** after hydrolytic treatment and subsequent cyclization (Scheme 26).

Michael additions to Ni(II) complexes derived from dehydroalanine

1,4-Additions involving Ni(II) complexes can also be implemented in the opposite direction to those reactions depicted in the previous section, namely using Ni(II) complexes derived from dehydroalanine Schiff bases as Michael acceptors in the reaction with the corresponding

Scheme 27 Synthesis of dehydroalanine Ni(II) complex (*S*)-**2** and Michael additions of nucleophiles

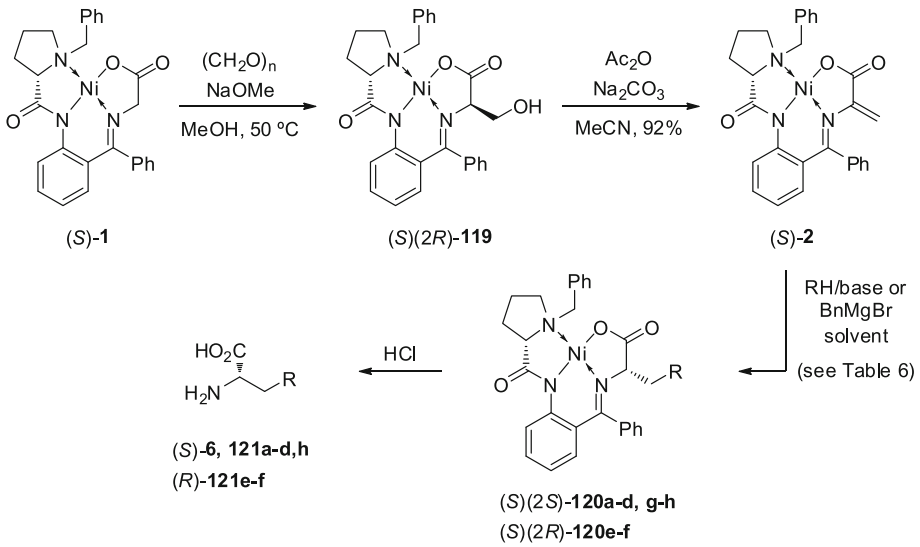


Table 6 Michael additions of nucleophiles to Ni(II) complex **2**

Entry	RH	Base	Solvent	Michael adduct **120**	Yield (%)	de (%)	Amino acid **121**	Yield (%)
1	MeOH	NaOMe	MeOH	(*S*,*S*)-**120a**	92	96	(*S*)-**121a**	90
2	Me_2NH	K_2CO_3	MeCN	(*S*,*S*)-**120b**	90	89	(*S*)-**121b**	93
3	$PhCH_2NH_2$	K_2CO_3	MeCN	(*S*,*S*)-**120c**	95	95	(*S*)-**121c**	75
4	Imidazole	K_2CO_3	MeCN	(*S*,*S*)-**120d**	95	89	(*S*)-**121d**	85
5	PhSH	K_2CO_3	MeCN	(*S*,*R*)-**120e**	98	90	(*R*)-**121e**	92
6	$PhCH_2SH$	K_2CO_3	MeCN	(*S*,*R*)-**120f**	93	94	(*R*)-**121f**	90
7	$(EtO_2C)_2CH_2$	K_2CO_3	MeCN	(*S*,*S*)-**120g**	98	83	(*S*)-**6**[a]	80
8	BnMgCl	N/A	THF	(*S*,*S*)-**120h**	55	50	(*S*)-**121h**	82

[a] The product of Ni(II) complex disassembly was decarboxylated to afford glutamic acid (*S*)-**6**

Scheme 28 Michael additions of complexes (*S*)- or (*R*)-**1** to (*S*)- or (*R*)-**2**

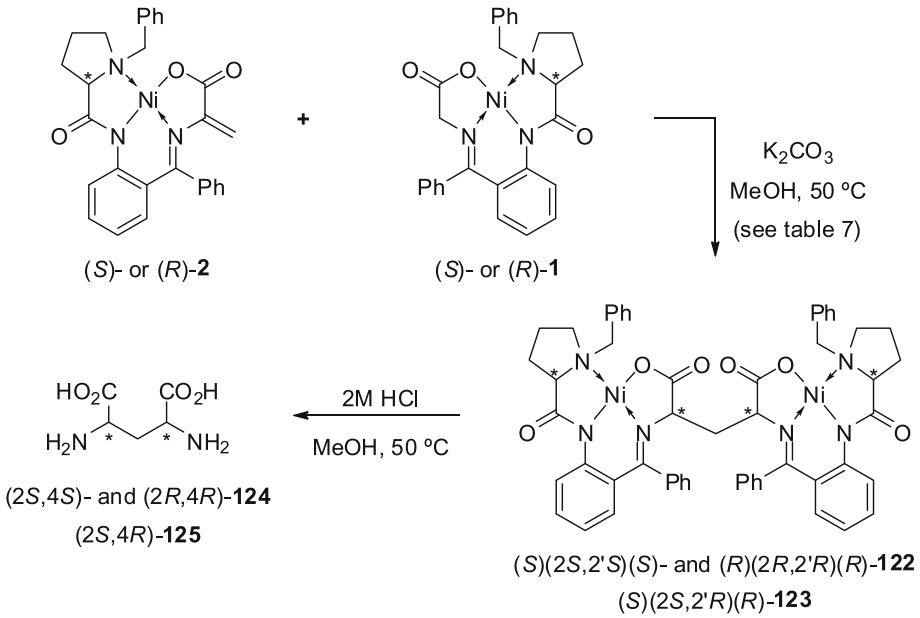
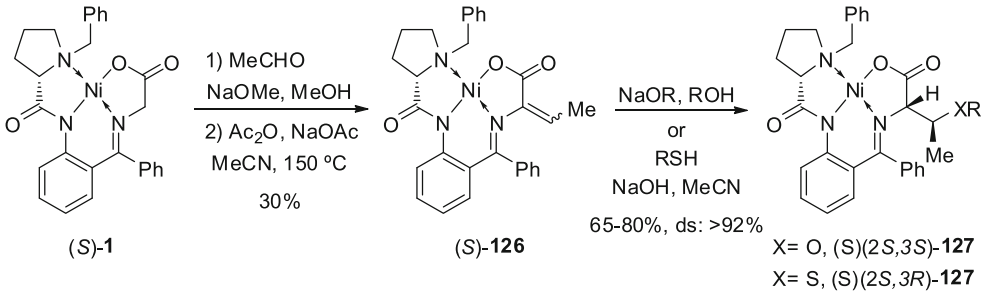


Table 7 Michael additions of glycine Ni(II) complex **1** to dehydroalanine Ni(II) complex **2**

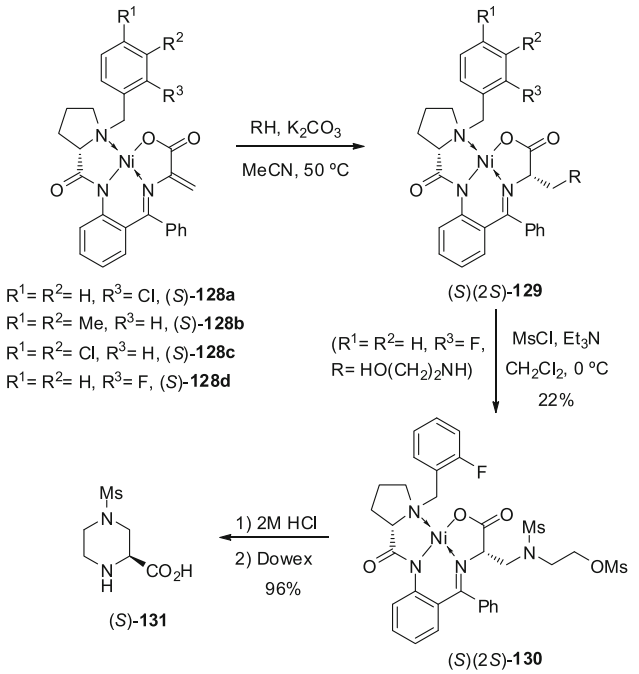
Entry	Michael acceptor	Nucleophile	Michael adduct	Yield (%)	Diaminoglutamic acid	Yield (%)
1	(*S*)-**2**	(*S*)-**1**	(*S*,*S*)(*S*,*S*)-**122**	90	(2*S*,4*S*)-**124**	71
2	(*R*)-**2**	(*S*)-**1**	(*S*,*S*)(*R*,*R*)-**123**	95	(2*S*,4*R*)-**125**	80
3	(*S*)-**2**	(*R*)-**1**				
4	(*R*)-**2**	(*R*)-**1**	(*R*,*R*)(*R*,*R*)-**122**	94	(2*R*,4*R*)-**124**	75

Scheme 29 Synthesis of dehydroaminobutanoic acid Ni(II) complex (*S*)-**126** and Michael additions of nucleophiles



nucleophiles. Therefore, this method would complement the synthetic access to some α-amino acids that might be difficult to obtain by means of alkylation (Sorochinsky et al. 2013a), aldol or Mannich reactions (Sorochinsky et al. 2013b) of glycine Ni(II) complexes, as well as the already discussed Michael additions.

In the chiral version, the required starting complex (*S*)-**2**, formally derived from *N*-benzylproline, 2-aminobenzophenone and dehydroalanine, was prepared from (*S*)-**1** by aldol reaction with formaldehyde and subsequent dehydration of the intermediate serine-derived complex (*S*)(2*R*)-**119** (Belokon et al. 1988a) (Scheme 27). Compound (*S*)-**2** was used in a number of Michael additions with a variety of nucleophilic reagents, including MeOH (Table 6, entry 1), amines (entries 2–3), imidazole (entry 4), thiols (entries 5–6) and diethyl malonate (entry 7). In contrast, complex (*S*)-**2** was unreactive towards the addition of phenol or halide anions. The corresponding adducts **120** were obtained in moderate-to-good diastereomeric ratios, the (*S*)(2*S*)-diastereomer being the major product of thermodynamic control [(*S*)(2*R*) in the case of sulfur-substituted products due to the CIP rules (Cahn et al. 1956, 1966; Prelog and Helmchen 1982)]. When the reactions were conducted under conditions of kinetic control, protonation of the carbanion intermediate took place on the hindered enolate face, but the stereoselectivity was rather low (33 % de in the case of the addition of $BnNH_2$). The addition of BnMgCl also took place under kinetic control (entry 8). Final disassembly of the Ni(II) complex in the Michael adducts furnished the free β-substituted α-amino acids **121**, whereas in the case of the malonic ester adduct **120g** a stronger hydrolytic treatment afforded glutamic acid (*S*)-**6**. As usual, the



Scheme 30 Michael additions of nucleophiles to complexes (*S*)-**128a–d**

starting ligand (*S*)-**5** could be isolated and recycled in the production of complexes (*S*)-**1** and (*S*)-**2**.

The above procedures were extended to the addition of different examples of amines (Saghiyan et al. 1997), thiols (Saghiyan et al. 2000) or heterocyclic-based reagents (Saghiyan et al. 2012, 2013) to complex (*S*)-**2**. Among the potential applications of the target amino acids, cysteines bearing a 1,2,4-triazole unit can be used for the microbiological production of proteinogenic amino acids strains

Scheme 31 Michael addition of diethyl malonate to complex **132**

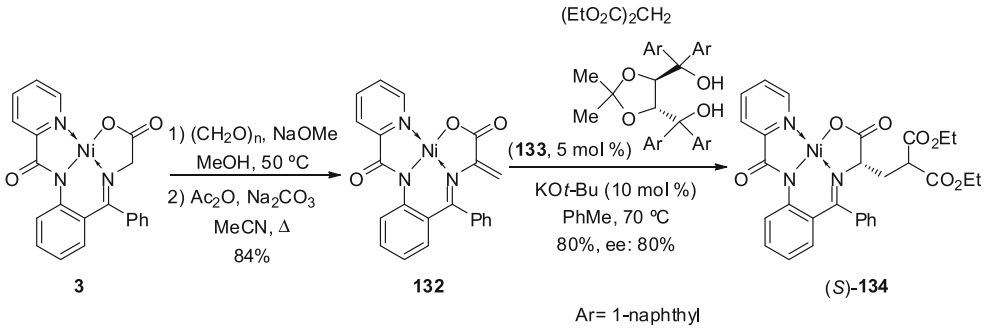
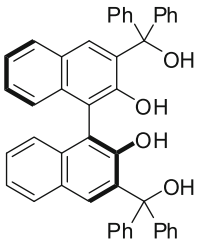


Fig. 4 Structure of BIMBOL **135**



(Saghiyan et al. 2004a, b), whereas imidazolyl amino acids are precursors of *N*-heterocyclic carbenes (Belokon et al. 2008; Maleev et al. 2010).

An interesting variation of this method dealt with the addition of nucleophilic glycine Ni(II) complex **1** to the electrophilic dehydroalanine complex **2** in order to produce binuclear dimers (Saghiyan and Geolchanyan 2006). Employing all four possible enantiomeric combinations in these reactants, the resulting adducts were the enantiomeric pair (*S*,*S*)(*S*,*S*)- and (*R*,*R*),(*R*,*R*)-**122**, as well as the meso form (*S*,*S*),(*R*,*R*)-**123** (Scheme 28; Table 7). These compounds were obtained with high diastereoselectivity (>94 % de), and upon disassembly of the binuclear Ni(II) complexes all possible isomers of 4-aminoglutamic acid were accessed. It should be noted that the synthesis of these bis-amino acids was also described by means of the phase-transfer catalyzed bis-alkylation of glycine Ni(II) complex (*S*)-**1** with CH_2Cl_2 (Taylor et al. 2004; Soloshonok et al. 2006).

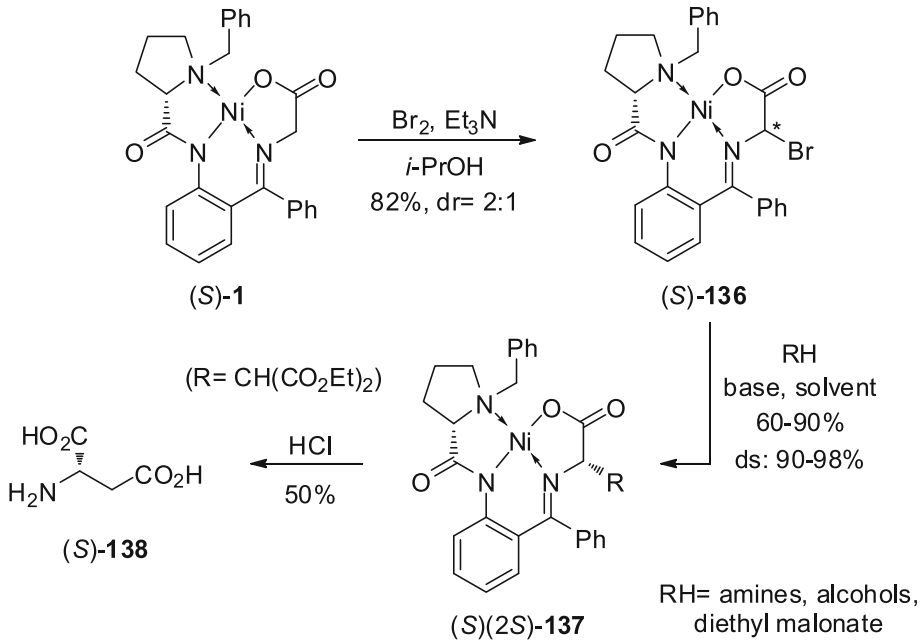
As a logical extension, a suitable dehydroaminobutanoic acid-derived Ni(II) complex (*S*)-**126** was also synthesized from (*S*)-**1** by aldol reaction with acetaldehyde followed by the usual elimination procedure (Belokon et al. 1990) (Scheme 29). However, compound (*S*)-**126** was obtained in much lower yield than the corresponding dehydroalanine counterpart, as a 5:1 mixture of *E* and *Z* isomers. The synthetic applications of complex (*S*)-**126** included the Michael additions of alcohols and thiols to render compounds **127**, which proceeded in good diastereomeric ratios in the formation of both stereogenic centers at α- and β-positions regardless of the initial geometrical isomer employed as a result of thermodynamic control. In contrast, amine reagents did not react with (*S*)-**126**.

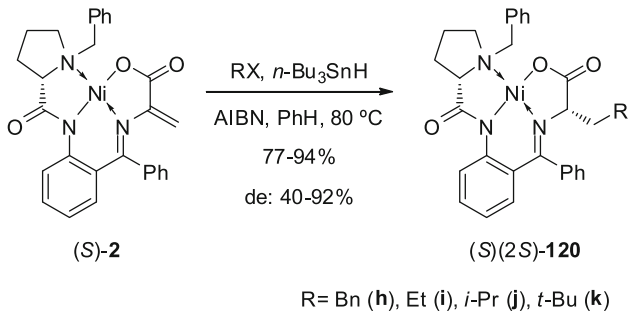
Some analogues of complex (*S*)-**2** have also been developed in order to improve the diastereoselective outcome as well as the reaction rate in this type of Michael additions. Thus, Ni(II) complexes (*S*)-**128a–d** containing modified *N*-benzylproline units were successfully employed in the conjugate addition of several amines and thiols to render adducts (*S*)(2*S*)-**129** (Saghiyan et al. 2010) (Scheme 30). The most efficient of these substitution patterns corresponds to fluorinated derivative (*S*)-**128d**, affording 92–96 % de on average. The resulting addition product of ethanolamine was further transformed into 4-mesylpiperazine-2-carboxylic acid (*S*)-**131**. In a similar fashion, modified analogues of dehydroaminobutanoic complex (*S*)-**126** were also investigated in the Michael additions of various nucleophilic reagents (Saghiyan et al. 2005, 2006a, b).

An achiral dehydroalanine Ni(II) complex **132** was also prepared using the standard protocol from picolinic acid-derived precursor **3** and was subsequently employed in enantioselective 1,4-additions (Belokon et al. 2004) (Scheme 31). For this purpose, several chiral catalysts were tested and the best outcome was achieved using TADDOL derivative **133** in the addition of diethyl malonate to **132** in the presence of KO*t*-Bu to afford (*S*)-**134** in reasonably good enantioselectivity. It is important to emphasize that the origin of the enantioselectivity lies in the protonation step of the transient enolate and not in the C–C bond formation, in contrast to the Michael additions performed with glycine Ni(II) complexes. Other TADDOL analogues, including the original catalyst **71** (Fig. 2), were less efficient and provided lower enantiomeric excesses as well as reduced chemical yields. 2-Substituted malonates also reacted with somewhat lower enantioselectivities, but the method could not be applied to other types of nucleophiles such as thiols or amines because the ee's observed were negligible.

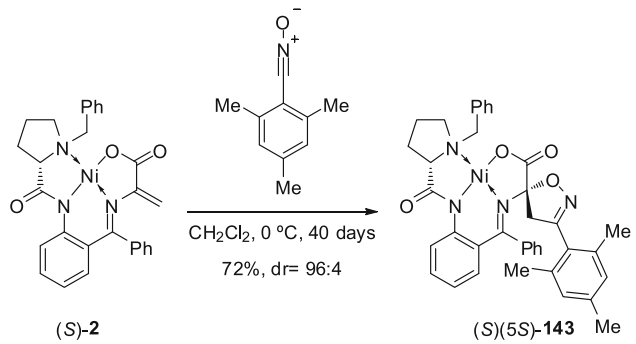
More recently, the BINOL family of chiral catalysts has been used in the Michael addition of diethyl malonate to achiral complex **132** (Belokon et al. 2012). It was shown that a preformed tetra-potassium salt of (*S*)-BIMBOL **135** (Fig. 4) catalyzed the above process under phase-transfer

Scheme 32 Bromination of complex (*S*)-**1**

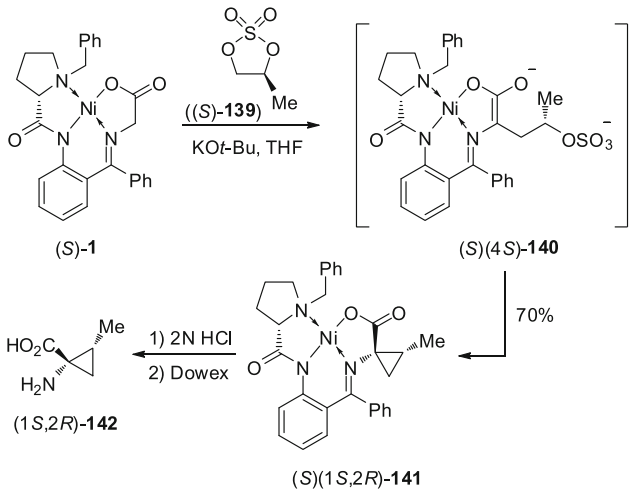




Scheme 33 Radical additions to complex (*S*)-**2**



Scheme 35 1,3-Dipolar cycloaddition of complex (*S*)-**2**



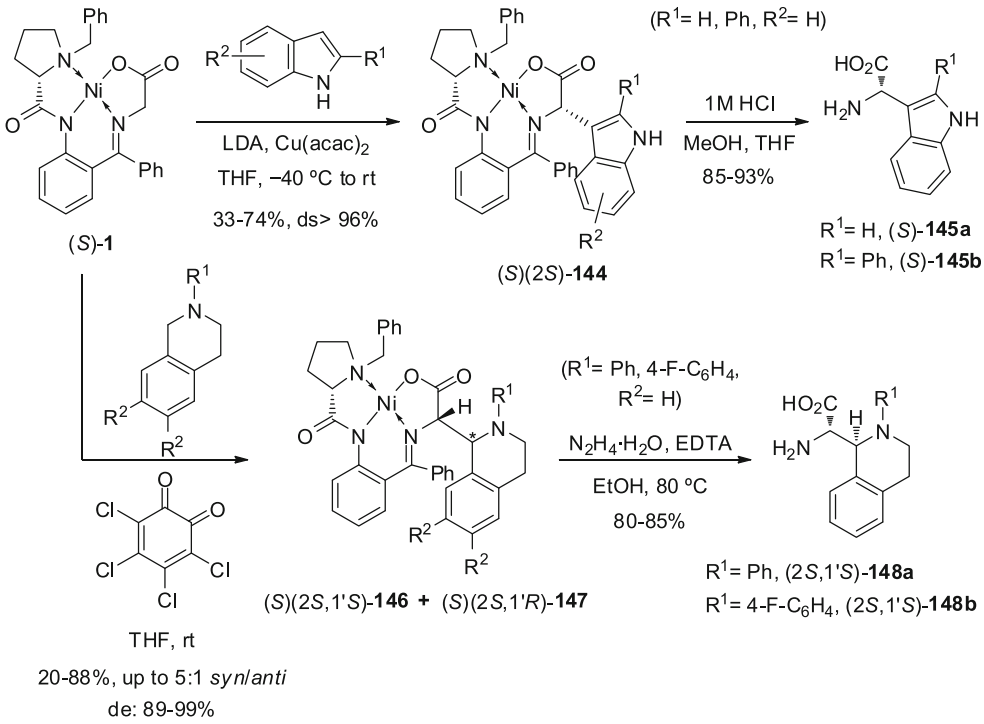
Scheme 34 Cyclopropanation of complex (*S*)-**1**

conditions in quantitative yield and 80 % ee. This protocol was superior compared to the in situ formed BIMBOL/KOH catalyst mixture, and also to the choice of other metal ions (Cs, Na, Li). On the other hand, (*S*)-BIMBOL was also successfully employed in the addition of glycine complex **3** to methyl acrylate as shown in Scheme 12 with up to 68 % ee but in the opposite stereochemical sense (that is, adduct (*R*)-**68** was produced). Therefore, it was possible to access precursors of both enantiomeric forms of glutamic acid from either glycine or dehydroalanine Ni(II) complexes through the same catalyst **135**.

Miscellaneous reactions

Bromination of Ni(II) complex (*S*)-**1** afforded α-bromoglycine-derived complex (*S*)-**136** in good yield as an epimeric 2:1 mixture (Belokon et al. 1988c) (Scheme 32).

Scheme 36 Couplings of complex (*S*)-**1** with heterocycles



Thus, the nucleophilic character of (*S*)-**1** turned out to be electrophilic in (*S*)-**136**, and therefore displacement by reagents such as amines, alcohols and diethyl malonate became feasible to furnish substitution products (*S*)(2*S*)-**137** in fairly good diastereomeric ratios under reaction conditions of thermodynamic control. In contrast, the reaction of (*S*)-**136** with organometallic reagents (alkyllithiums or Grignards) failed and mostly glycine complex (*S*)-**1** was recovered as a result of the reduction of (*S*)-**136**. The product arising from alkylation with diethyl malonate was hydrolyzed in the usual way to render aspartic acid (*S*)-**138**. More recently, brominated complex (*S*)-**136** was employed in a series of similar reactions with aliphatic and aromatic amines that were performed in aqueous media (Liu et al. 2010).

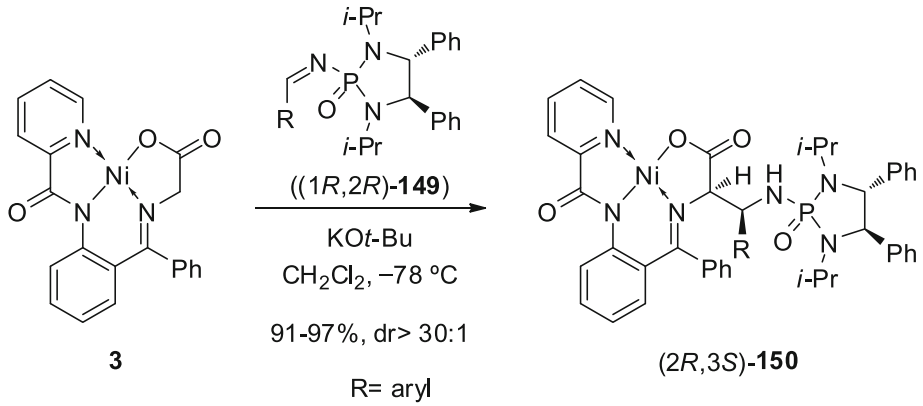
Another type of functionalization consisted in the alkylation of dehydroalanine complex (*S*)-**2** with alkyl halides in the presence of *n*-Bu_3SnH and AIBN (Gasanov et al. 1994). The reaction proceeded under kinetic control upon trapping of radical adduct-intermediates with *n*-Bu_3SnH through the most accessible side of the molecule. Accordingly, the diastereoselectivity in the formation of products **120** increased with the size of the R group, and reached its maximum when R = *t*-Bu (92 % de) (Scheme 33). In fact, the observed selectivity in the case of compound **120h** (R = Bn, 40 % de) was similar to the previously discussed addition of BnMgCl to (*S*)-**2** (Table 6, entry 8), thus showing no stereochemical differences between homolytic and hetereolytic transfer of a hydrogen atom. In any case, the mixtures of (*S*,*S*)- and (*S*,*R*)-**120** could be equilibrated under thermodynamically controlled conditions by the reaction with NaOMe/MeOH in order to improve the initially achieved diastereomeric ratio.

Optically active cyclic amino acids could be prepared from glycine Ni(II) complex (*S*)-**1** by means of a one-pot, two consecutive alkylation steps sequence by choosing the appropriate reagent. An illustrative example is the reaction of (*S*)-**1** with chiral cyclic sulfate (*S*)-**139** that proceeded through the transient intermediate **140** giving rise to cyclopropyl-containing complex (*S*)(1*S*,2*R*)-**141** as a single diastereomer (Debache et al. 2001) (Scheme 34). Hydrolysis of **141** afforded allonorcoronamic acid (1*S*,2*R*)-**142**, which also served to confirm the stereochemistry of the cyclopropanation process. The high selectivity observed is a consequence of full kinetic control in the generation of the quaternary stereogenic center that depends exclusively on the configuration of the starting sulfate and hence surpassing the inherent facial selectivity of Ni complex (*S*)-**1**; in fact, the analogous process employing (*S*)-**1** and (*R*)-**139** led to (1*R*,2*S*)-allonorcoronamic acid.

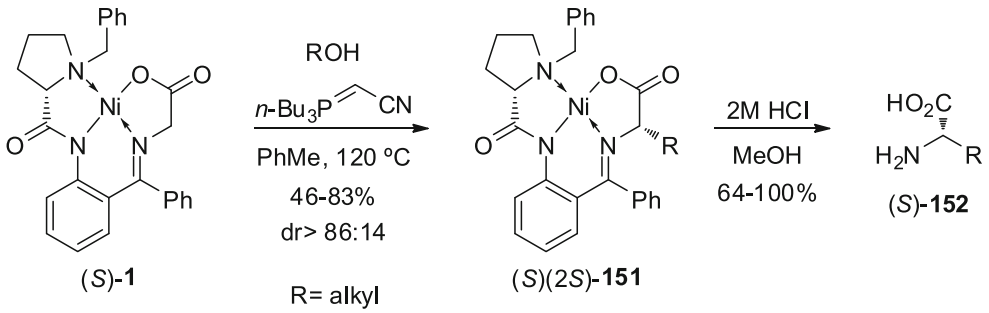
A 1,3-dipolar cycloaddition of mesitylene nitrile oxide to dehydroalanine complex (*S*)-**2** was described affording adduct (*S*)(5*S*)-**143** with very good diastereoselectivity (Mičúch et al. 2006) (Scheme 35). This strategy would potentially be useful for the synthesis of isoxazoline-containing amino acids.

Recently, an oxidative heterocoupling reaction between chiral glycine Ni(II) complex (*S*)-**1** and unprotected indoles

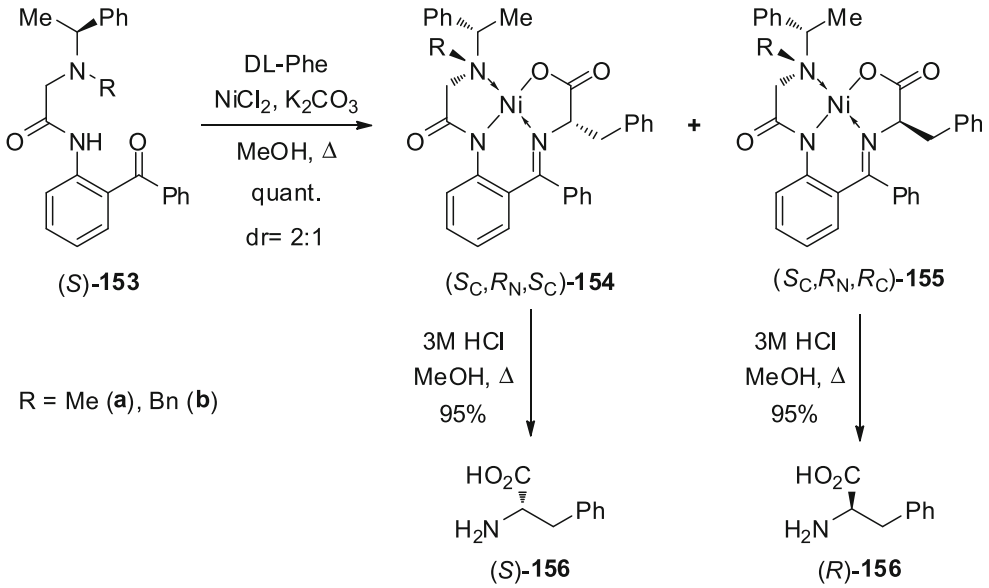
Scheme 37 Mannich additions of complex **3** to phosphonyl imines **149**



Scheme 38 Mitsunobu-Tsunoda alkylations of complex (*S*)-**1**



Scheme 39 Resolution of racemic phenylalanine with chiral ligand (*S*)-**153**



was developed as a convenient method for the synthesis of 3-indolylglycines (Lin et al. 2013). The C–C bond formation was promoted by $Cu(acac)_2$ as oxidant in the presence of a base to afford compounds (*S*)(2*S*)-**144** in moderate-to-good yields (Scheme 36). It should be noted that the excellent diastereoselectivity observed was not dependent on the substituents introduced onto the indole ring. Two examples of 3-indolylglycines, namely compounds (*S*)-**145a**, **b**, were described upon disassembly of the Ni(II) complex fragment. A similar protocol was also reported for the coupling between complex (*S*)-**1** and tetrahydroisoquinolines (Zhou et al. 2013). In this case, the reaction occurred by the action of *o*-chloranil as oxidant to produce mixtures of *syn*-(*S*)(2*S*,1′*S*)-**146** and *anti*-(*S*)(2*S*,1′*R*)-**147**, in moderate ratio albeit with good facial selectivity on the glycine moiety. The free amino acid could not be released by the usual acidic treatment because of iminium ion formation followed by β-elimination, and therefore an

alternative procedure was pursued including the reaction of **146** (R^1 = Ph or 4-F-C_6H_4, R^2 = H) with hydrazine and EDTA to render tetrahydroisoquinolin-1-yl glycines (2*S*,1′*S*)-**148a**, **b**.

The chiral aryl *N*-phosphonyl imines (1*R*,2*R*)-**149** have been reacted with picolinic acid-derived Ni(II) complex **3** in basic media to furnish the corresponding Mannich adducts (2*R*,3*S*)-**150** with excellent yields and diastereomeric ratios (Sun et al. 2013) (Scheme 37). Furthermore, the *N*-phosphonyl imino functionality also enabled the group-assisted purification (GAP) of the reaction products by means of simple washings with organic solvents, avoiding the use of chromatographic techniques.

The Mitsunobu–Tsunoda alkylation protocol has been successfully applied to chiral Ni(II) complex (*S*)-**1** as an alternative to typical alkylation methods (Sorochinsky et al. 2013a). It consists in the reaction of (*S*)-**1** with alcohols and cyanomethylene tributylphosphorane (CMBP) to yield alkylation products (*S*)(2*S*)-**151** in good diastereoselectivities (Noisier et al. 2013) (Scheme 38). The advantage of this procedure lies on the synthetic accessibility to amino acids (*S*)-**152** that are more difficult to obtain using the standard alkylation processes, such as long chain-containing amino acids. Given the biological relevance of fluorinated amino acids and the current interest on their asymmetric synthesis (Smits et al. 2008; Kukhar et al. 2009; Sorochinsky and Soloshonok 2010; Aceña et al. 2010, 2012; Mikami et al. 2011; Qiu and Qing 2011; Turcheniuk et al. 2013), this strategy has also been applied very recently to the preparation of fluorine-containing derivatives of phenylalanine as well as α-fluoroalkyl α-amino acids (Drouet et al. 2014).

Finally, it should be mentioned the synthetic applications of chiral ligands (*S*)-**153** of the new generation including an α-phenylethylamine moiety (Moriwaki et al. 2014a, b) (Scheme 39). Complexation of these ligands with amino acids and a nickel salt render the nitrogen atom chiral as well as configurationally stable, in contrast to the "NH-type" complexes previously referred. For example, a mixture of two out of four possible diastereomeric complexes **154** and **155** were formed in quantitative yield and moderate selectivity upon complexation of (*S*)-**153** with racemic phenylalanine, with only trace amounts detected of a third diastereomer. After chromatographic separation, complexes **154** and **155** were transformed into both enantiomeric forms of phenylalanine (*S*)- and (*R*)-**156**, respectively.

Conclusions

The data discussed in this review convincingly suggest that homologation of Ni(II) complexes via Michael addition reactions is a mature, well-developed methodology allowing truly practical preparation of some types of biologically important α-AAs (Wang et al. 2008b, 2011c). In particular, the addition reactions between chiral or achiral glycine Schiff bases with chiral oxazolidinone-derived Michael acceptors is arguably the most advanced approach available in the literature for preparation of various β-substituted pyroglutamic acids and related compounds. On the other hand, only one diastereomeric form [for example (2*R*,3*S*), R = Ar] can be prepared. Therefore, still, there is a room for new developments in this area. Another class of α-AAs readily available by this Michael additions methodology is fluorine-containing derivatives of glutamic acid. Considering the ever growing importance of fluorinated compounds in the modern pharmaceutical industry (Wang et al. 2014) one may expect more research will be published in this area.

Particularly interesting for us were the discussions in the "miscellaneous" chapter. Thus, the readers may see that applications of Ni(II) complexes as chiral or achiral glycine nucleophilic equivalents are growing in importance and new, untraditional homologation methods are being developed. Furthermore, structural concept of the Ni(II) complexes is also currently undergoing significant changes. As readers could notice in the discussion, "new generation", "NH" types of Ni(II) complexes have been developed allowing more design opportunities to fit any particular reactivity or physico-chemical property of the target Ni(II) complexes. For example, the design of the "NH" type led to the development of new chemistry dealing not with the synthesis of α-AAs via homologation, but with deracemization of racemic α-AAs and conversion of natural L-α-AAs into unnatural D-configured derivatives (Soloshonok et al. 2009c; Sorochinsky et al. 2013c, d). Also, one may mention the new and growing field of research in application of Ni(II) complexes for β-AAs synthesis (Ding et al. 2009, 2013; Lin et al. 2011). In this line, it should also be mentioned that structural design of Ni(II) complexes has inspired development of macromolecular bimetal complexes with inherent helical chirality (Soloshonok and Ueki 2007; Soloshonok et al. 2010) as well as new type of molecules possessing property of optical, chiral switches (Soloshonok et al. 2007, 2012; Soloshonok and Ueki 2010; Han et al. 2014). All these provide an impression that chemistry of Ni(II) complexes of α-AA Schiff bases is a living methodology in which we can expect new and exciting developments in the future.

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

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