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REVIEWS

Asymmetric synthesis of pyroglutamic acids *via* Ni(II) complex methodology

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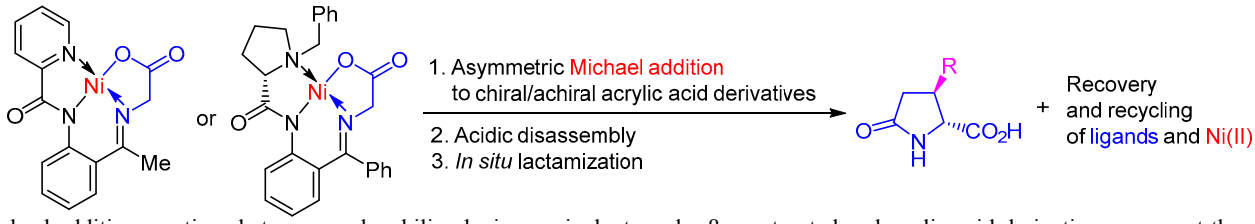


Michael addition reactions between nucleophilic glycine equivalents and α,β-unsaturated carboxylic acid derivatives represent the most methodologically concise and generalized approach to the family of sterically constrained heterocyclic amino acids. Such amino acids are of critical importance in the *de novo* peptide design and for elucidation of peptide/protein three-dimensional structure and its biological function/activity. This review summarizes key aspects of Michael addition reactions using Ni(II)-templated Schiff bases of glycine in various asymmetric versions placing chiral auxiliary on either Michael donor or acceptor or both.

Keywords: chiral Schiff bases, heterocycles, substituted pyroglutamic acids, tailor-made amino acids, asymmetric synthesis, Michael addition reactions.

Cyclic tailor-made amino acids[1] play an important role in the development of modern pharmaceuticals and drug formulations.[2] In particular, pyroglutamic acid derivatives constitute essential structural units of many bioactive natural products (Fig. 1).[3] Prompted by wide range of synthetic applications of pyroglutamic acid, many research

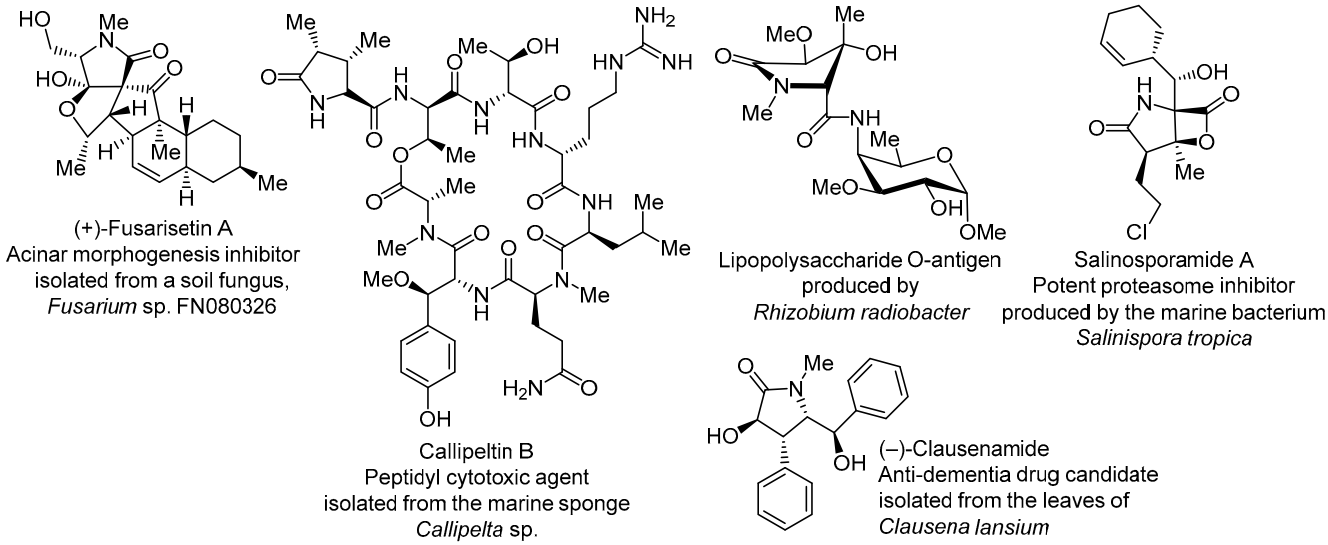
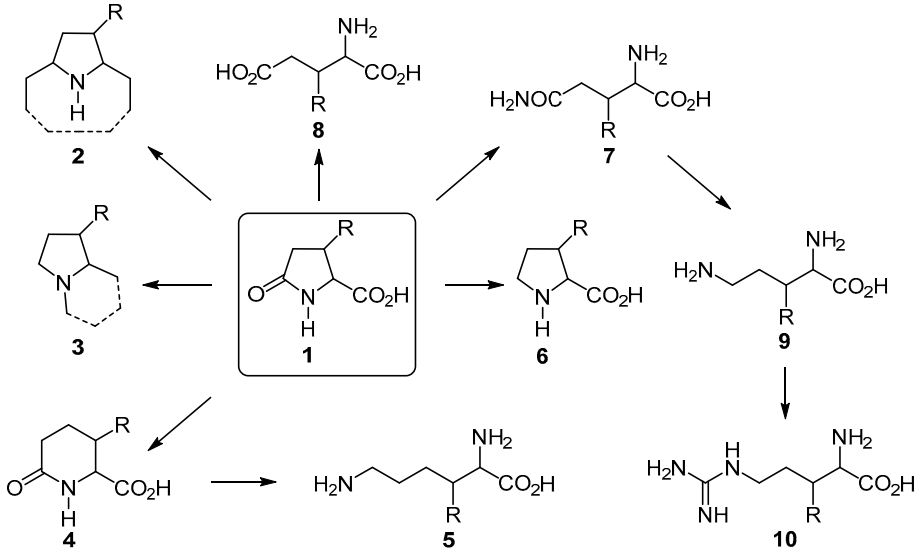


Figure 1. Bioactive naturally occurring pyroglutamic acid derivatives.

* Here and further the corresponding author is marked with *.

Scheme 1. Elaboration of pyroglutamic acid **1** to various structural types of tailor-made amino acids **2**–**10**



groups have focused on the development of synthetic routes to various substituted derivatives of this heterocyclic amino acid.[4] Among numerous types of skeletal substitution, asymmetric preparation of β-substituted analogs of compound **1** (Scheme 1) has received significant attention.[5] Some of synthetically important types of synthetic elaboration of pyroglutamic acids are presented in Scheme 1. Thus, compound **1** can be efficiently transformed to the N-bridged bicyclic compounds **2**,[4,6] 1,4-pyrrolizidines, indolizidines[4,7] and various fused azabicyclic derivatives **3**.[4,8] Of special interest are transformations of pyroglutamic acid to a family of sterically constrained β-substituted amino acids **4**–**10**[4] that serve as indispensable c-(chi)-constrained[9,10] scaffolds in the *de novo* design of peptides and peptidomimetics with a predetermined three-dimensional structure.[9–11]

Another important class of compounds available from elaboration of compound **1** is the β-substituted γ-amino acid derivatives **11**–**14** (Fig. 2), of which baclofen is a well-known commercial blockbuster drug.[12]

Among the various methods available in the literature, Michael addition of nucleophilic glycine equivalents to β-substituted acrylic acid derivatives offers a synthetically concise and attractive preparative route to the corresponding β-substituted pyroglutamic acids **1**. Considering preferred application of pure enantiomers in the drug design as well as the exceptionally high magnitude of the self-disproportionation of enantiomers properties of amino acids and their derivatives,[13] the asymmetric version of this approach has been in focus of numerous of research groups.[4,5,11] In this article, we would like to apprise the readers with general approach to asymmetric synthesis of amino acids, and in particular β-substituted pyroglutamic acids, based on the reactions of Ni(II)-templated nucleophilic glycine equivalents.

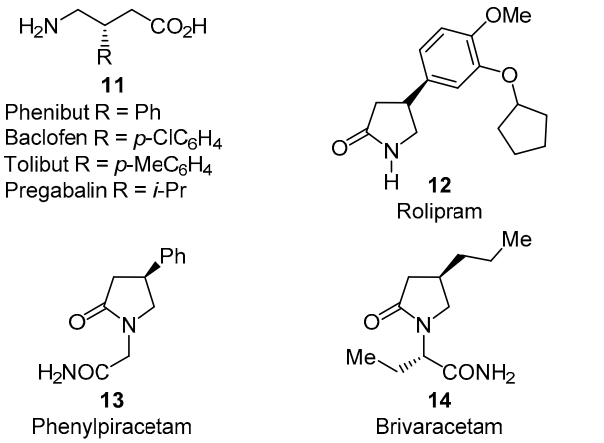


Figure 2. Pharmaceutical drugs **11**–**14** elaborated from pyroglutamic acid **1**.

Ni(II) complexes of Schiff bases as general reagents for the preparation of tailor-made amino acids

Application of Schiff bases derived from glycine **15** (Fig. 3) for the synthesis of amino acids was described by the Stork group in 1976.[14] Since then, these derivatives have been widely used as a preferred type of nucleophilic glycine equivalent. Some key properties, such as structural simplicity, ready availability, high C−H acidity, and chemical versatility underscore synthetic application of these derivatives, especially from the practical standpoint. Chiral Schiff base derivatives **16** and **17** were reported in 1976 by Yamada[15] and in 1985 by Belokon[16] groups, respectively. Further structural modifications of square-planar Ni(II) complex **17**[17] were found particularly useful

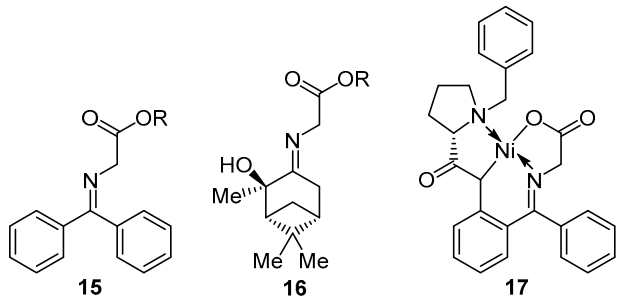
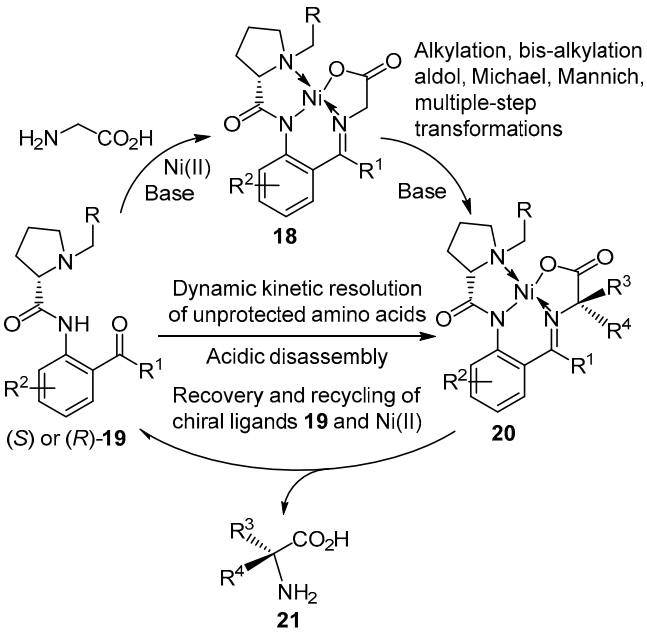


Figure 3. Schiff bases as nucleophilic glycine equivalents.

for practical large scale synthesis of various types of tailor-made amino acids.[18]

In particular, Ni(II) complexes **18** were shown (Scheme 2) to serve as a chiral nucleophilic glycine equivalent in reactions with numerous electrophilic reagents. Typically, enantiomerically pure (*S*)- or (*R*)-tridentate ligands **19** are used for preparation of glycine equivalents **18** which serve as the general templates for introduction of desired side chain using electrophilic reagents under basic conditions. Commonly used approaches include alkyl halide alkylations with primary[19] or secondary[20] halides, α,α-dialkylation[21] and bis-alkylations,[22] aldol,[23] Mannich,[24] and Michael addition reactions, which will be discussed in greater detail in this review article.

Scheme 2. General asymmetric synthesis of α-amino acids **21** using Ni(II) complex methodology

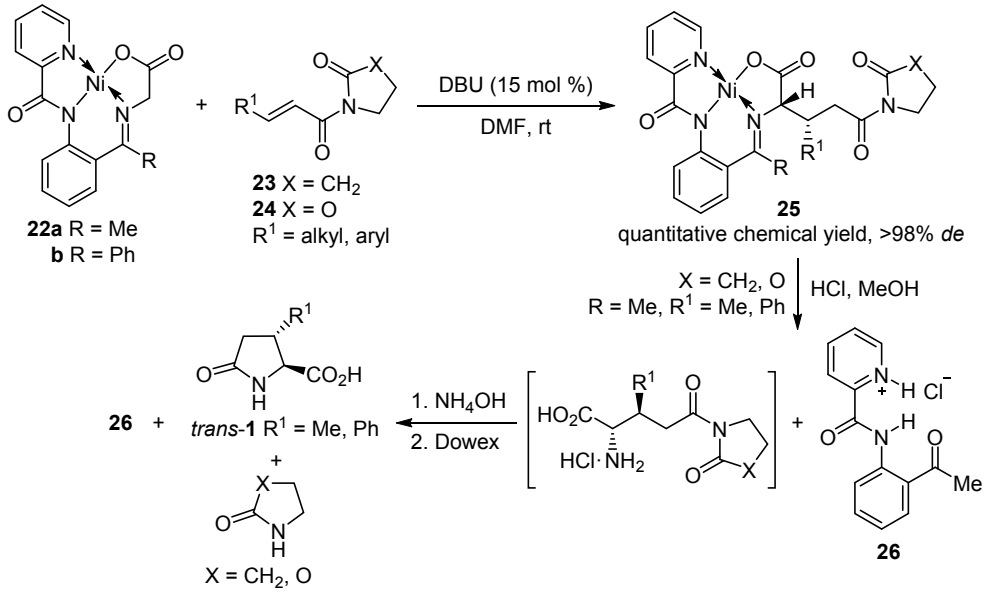


Furthermore, multiple-step reaction sequences can be used for preparation of various types of cyclic amino acids.[25] Another principle of chiral ligands **19** application comprises the direct reactions with unprotected α-[26] or β-amino acids[27] to afford Ni complexes **20**, followed by thermodynamic equilibration. This process was shown to be quite efficient to perform deracemization *via* dynamic thermodynamic resolution or (*S*) to (*R*) interconversion of unprotected amino acids, rivaling in practicality enzymatic processes.

Achiral Ni(II) complexes and achiral Michael acceptors

Chemically stable yet highly reactive achiral picolinic acid-derived Ni(II) complexes **22a**,**b** were successfully used in the organic base-catalyzed Michael addition reactions with readily available and inexpensive pyrrolidin-2-one and 1,3-oxazolidin-2-one amides of unsaturated carboxylic acids **23** and **24** allowing access to β-substituted pyroglutamic acids **1** (Scheme 3).[28] Synthetic method for the preparation of Ni(II) complexes **22a**,**b** used commercially available picolinic acid and *o*-aminoacetophenone or picolinic acid and *o*-aminobenzophenone respectively as the starting materials.[29] The Michael reactions were conducted under kinetically controlled conditions in DMF at room temperature in the presence of catalytic amounts of organic base DBU. The use of highly reactive Michael acceptors **23** and **24**, existing exclusively in the *s-cis* conformation to minimize electrostatic repulsive interactions between oxygens of the carbonyl groups, allowed to provide diastereomerically pure products **25** in quantitative yield, regardless of the steric or electronic nature of the β-substituents. It should be noted that Michael reactions with acetophenone-derived complex **22a** possessing less sterically shielded glycine fragment occurred at a significantly higher rate as compared to the corresponding reactions with benzophenone-derived complex **22b**. According to calculations of molecular mechanics, the stereochemical outcome of Michael reactions was determined both by steric interactions

Scheme 3. Michael additions of achiral complexes **22a**,**b** to achiral Michael acceptors **23** and **24**



between substituents in the starting compounds and by electron donor–acceptor attractive interactions between the amide carbonyl group of carboxylic acids **23** or **24** and the Ni(II) atom of complexes **22**. Decomposition of products **25** in presence of 2 N HCl in MeOH afforded glutamic acid derivatives and hydrochloric salt of ligand **26**. Treatment of the reaction mixture with ammonia gave rise to *trans*-pyroglutamic acids **1** isolated from aqueous solution using ion-exchange resin along with quantitative recovery of free ligand **26** and the corresponding pyrrolidin-2-one or 1,3-oxazolidin-2-one.

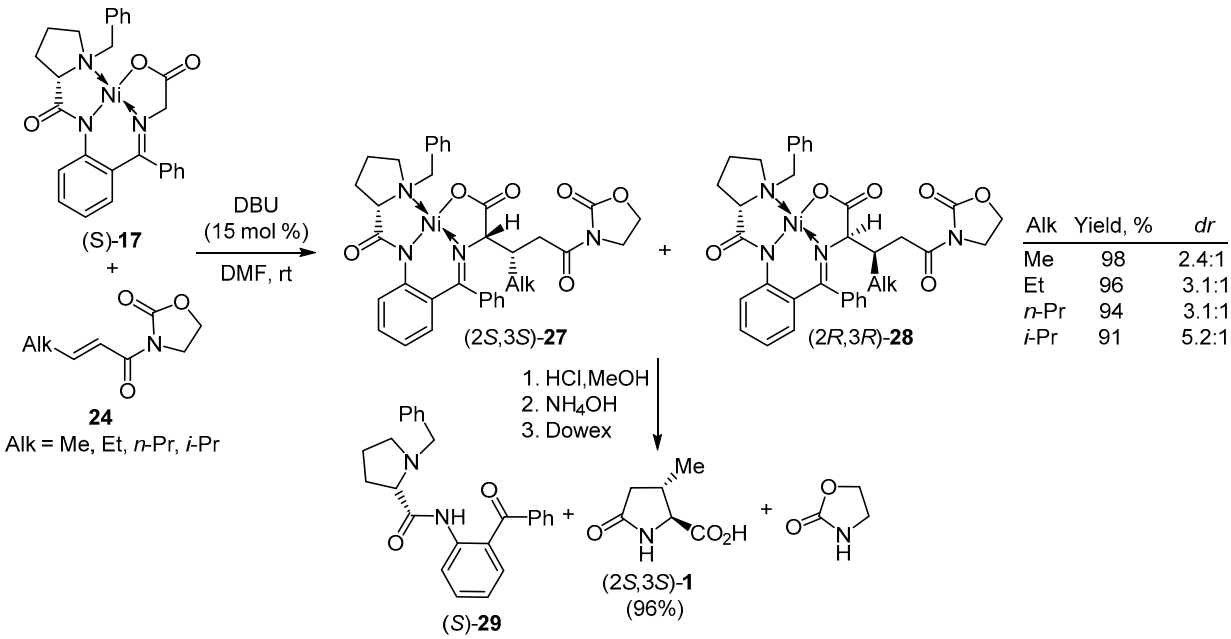
Chiral Ni(II) complexes and achiral Michael acceptors

The asymmetric version of Michael addition reaction applying readily available chiral *N*-benzylproline-derived Ni(II) complex (*S*)-**17**[30] and β-alkyl-substituted α,β-unsaturated *N*-acyloxazolidinones **24** in a solution of DMF at ambient temperature using 15 mol % of DBU was conveniently performed for synthesis of enantiomerically pure β-alkyl-substituted pyroglutamic acids **1** (Scheme 4).[31] Although addition of chiral Ni(II) complex (*S*)-**17** to β-alkyl-substituted α,β-unsaturated *N*-acyloxazolidinones **24** gave quantitatively corresponding adducts (2*S*,3*S*)-**27** and (2*R*,3*R*)-**28**, only moderate diastereoselectivity was achieved due to incomplete facial selectivity at the α-carbon. The stereochemical outcome of the Michael additions depended on the steric bulk of the β-alkyl group of the starting α,β-unsaturated *N*-acyloxazolidinones **24**, and the highest diastereomeric ratio of adducts (2*S*,3*R*)-**27** and (2*R*,3*S*)-**28** was achieved in the case of Michael acceptor bearing β-isopropyl group. It should be noted that (2*S*,3*S*) or (2*R*,3*R*) configuration of *n*-alkyl derivatives is stereochemically equivalent to the (2*S*,3*R*) or (2*R*,3*S*) configuration of isopropyl and aromatic derivatives because of the Cahn–Ingold–Prelog priority. The diastereomerically pure major adducts **27** could be isolated by crystallization of the resulting mixture of diastereomers and readily transformed to enantiomerically pure β-methyl-pyroglutamic acid (2*S*,3*S*)-**1** along with the recovered chiral ligand (*S*)-**29** and 1,3-oxazolidin-2-one.

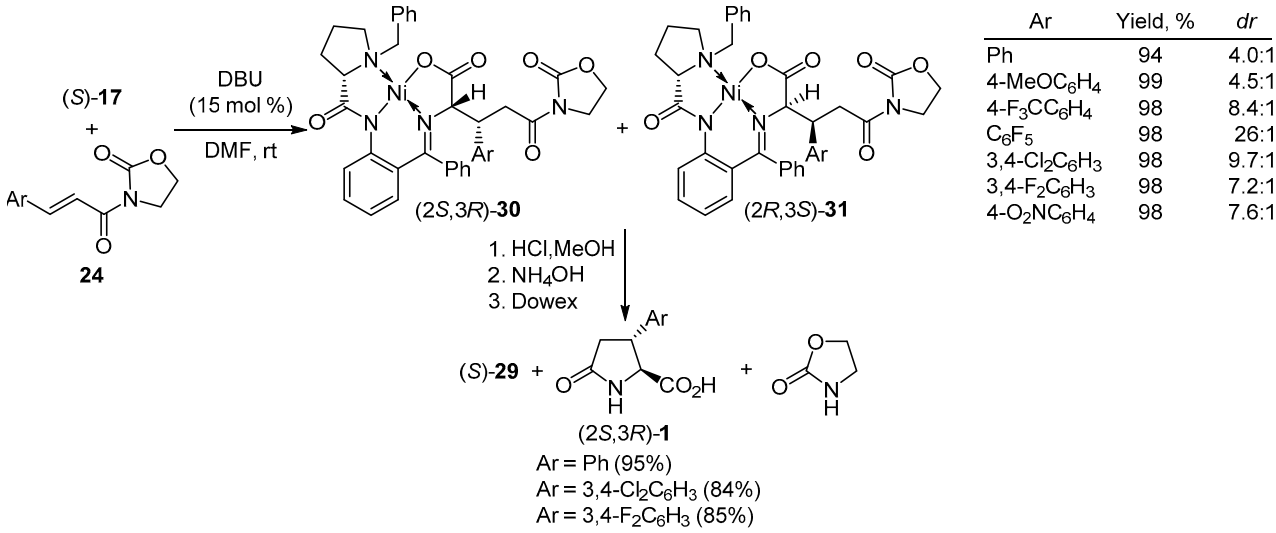
At the same time, the diastereoselectivity of the Michael addition reaction between Ni(II) complex (*S*)-**17** and β-aryl-substituted α,β-unsaturated *N*-acyloxazolidinones **24** was shown to be controlled by electronic properties of the aryl substituents (Scheme 5).[31] For example, α,β-unsaturated *N*-acyloxazolidinones **24** bearing electron-withdrawing substituents on the aromatic ring provided the mixtures of (2*S*,3*R*)-**30** and (2*R*,3*S*)-**31** diastereomers with higher stereoselectivity as compared to the unsubstituted phenyl-containing derivative. The diastereomerically pure major products (2*S*,3*R*)-**30** obtained after crystallization of the resulting reaction mixtures were transformed to the enantiomerically pure β-arylpyroglutamic acids (2*S*,3*R*)-**1** using standard procedures with quantitative recovery of ligand (*S*)-**29**.

The Michael reactions between Ni(II) complex (*S*)-**17** and series of trifluoromethyl-containing acrylates provided straightforward access to the biologically important fluorinated derivatives of pyroglutamic acids. Initially, the Michael reaction between chiral Ni(II) complex (*S*)-**17** and ethyl 4,4,4-trifluorocrotonate **32** was conducted in a solution of DMF at ambient temperature using organic base (Scheme 6).[32] Due to the high electrophilicity of the 4,4,4-trifluorocrotonate **32**, the addition was completed within 1 h in the presence of only 5 mol % of DBU. The observed kinetically controlled stereochemical outcome of the corresponding diastereomeric products (2*S*,3*S*)-**33** and (2*S*,3*R*)-**34** was reasonably good (*dr* 5.6:1), and the major diastereomer (2*S*,3*S*)-**33** was isolated in 65% yield by washing the crude product with Et_2O. The minor diastereomer (2*S*,3*R*)-**34** was isolated by chromatography of the ethereal solution in 11% yield. Decomposition of

Scheme 4. Michael additions of chiral Ni(II) complex (*S*)-**17** to β-alkyl-substituted α,β-unsaturated *N*-acyloxazolidinones **24**

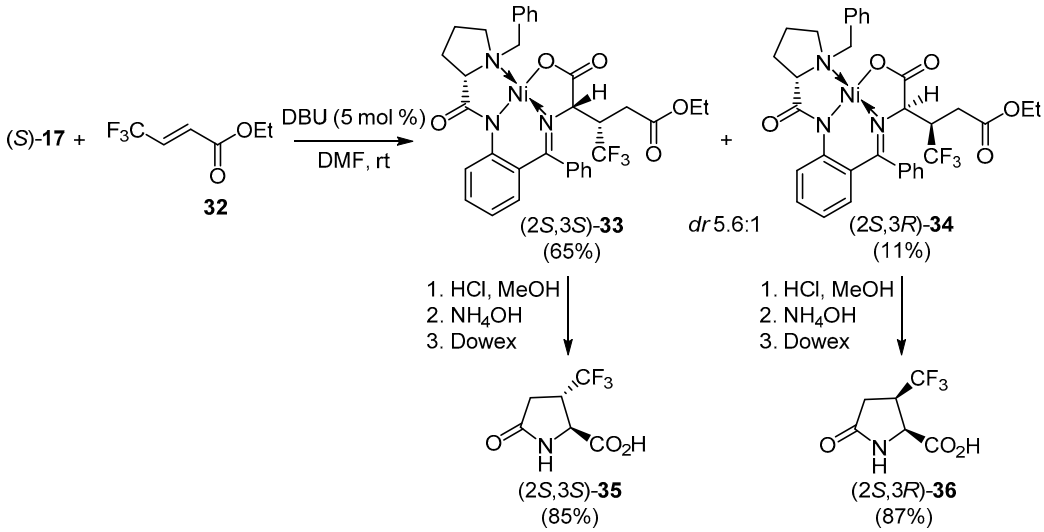


Scheme 5. Michael additions of chiral Ni(II) complex (*S*)-**17** to β-aryl-substituted α,β-unsaturated *N*-acyloxazolidinones **24**



Ar	Yield, %	*dr*
Ph	94	4.0:1
4-$MeOC_6H_4$	99	4.5:1
4-$F_3CC_6H_4$	98	8.4:1
C_6F_5	98	26:1
3,4-$Cl_2C_6H_3$	98	9.7:1
3,4-$F_2C_6H_3$	98	7.2:1
4-$O_2NC_6H_4$	98	7.6:1

Scheme 6. Michael addition of chiral Ni(II) complex (*S*)-**17** to ethyl 4,4,4-trifluorocrotonate **32**

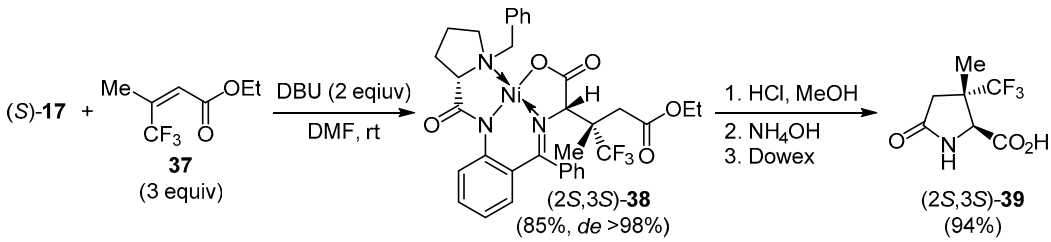


both diastereomerically pure complexes (2*S*,3*S*)-**33** and (2*S*,3*R*)-**34** under standard conditions afforded respectively enantiomerically pure 3-trifluoromethylpyroglutamic acids (2*S*,3*S*)-**35** and (2*S*,3*R*)-**36** in 85 and 87% yields.

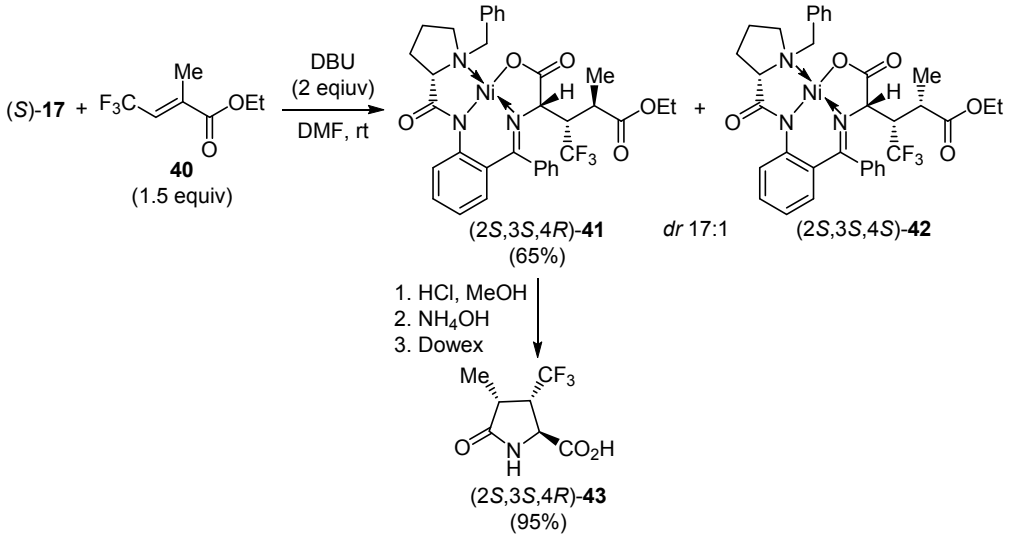
Diastereoselective Michael addition reaction between Ni(II) complex (*S*)-**17** and ethyl 3-trifluoromethylcrotonate **37** was developed for synthesis of highly sterically constrained 3-methyl-3-trifluoromethylpyroglutamic acids (2*S*,3*S*)-**39** (Scheme 7).[1] Despite of instability and low reactivity of ethyl 3-trifluoromethylcrotonate **37** under reaction conditions using of 3 equiv excess of compound **37** as well as 2 equiv of DBU in DMF made it possible to achieve 85% conversion of Ni(II) complex (*S*)-**17**, and the addition adduct (2*S*,3*S*)-**38** was obtained with excellent diastereoselectivity (*de* >98%) according to ^{1}H NMR and HPLC analyses of the crude reaction mixture. The crude reaction mixture containing addition adduct (2*S*,3*S*)-**38** and the starting complex (*S*)-**17** without purification was successfully transformed under standard conditions into the enantiomerically pure pyroglutamic acid (2*S*,3*S*)-**39** in 94% isolated yield.

Of particular synthetic interest was the Michael addition reaction between Ni(II) complex (*S*)-**17** and ethyl 2-methyl-

Scheme 7. Michael addition of chiral Ni(II) complex (*S*)-**17** to ethyl 3-trifluoromethylcrotonate **37**



Scheme 8. Michael addition of chiral Ni(II) complex (*S*)-**17** to ethyl 2-methyl-4,4,4-trifluorocrotonate **40**



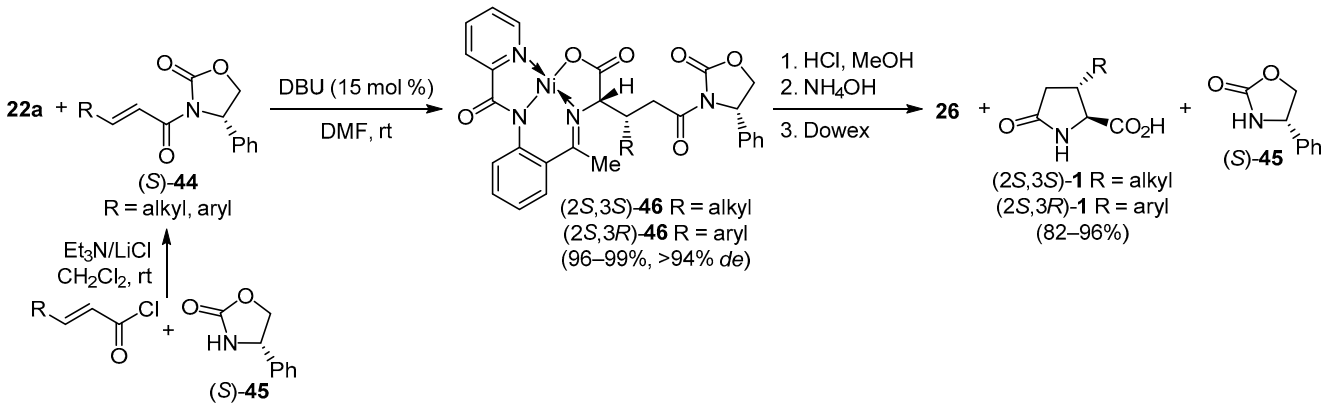
4,4,4-trifluorocrotonate **40** leading to simultaneous formation of three stereogenic centers in a single reaction step and therefore eight possible stereoisomeric products could be observed in the reaction mixture (Scheme 8).[1] It was found that Michael addition to ethyl 2-methyl-4,4,4-trifluorocrotonate **40** readily occurred using 2 equiv of DBU in DMF solution affording mixture of diastereomeric complexes (2*S*,3*S*,4*R*)-**41** and (2*S*,3*S*,4*S*)-**42** in ratio 17:1. Finally, the major product (2*S*,3*S*,4*R*)-**41** was isolated in enantiomerically pure form in 65% yield and according to standard procedure transformed to 4-methyl-3-trifluoromethylpyroglutamic acid (2*S*,3*S*,4*R*)-**43**.

Study of the mechanistic details of organic base-catalyzed Michael addition reactions between Ni(II) complex (*S*)-**17** and β-trifluoromethyl-containing acrylates **32**, **37**, and **40** showed that the high diastereoselectivities were the result of electrostatic attractive interactions between the CF_3 group and the Ni atom in the most energetically favorable transition states leading to the major diastereomers.

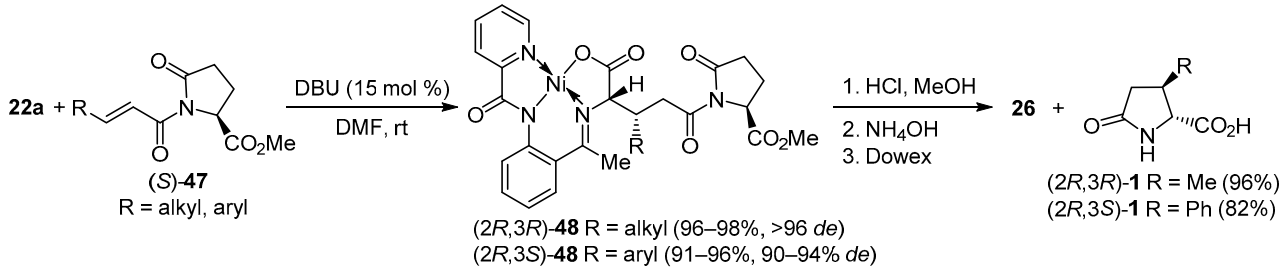
Achiral Ni(II) complexes and chiral Michael acceptors

The achiral picolinic acid-derived Ni(II) complex **22a** was also successfully used in the organic base-catalyzed Michael addition reactions with the α,β-unsaturated *N*-acyl-4-phenyl-1,3-oxazolidin-2-ones (*S*)-**44** for accessing enantiomerically pure β-substituted pyroglutamic acids **1** (Scheme 9).[33] The starting Michael acceptors (*S*)-**44** could be easily obtained in excellent yields from the corresponding acyl chlorides and 4-phenyl-1,3-oxazolidin-2-one (*S*)-**45** as chiral auxiliary in the presence of Et_3N/LiCl.[34] Michael acceptors (*S*)-**44** existed exclusively in the *s-cis* conformation with the phenyl group on oxazolidine ring pointed away from the C=C double bond to realize effective control of the face selectivity of the addition reactions.[35] Under standard kinetically controlled conditions, the addition of Ni(II) complex **22a** to α,β-unsaturated *N*-acyl-4-phenyl-1,3-oxazolidin-2-ones (*S*)-**44** bearing alkyl as well as aryl groups occurred in the presence of catalytic amounts of DBU at a high reaction rate and provided correspondingly compounds (2*S*,3*S*)-**46** and (2*S*,3*R*)-**46** as single diastereomers with quantitative yields. However, the reaction of isopropyl group containing Michael acceptor (*S*)-**44** proceeded at very low reaction rate, allowing for less than 30% conversion of the starting materials in 4 h. In the case of α-aryl-containing α,β-unsaturated *N*-acyl-oxazolidinones (*S*)-**44**, electron-donating or electron-withdrawing substituents on the phenyl ring had no significant influence on the chemical yields and stereochemical outcome of the reaction. However, the strong electron-

Scheme 9. Michael additions of achiral Ni(II) complex **22a** to 4-phenyl-1,3-oxazolidin-2-ones (*S*)-**44**



Scheme 10. Michael additions of Ni(II) complex **22a** to α,β-unsaturated *N*-acylpyroglutamates (*S*)-**47**



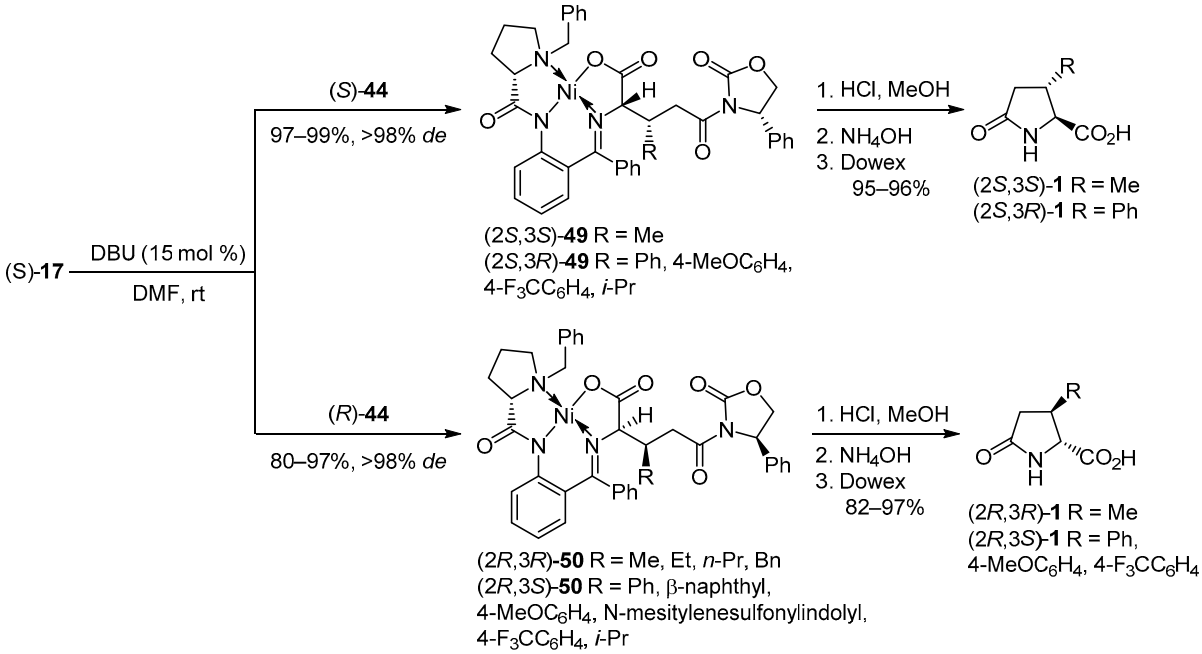
donating substituents could result in substantially lower reaction rate. Thus, stereochemical outcome of Michael addition reactions with α,β-unsaturated *N*-acyl-4-phenyl-1,3-oxazolidin-2-ones (*S*)-**44** bearing alkyl as well as aryl groups was the same and the Michael acceptors (*S*)-**44** were effective in controlling stereoselectivity at both newly formed stereogenic centers. The use of (*R*)-configured Michael acceptors **44** mirrored the stereochemical results obtained with *N*-acyloxazolidinones (*S*)-**44**. Acidic decomposition/cyclization of both alkyl- and aryl-containing addition products **46** without purification led to 10 g scale syntheses of the corresponding enantiomerically pure pyroglutamic acids **1** with absolute configuration (2*S*,3*S*) for β-alkyl- and (2*S*,3*R*) for β-aryl-containing derivatives in 82–96% yield along with the quantitative recovery of chiral auxiliary (*S*)-**45** and the glycine Schiff base precursor **26**.

Subsequently, it was demonstrated that α,β-unsaturated *N*-acylpyroglutamates (*S*)-**47** derived from inexpensive naturally occurring pyroglutamic acid could also serve as efficient Michael acceptors in the organic base-catalyzed addition reactions with achiral picolinic acid Ni(II) complex **22a** (Scheme 10).[36] The reactions were conducted in DMF using 15 mol % of DBU as a catalyst. The Michael acceptors (*S*)-**47** bearing β-alkyl groups reacted very fast furnishing addition products (2*R*,3*R*)-**48** in high yields with almost complete diastereoselectivity. At the same time, β-aryl derivatives (*S*)-**47** provided the addition products (2*R*,3*S*)-**48** with slightly lower yields and diastereoselectivity. Methyl- and phenyl-containing products (2*R*,3*R*)-**48** and (2*S*,3*R*)-**48** were transformed to the corresponding β-substituted pyroglutamic acids (2*R*,3*R*)-**1** and (2*R*,3*S*)-**1** as well as ligand **26**. It should be noted that after the acidic disassembly of the Ni(II) complexes **48**, the achiral ligand **26** and the corresponding β-substituted glutamic acids formed HCl salts, while the pyroglutamic acid chiral auxiliary was in a neutral form and could be extracted with ethyl acetate. Upon treatment with NH_4OH the salts of β-substituted glutamic acids underwent cyclization to the target β-substituted pyroglutamic acids **1**.

Chiral Ni(II) complexes and chiral Michael acceptors

The asymmetric synthesis of enantiomerically pure β-substituted pyroglutamic acids **1** using both chiral *N*-benzylproline-derived complex (*S*)-**17** as well as chiral α,β-unsaturated *N*-acyloxazolidinones (*S*)-**44** and (*R*)-**44** in the presence of DBU as a base and DMF as a solvent was carried out to study the stereocontrolling ability of each reagent (Scheme 11).[37] It was found that both processes afforded the corresponding addition products **49** and **50** in excellent yields with very high stereoselectivity at both

Scheme 11. Additions of chiral Ni(II) complex (*S*)-**17** to chiral Michael acceptors (*S*)-**44** and (*R*)-**44**



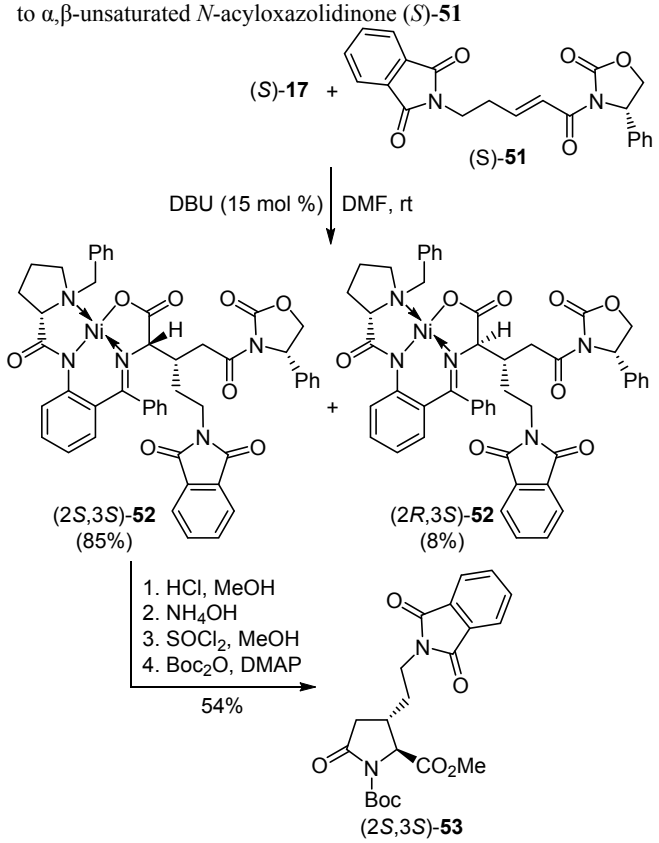
newly formed stereogenic centers. At the same time, high reaction rate was observed for addition reactions of (*S*)-configured Michael acceptors **44**, whereas the reactions of (*R*)-configured Michael acceptors **44** proceeded with a substantially lower rate.

It is interesting to note that combination of guanidine as a base with THF as a solvent was also effective for these addition reactions providing high reaction rates and stereoselectivity. Thus, these results indicated that stereochemical outcome of Michael addition was controlled by the stereochemical preferences of the Michael acceptors **44** and the chirality of the Ni(II) complex (*S*)-**17**, in turn bases or solvents affected only the reaction rate. According to the standard protocol, addition products **49** were decomposed to afford the corresponding glutamic acid derivatives (2*S*,3*S*)-**1** and (2*S*,3*R*)-**1**, and both chiral auxiliaries (*S*)-**29** and (*S*)-**45** were recycled. Diastereomers **31** were also converted to corresponding pyroglutamic acids (2*R*,3*R*)-**1** and (2*R*,3*S*)-**1** using this protocol.

The above method allowed an efficient addition of Ni(II) complex (*S*)-**17** to the α,β-unsaturated *N*-acyloxazolidinone (*S*)-**51** bearing β-(phthalimido)ethyl group (Scheme 12).[38] Under optimized conditions, the reaction was complete in 0.5 h giving rise to mixture of diastereomers (2*S*,3*S*)-**52** and (2*R*,3*S*)-**52** with the total yield 93% and diastereoselectivity 10:1. The recrystallization from EtOAc/hexanes afforded the diastereomerically pure compound (2*S*,3*S*)-**52** in 85% yield.

Hydrolysis of Ni(II) complex (2*S*,3*S*)-**52** by heating with HCl in MeOH and cyclization under basic conditions afforded the crude product that was finally protected to give the *N*-Boc-pyroglutamate (2*S*,3*S*)-**53** in 54% yield.

Scheme 12. Additions of chiral Ni(II) complex (*S*)-**17** to α,β-unsaturated *N*-acyloxazolidinone (*S*)-**51**



In summary, we have highlighted that the strategy to control the stereochemical outcome of the asymmetric Michael addition reactions by application of the Ni(II)-templated glycine Schiff bases is methodologically superior to other methods, most notably in terms of the generality and synthetic efficiency. Excellent chemical yields and diastereoselectivities, combined with the operational convenience of simple experimental procedures, render the presented method of immediate use for preparation of variety of 3-substituted pyroglutamic acids, related amino acids, and biologically relevant compounds available *via* conventional transformations of the pyroglutamic acids.

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