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ASYMMETRIC SYNTHESIS OF CHI-CONSTRAINED GLUTAMIC ACIDS AND RELATED COMPOUNDS VIA MICHAEL ADDITION REACTIONS

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Michael addition reactions involving nucleophilic glycine equivalents and α,β-unsaturated carboxylic acid derivatives offer a concise and generalized methodological approach to synthesizing a family of χ-constrained five-carbon-atom amino acids. These amino acids play a crucial role in de novo peptide design and the elucidation of peptide/protein three-dimensional structures and their biological functions/activities. This review encapsulates the significant synthetic and methodological advancements in the field to date. Each method discussed includes an evaluation of synthetic opportunities and limitations, practicality and efficiency of the procedures, and mechanistic rationale behind the observed stereochemical preferences.

Keywords: Asymmetric synthesis, Michael additions, glycine equivalents, metal complexes, Schiff bases, conformations, steric constrain. Glutamic acid, pyroglutamic acid, proline.

INTRODUCTION. Amino acids (AAs) are fundamental to the fabric of life, acting as the building blocks of proteins that drive countless biological processes [1]. In general sciences, their study has provided crucial insights into the mechanisms of life, from understanding metabolic pathways to uncovering the genetic code. Researchers delve into amino acid sequences to elucidate protein structure and function, enabling advances in fields like biochemistry, molecular biology, and genetics. The versatility and functionality of AAs make them indispensable for exploring the intricacies of cellular functions and organismal development [2–6].

In the pharmaceutical industry, amino acids hold a pivotal role in the development of drugs and therapeutic agents [7–10]. Many medications are designed to mimic or modulate the activity of naturally occurring AAs and their derivatives, targeting specific pathways to treat a variety of diseases. For instance, amino acid derivatives are used in the synthesis of antiviral drugs, antibiotics, and treatments for metabolic disorders[11–13]. Additionally, the role of AAs in protein synthesis is harnessed to develop biologics, such as monoclonal antibodies and vaccines, which are essential for modern medicine. The continuous exploration of AAs and their properties drives innovation, leading to more effective and targeted therapies that improve human health and well-being[14–20].

Glutamic acid and its cyclic derivative, pyroglutamic acid, play pivotal roles in peptides and drug design [21]. Glutamic acid, an essential amino acid, contributes to protein structure and function through its side chain, which can participate in ionic interactions and hydrogen bonding. This property is critical in stabilizing protein structures and facilitating enzyme catalysis [22]. Pyroglutamic acid, formed by the cyclization of glutamic acid, introduces rigidity into peptide chains, thereby reducing conformational flexibility. This structural constraint is advantageous in drug design, as it enhances binding specificity and stability, improving the efficacy of peptide-based therapeutics [23]. Both glutamic and pyroglutamic acids are integral in designing peptides with optimized pharmacological properties, making them invaluable in the development of novel drugs and therapeutic agents [24].

In this review article, we will discuss the synthesis of a specialized class of glutamic acid and related compounds: stereochemically constrained glutamic/pyroglutamic acids formed via the Michael addition reaction of nucleophilic glycine equivalents. These amino acids (AAs) adopt a relatively limited number of conformations and play a crucial role in the de novo design of peptides with predetermined 3D structures and enhanced peptide-receptor interactions.

Role of χ(chi)-constrained amino acids in the de novo design of peptides and peptidomimetics.

Reducing the number of amino acid (AA) conformations is crucial for optimizing peptide-receptor interactions, which play a vital role in various biological processes and therapeutic applications [25]. By limiting the conformational flexibility of peptides, researchers can design more specific and stable interactions between peptides and their target receptors. This precision enhances binding affinity and selectivity, leading to improved efficacy and reduced off-target effects in drug development. Tailoring peptide structures to adopt fewer conformations not only streamlines the identification of potent therapeutic candi-

dates but also contributes to the stability and bioavailability of the peptides in physiological environments. Ultimately, this approach holds promise for developing highly effective and targeted treatments for a wide range of diseases [26].

The 3D structure of peptides is determined by three key components: peptide sequence (primary structure), conformation (secondary structure), and the topographical positioning of side-chain functional groups. While the importance of peptide sequence and conformation in biological activity has been widely acknowledged, the third factor – the spatial arrangement of side chains on the peptide backbone (referred to as χ-space) – has only recently gained attention [26].The importance of the torsional angles φ (phi), ψ (psi), and ω (omega) (Figure 1. **A**) in determining the 3D structure of the peptide backbone [27–30], as well as the χ (chi) torsional angles (Figure 1, **B**) in defining the position of side-chain functional groups, for elucidating peptide biological activity, has been demonstrated [31–37]. While φ, ψ, and ω angles are generally influenced by the nature of amino acid residues and the peptide's secondary structure (e.g., cyclization or global constraints), controlling χ angles is much more challenging.

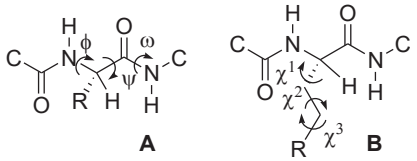

Fig. 1**.** Dihedral angles φ (phi), ψ (psi), ω (omega) (**A**), and χ (chi) (**B**), leading to numerous conformations of amino acid residues in peptides.

It was demonstrated that, in contrast to α-substitution in amino acids, which has little effect on the χ angles, the introduction of a methyl group in the β-position substantially enhances the population of one out of three [gauche-(+), trans, and gauche-(-)] χ1-rotamers. For instance, as illustrated for methylphenylalanines **1** (Figure 2), unfavorable steric interactions between the vicinal substituents (β-methyl and amino/carboxylic groups) resulted in a strong preference for the corresponding trans rotamer over the two gauche conformations [38, 39]. Considering β-substituted prolines **2**, as proline-phenylalanine chimeras, one could expect that rotational freedom in these derivatives might be much more limited for χ1, compared to that of β-methyl substituted phenylalanine**1** [40–42]. Indeed, it was shown that in both cis and trans diastereomers of **2**, the corresponding (-)-gauche conformers are physically inaccessible. Moreover, molecular calculations of proline-tyrosine chimeras of type**2** revealed that the trans rotamer is preferred by up to 2 kcal/mol over the corresponding (-)-gauche conformer [43–64].

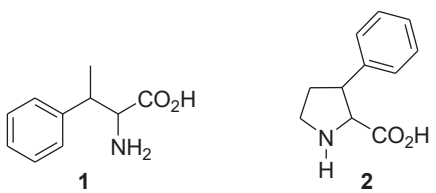

Fig. 2. β-Substitution and proline chimera with limited rotational freedom around the χ1 (chi) torsional angle.

The challenge associated with the asymmetric synthesis of χ-constrained amino acids stems from their sterically congested nature, the presence of at least two stereogenic centers, and the necessity of preparing all (in most cases four) stereoisomers for SAR studies. The

unique potential of χ-constrained amino acids in the rational design of peptides and peptide mimetics has generated significant research efforts aimed at developing various synthetic methods to prepare these amino acids in stereochemically defined forms.

Asymmetric Michael addition reactions of glycine equivalents.

The ever-growing demand for proteinogenic and tailor-made amino acids has spurred extensive research in the field of asymmetric synthesis of amino acids [55–64]. Chiral glycine equivalents have garnered significant attention, as nucleophilic or electrophilic homologation of glycine offers a generalized approach to synthesizing various α-amino acids. The primary challenge in designing chiral nucleophilic glycine equivalents lies in controlling enolate face selectivity, i.e., the configuration of the α-stereogenic center in the resulting amino acids. Conversely, the Michael addition reactions of glycine equivalents with β-substituted acrylic acid derivatives present an issue with Michael acceptor face selectivity, crucial for determining the configuration of the β-carbon stereogenic center.

Most well-designed chiral glycine equivalents achieve high levels of stereocontrol at the α-stereogenic carbon when reacting with β-substituted acrylic acid derivatives, but they are less effective in controlling the absolute configuration at the β-position. However, in certain cases, the stereochemical requirements of both the chiral glycine derivative and the Michael acceptor can align, resulting in a synthetically valuable stereochemical outcome.

Bis-lactim ether methodology (Scheme 1) [65] has been widely used for preparing various α-amino acids. The corresponding anion is typically generated by treating the bis-lactim ether of cyclo-(R)-Val-Gly **3** with BuLi at –78 °C. Electrophilic attack on the in situ generated anion by alkyl halides, carbonyl compounds, or acrylic acid derivatives occurs almost exclusively from the least hindered face, away from the bulky iso-Pr group, giving rise to the corresponding derivatives of α-amino acids with an α-(S) absolute configuration and very high enantiomeric excess (ee) [65].

In the original protocol [66], the Michael addition of alkyl crotonates**4** to (R)-**3** produced a mixture of two diastereomeric products, (2S, 3R) and (2S, 3S) **5**, in a ratio of 3 to 1. However, another report on the same reaction claimed much higher stereoselectivity, with no other diastereomers identified among the by-products [67]. The reactions of **3** with alkyl trans-cinnamates led to the formation of the corresponding derivatives of (2S, 3R)-3-phenylglutamic acid [68] in synthetically useful chemical yields (>75%) and with high diastereoselectivity (>90% de). In this case, there is no discrepancy between the original report [66] and the followingreports reproducing these additions on a relatively large scale (>25 g) [69].

The *bis*-lactim ether method also provides access to cis-diastereomers of glutamic/pyroglutamic acids **10** as illustrated in Scheme 1, through additions of **3** with cis-configured Michael acceptors. Thus, the reactions of **3** with alkyl cis-crotonates and -cinnamates gave rise to the corresponding addition products **7** as the major product, along with three other diastereomeric products [65–67, 69]. The stereochemical outcome in this case is slightly lower compared to the additions with trans-configured Michael acceptors.

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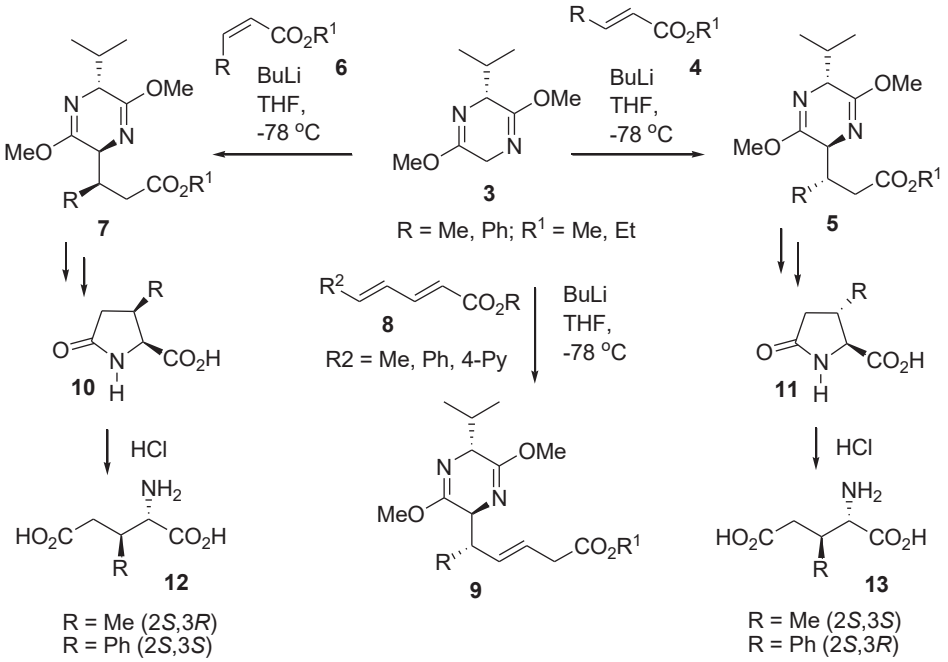


Scheme 1. *bis*-Lactim ether methodology for Machiel addition reactions.

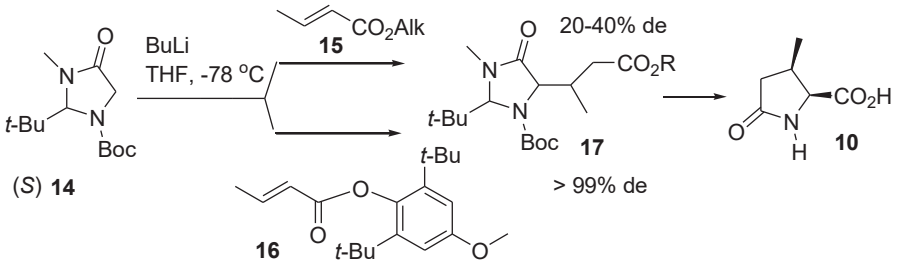
The additions between (S)-**3** and methyl 2,4-pentadienoates **8** (Scheme 1) were reported to proceed with virtually complete diastereoselectivity [70]. The reaction conducted under standard conditions for this method resulted in only one detectable diastereomer by NMR, with spectral characteristics consistent with the corresponding 1,6-addition product **9**. Unfortunately, the stereochemistry of the β-stereogenic center of the newly formed amino acid residue was not determined, while the configuration of the α-carbon atom was found to be (R) [70].

In principle, the *bis*-lactim ether method allows for generalized access to various β-alkyl and β-aryl substituted glutamic/pyroglutamic acids, including both cis and trans-diastereomeric forms. However, this method has several inherent drawbacks that make it less attractive from a synthetic standpoint. Besides usually moderate chemical yields and, in most cases, incomplete stereoselectivity at the β-stereogenic carbon of the target glutamic/pyroglutamic acids, hydrolysis of the addition products **7**, **5**, **9** to the target amino acids involves painstaking separations, usually by distillation, of the resultant amino acid esters from methyl valinatecoming from the starting chiral auxiliary. Since this type of separation depends on the physical properties of the compounds, it necessitates the development of a work-up procedure for each particular case.

Another highly diastereoselective approach to β-substituted glutamic/pyroglutamic acids is based on Michael addition reactions of the enolate of (S)-imidazolidinone **14** (Scheme 2). These reactions were studied using conventional alkyl esters (Me, Et) of β-substituted acrylic acids **15** as well as specially designed «sterically protected but electronically effective»

2,6-di-t-butyl-4-methoxyphenyl esters **16** [71, 72]. The stereochemical outcome of the additions between anion (S)-**14** and alkyl esters **15** was rather disappointing. The addition products **17** were isolated in moderate chemical yields [68% (Me), 78% (Et)] and with low diastereoselectivity (20–40% de).

In contrast, the reactions of (S)-**14** with 2,6-di-t-butyl-4-methoxyphenyl esters **16** occurred at higher reaction rates, resulting in sole diastereomeric products **17** with good chemical yields (78–96%) and complete (>99% de) diastereoselectivity. The stereochemical outcome in these addition reactions is assumed to be kinetically controlled. It is important to emphasize that this approach offers cis-pyroglutamic acids, which are hardly attainable by the *bis*-lactim ether method.



Scheme 2. Imidazolidinonederived chiral glycine equivalent in Michael addition reactions.

The mechanistic rationale for the very high stereoselectivity at the α-stereogenic center of the newly formed amino acids is rather straightforward, as the Michael acceptor attacks the corresponding anion generated from **14** almost exclusively from the side opposite the bulky t-buty l group. On the other hand, explaining the virtually complete face- and diastereoselectivity observed in the additions of (S)-**14** with bulky aryl esters **16** was not straightforward. Molecular mechanics calculations revealed that the energy difference between two conformers, s-cis **18** and s-trans **19** (Fig. 3), of the Michael acceptor is minimal. However, the calculations suggested that the s-cis **18** conformer should be substantially more reactive than the s-trans **19** because the reactive β-carbon atom in the former is shielded by bulky t-butyl groups. This rationale seems reasonable and, most importantly, emphasizes for the first time the relevance of s-cis and s-trans conformers of the Michael acceptor to the stereochemical outcome in these addition reactions.

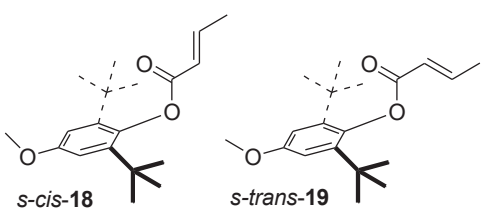
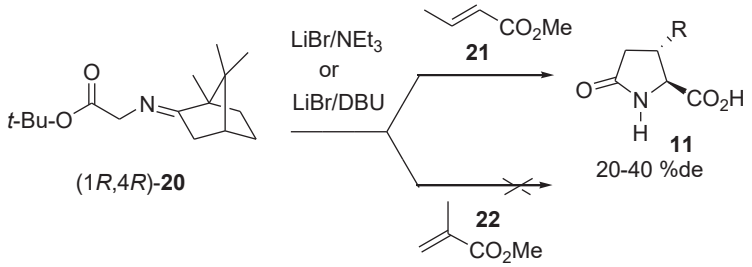


Fig. 3. *s-cis* and *s-trans* Conformers of 2,6-di-t-butyl-4-methoxyphenyl esters **16**.

Considering the substrate generality (alkyl, i-Pr, Bn, aryl groups), high chemical yields, and virtually complete diastereoselectivity, the imidazolidinonemethod could be regarded as nearly perfect for preparing cis-configured pyroglutamic/glutamic acids and their derivatives. However, from the standpoint of synthetic efficiency and practicality, this method is hardly at-

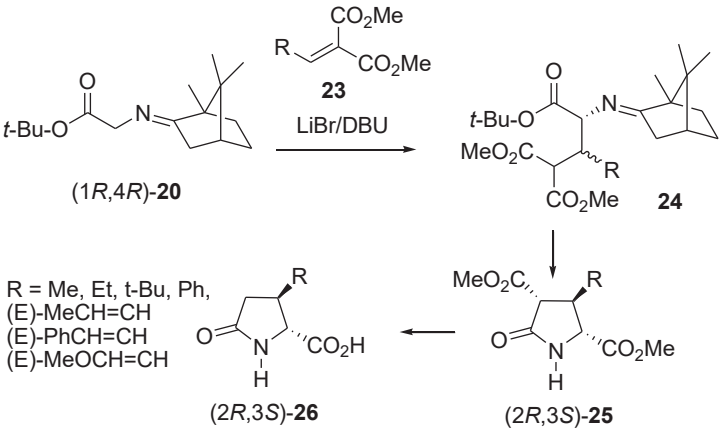
tractive for multigram preparation of the target compounds. Besides the general disadvantages of the Seebach method, such as the generation of the enolate of **14** at –78 °C with BuLi and the relatively drastic reaction conditions required to remove the chiral auxiliary (0.75 N HCl for 16 h at 105 °C), the multistage (3–4 stages) preparation of the aryl esters **16**, as well as the oxidative deprotection of the ester moiety with Ce(IV) [73–77], render the whole procedure problematic for large-scale preparations.

The application of chiral equivalents of nucleophilic glycine, characterized by the high CH acidity of the glycine methylene group, offers a significant synthetic advantage. In this approach, the corresponding enolate can be generated under mild reaction conditions, which are much easier to control and more practical than using highly reactive and hygroscopic BuLi at –78 °C. It was demonstrated that the generation of the corresponding enolate from Schiff base **20** (Scheme 3) could be easily achieved by treating **20**, derived from t-butyl glycinate and natural (1R, 4R)-camphor, with a mixture of LiBr and triethylamine in THF [78]. The enolate thus generated readily reacted at room temperature with methyl acrylate**21**, furnishing a mixture of two b-(R)- and b-(S)-diastereomers in a ratio of up to 84/16, respectively, indicating relatively poor face-diastereoselectivity in the addition. The Michael addition of **20** with methyl crotonate **22** completely failed, presumably due to the greater steric bulkiness and lower electrophilicity of the latter.



Scheme 3. Michael addition reactions of Schiff base **20** derived fromt-butyl glycinate and (1R, 4R)-camphor.

It was found that the application of α-methoxycarbonyl-substituted derivatives **23** (Scheme 4) led to a significant increase in the diastereoselectivity of the additions. Except for the reaction of **20** with dimethyl ethylidenemalonate **23** (R = Me), which furnished a mixture of two diastereomeric products (ratio 86/15), all other studied additions yielded only a single diastereomer in the reaction mixture. The remarkable difference in the stereochemical outcomes between the reactions of ethylidenemalonate **23** (R = Me) (72% de) and propylidenemalonate **23** (R = Et) (over 99% de) with enolate of **20** was attributed by the authors to the simple difference in steric bulk between the Me and Et groups. To the best of our knowledge, this is a rare example of such dramatic stereochemical consequences resulting from the difference in steric bulk between methyl and ethyl groups [79]. The transformation of the addition products **24** to the final amino acids **26** involves simple hydrolytic removal of the chiral auxiliary and decarboxylation of the intermediate **25**.



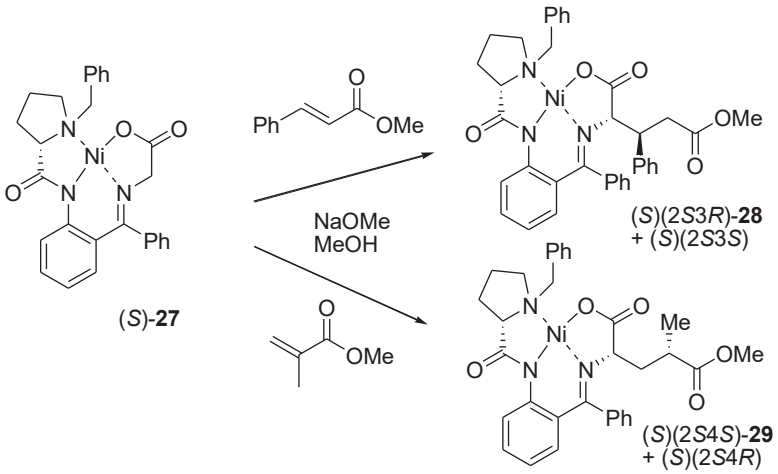
Scheme 4. Michael addition reactions of Schiff base **20** with a-methoxycarbonyl-substituted acrylic acids **23**.

This method appears to be quite general for preparing various β-substituted pyroglutamic/glutamic acid derivatives. Of particular importance is the successful reaction of 2,2-dimethylpropylidenemalonate **23** (R = t-Bu) with **20**, which ultimately leads to sterically constrained β-t-butyl derivatives of the target amino acids **26**. Notably, in contrast to the *bis*-lactim ether methodology(Scheme 1), the reactions between **20** and derivatives **23** containing conjugated C,C double bonds featured only 1,4-addition. This allowed for the preparation of the corresponding pyroglutamic/glutamic acids bearing potentially useful unsaturated functionality. However, the general applicability of this method is greatly limited by the use of naturally occurring camphor as a chiral auxiliary, as its (1S, 4S) enantiomeric form is scarcely available.

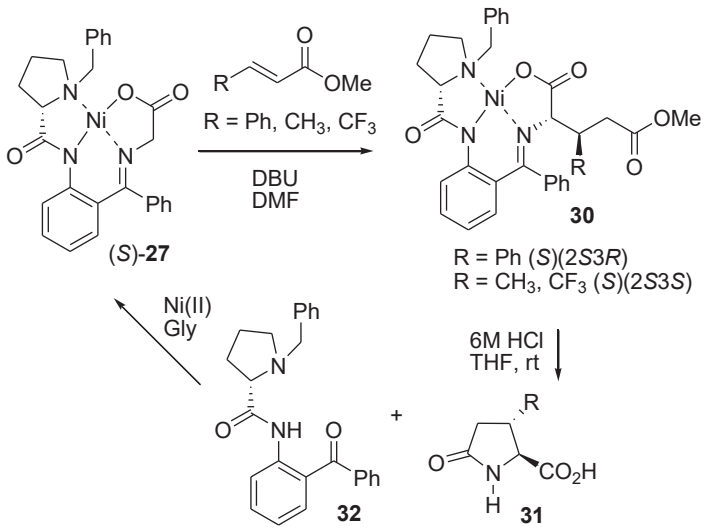
Another example of Michael addition reactions between chiral Schiff bases of glycine and α, β-unsaturated carboxylic acid derivatives was developed based on Ni(II) complex **27**shown in Scheme 5 [80–83]. The Ni(II) complex **27** was found to react easily in MeOH and in the presence of NaOMe as a base, with methyl cinnamate and methacrylate, giving rise to the corresponding diastereomeric products **28** and **29**. In both cases, the enolate face-diastereoselectivity was very high as α-(R)-configured products were not detected in noticeable amounts. However, diastereoselectivity at C-3 and C-4 positions was disappointingly low, furnishing the products in approximately a 2/1 and 1/1 ratio respectively. It is interesting to note that in this case the stereochemical outcome is kinetically controlled, these reactions are highly reversible and thus the ratios of diastereomeric products are thermodynamically controlled.

Taking advantage of high C-H acidity of the glycine methylene group in **27**, it was found that the corresponding Michael addition reactions with ethyl crotonate, 4,4,4-trifluorocrotonate andcinnamate [84,85]can be conducted in DMF in the presence of DBU as a base. The stereochemical outcome of the reactions was found to be kinetically controlled. The diastereoselectivity in the additions of (S)-**27** with ethyl crotonate and cinnamate was found to be noticeably better compared to the outcomes observed under the thermodynamically con-

trolled conditions (Scheme 5).The major products **30**(R = Me, Ph) were obtained in a ratio of 4/1, respectively. The stereochemical outcome of the reaction between (S)-**27** and ethyl 4,4,4-trifluorocrotonate was slightly higher, with a diastereomeric ratio of up to 5.6/1. This can be attributed to the more sterically demanding nature of the trifluoromethyl group [86–88]. The major diastereomers **30** were purified by crystallization of the reaction mixture and disassembled to afford the target pyroglutamic acids **31**, along with the recovery of the chiral ligand (S)-**32**. The ability to recycle the chiral ligand (S)-**32**, which can be reused for preparation of new batches of Ni(II) complex **27** is a significant advantage of this method.

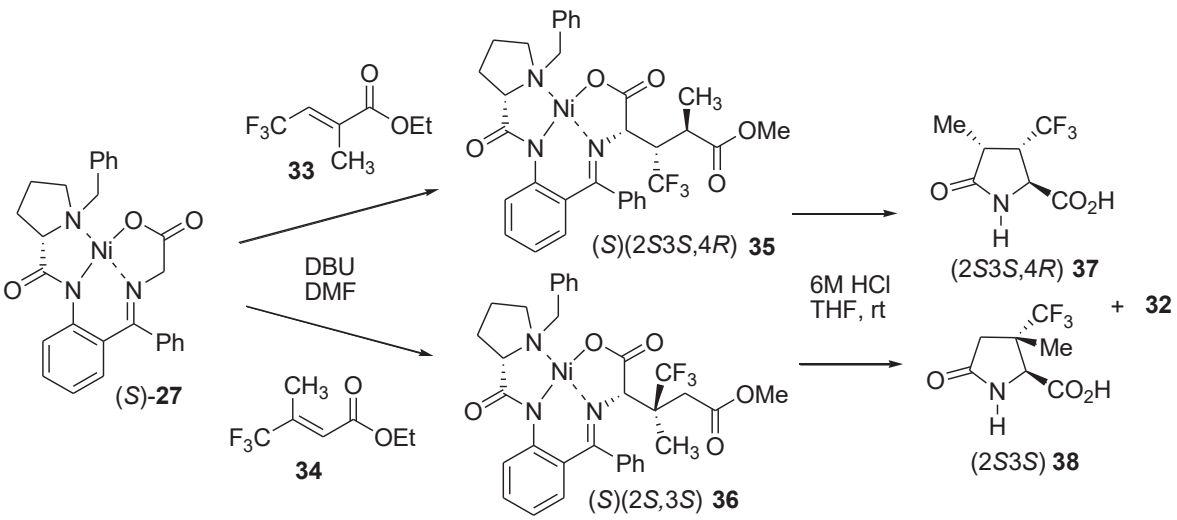


Scheme 5. Michael addition reactions of chiral Ni(II) complex **27**.



Scheme 6. DBU-catalysed Michael addition reactions of chiral Ni(II) complex **27**.

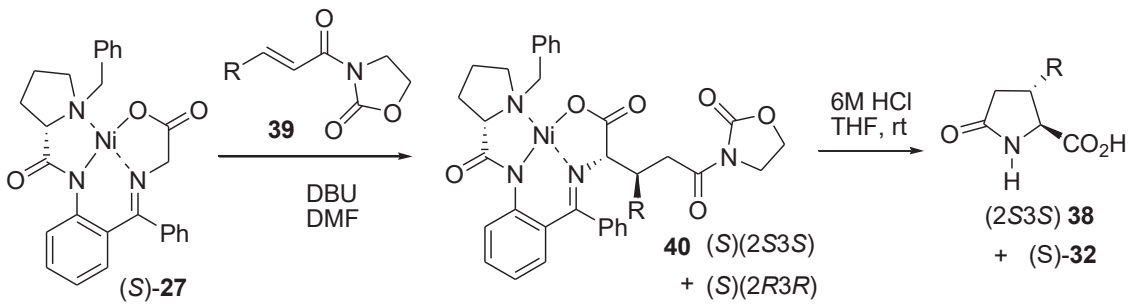
Of particular interest are the reactions between the Ni complex (S)-**27** and bis-substituted Michael acceptors **33** and **34** (Scheme 7) [89]. For instance, the simultaneous formation of α-, β-, and γ-stereogenic centers (eight theoretically possible stereoisomers) in the reaction of complex (S)-**27** with ester **33** represents a challenging stereochemical problem. The Michael addition between (S)-**27** and **33**, conducted in DMF in the presence of DBU, resulted in only two diastereomers (major **35**), in a synthetically useful ratio of 17/1, respectively. The reaction of complex (S)-**27** with ester **36**, conducted under the same reaction conditions, proceeded with virtually complete diastereoselectivity, furnishing a sole reaction product **36**. Diastereomerically pure products **35** and **36** were disassembled to release interesting bis-substituted pyroglutamic acids **37** and **38**. The high diastereoselectivity in these reactions, particularly the complete stereochemical discrimination between the methyl and trifluoromethyl groups in the addition of (S)-**27**, can be attributed to the steric and electronic effects of the trifluoromethyl group [90, 91].



Scheme 7. Michael addition reactions of complex **27** with fluorinated derivatives **33** and **34**.

Interesting results were obtained in the reactions of chiral Ni-complex (*S*)-**27** [92–94] with oxazolinin-2-one derived Michael acceptors **39** (Scheme 8). These additions were studied using DMF as a solvent and DBU as a base. The reactions were found tooccur at high reaction rates with perfect simple diastereoselectivity. On the other hand, the glycinecomplex enolate *re*/*si*face-selectivity was rather poorresulting generally in mixtures of two diastereomeric products **40**. The highest diastereoselectivity, 5.2/1ratio of (S)(2S3S) and (S)(2R3R) diastereomers **40**, in the aliphatic series was obtained in thereaction of (*S*)-**27** with *i*-Pr-containing **39**. Rather interesting and unexpected results were observedin the reactions of (*S*)-**27** with Michael acceptors bearing aromatic substituents. Thus, the addition between (*S*)-**27** and

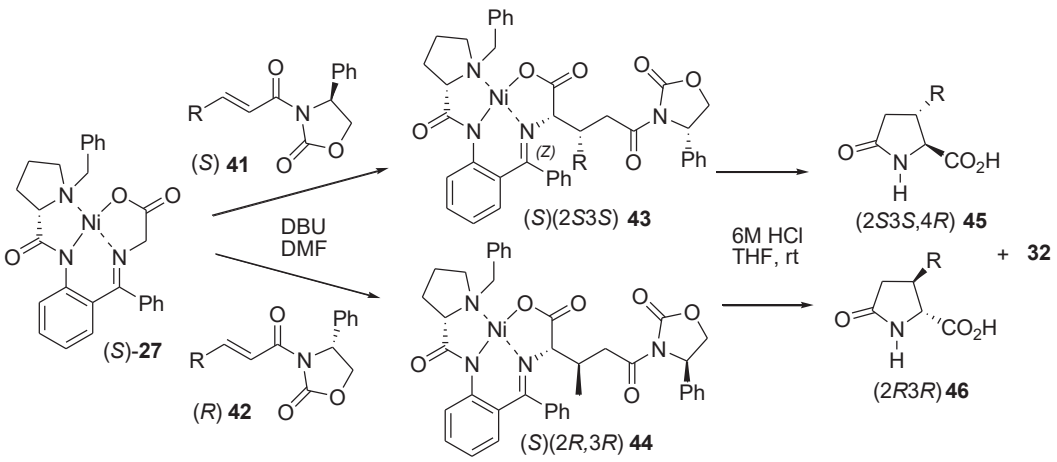
phenyl-containing **39** furnished a mixture of diastereomers **40** in a ratio of 4/1, respectively. In sharp contrast,the reaction between (*S*)-**27** and pentafluorophenyl-containing **39** occurred almost instantly (<2 min) giving rise to product **40** with excellent diastereoselectivity (ratio > 26/1). Further detailed study of the electronic and steric effects ofthe substituents on stereochemical outcome in these reactions revealed a general trend that presence of the electron with drawing substituents on starting **39** led to higher reaction rates and diastereoselectivity, while the presence ofthe electron-releasing substituents resulted in low rates and moderate selectivity. To account for these electronic effects dramatically influencing the stereochemical outcome, one can consider electron donor-acceptor attractive interactions between electrondeficient aromatic rings, such as pentafluorophenyl [95–97] in particular, and the ketimine phenyl of the starting Ni-complex **27**. The target pyroglutamic acids **38** were obtained after standard disassembly procedure along with the recovery of chiral auxiliary (S)-**32**.



R = Me, Et, n-Pr, i-Pr, t-Bu, Ph, a-naphthyl, b-naphthyl, 2-MeO-C_6H_4, 3-MeO-C_6H_4, 4-MeO-C_6H_4, 2-CF_3-C_6H_4, 3-CF_3-C_6H_4, 4-CF_3-C_6H_4, N-Mts-b-indolyl, C_6F_5, 2,6-F_2-C_6H_3, 2-F-C_6H_4, 3,4-F_2-C_6H_3, 4-MeO-C_6F_4, 3,4-Cl_2-C_6H_3, 4-NO_2 -C_6H_4

Scheme 8. Michael addition reactions ofchiral N(II) complex **27** with oxazolinin-2-one derived Michael acceptors **39**.

Considering the strong stereocontrolling effect of oxazolinin-2-one chiral auxiliaries [98–100], it was interesting to investigate the corresponding Michael addition reactions using chiral Michael acceptors **41** and **42** (Scheme 9) with the chiral Ni(II) complex **27** [101–103]. The addition reaction between (S)-**27** and crotonyl-derived (S)-**41**, conducted in DMF/DBU at ambient temperature, proceeded to completion at a high rate, furnishing a sole reaction product **43** with the (2S, 3S) configuration of the glutamic acid residue in quantitative chemical yield. This outcome was considered a match case, as both chiral auxiliaries showed a preference for the α-(S) configuration of the addition product. The reaction of (S)-**27** with crotonyl-derived (R)-**42** was expected to be a mismatch case. The addition was conducted under the same conditions and occurred at a slightly slower rate, giving rise to a sole diastereomerically pure product **44**. The absolute configuration of the glutamic residue in **44** was found to be (2R, 3R). This result was quite unexpected, suggesting that the stereochemical preferences of the chiral Michael acceptor **42** completely overwhelmed those of the chiral Ni-complex (S)-**27**.



R = Me; Et; n-Pr; i-Pr; Bn; Ph; b-naphthyl; 4-MeO-C_6H_4; 3-MeO-C_6H_4; N-Mts-b-indolyl; 4-CF_3-C_6H_4

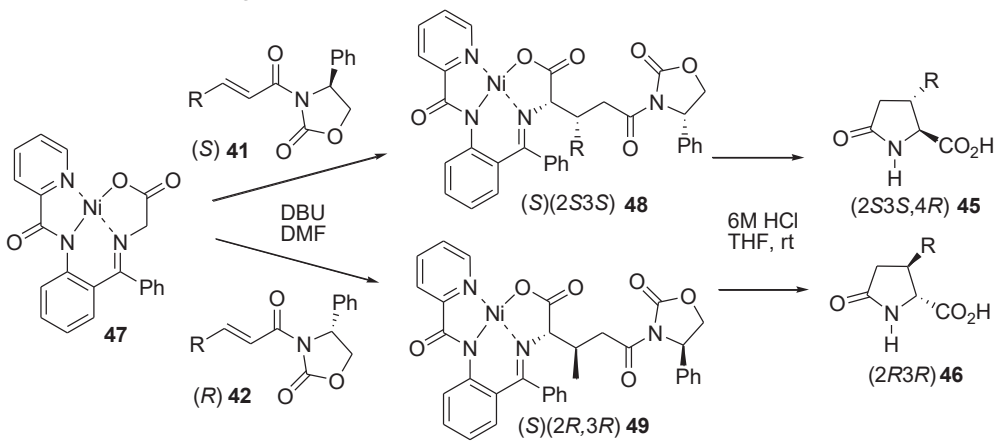
Scheme 9. Michael addition reactions between chiral Ni(II) complex **27** and Michael acceptors **41** and **42**.

The same pattern of reactivity and stereochemical preferences was observed in the reactions of (S)-**27** with various Michael acceptors **41** and **42**, bearing, in principle, any alkyl or aromatic substituents (Scheme 9). Of particular interest was the addition between (S)-**27** and the bulky i-Pr-containing **41**/**42**. When (S)-**41** (R = i-Pr) was used, the reaction proceeded to completion in 30 minutes, affording the product (2S, 3R)-**43** in quantitative chemical yield. In the mismatch case, the addition between (S)-**27** and (R)-**42** (R = i-Pr) was considerably slower and accompanied by the formation of some by-products. Nevertheless, within 4 hours the reaction was completed, and the target product (2R, 3S)-**44** was isolated in 67% yield [101–103]. The results obtained clearly indicated that the steric and electronic nature of the substituents on the starting Michael acceptors **41**/**42** do not influence the stereochemical outcome of reactions with (S)-**27**, suggesting that the substituents on the C,C double bond of **41**/**42** are not involved in the stereocontrolling step of the additions. This observation highlighted the generality of the method and underscored the intriguing stereocontrolling power of the chiral oxazolidine-2-one-derived Michael acceptors **41**/**42** [101–103].The final amino acids **45** and **46** were prepared by acidic disassembly of the addition products, along with the recovery and reuse of the chiral ligand **32**.

To take advantage of this discovery, the reactions of achiral Ni(II) complex **47** (Scheme 10) with chiral Michael acceptors **41**/**42** were investigated [104–106]. Picolinic acid-derived achiral complex **47** [107] was reacted with Michael acceptor **42** in DMF at room temperature in the presence of 15 mole % DBU. The addition occurred at a high rate, affording a sole reaction product **48** in quantitative chemical yield. Application of (S)-configured **41** mirrored the result obtained for (R)-**42**, affording individual product **48** containing the (2S, 3S)-enantiomer of β-methyl glutamic acid. The same excellent stereochemical outcome was observed in the reaction of all alkyl-containing **41**/**42** (R = Et, n-Pr, Bn), except for the addition between

complex **47** and bulky i-Pr-containing **41**/**42**. In this case, the reaction proceeded very slowly, allowing for about 30% conversion of the starting compounds in 4 hours. Though the corresponding products **48** and **49** were isolated in 15% yield, these results suggested that the present method could not be extended to substrates containing tertiary alkyl groups.

To examine the applicability of the method to an aromatic series, which would lead to the synthesis of the corresponding 3-aryl substituted amino acids, the reactions of complex **47** with (S)- and (R)-configured Michael acceptors **41**/**42** containing classical phenyl and naphthyl groups, as well as derivatives bearing a phenyl ring with electron-withdrawing and electron-donating substituents, were studied. In all cases, regardless of the steric or electronic nature of the substituent on the starting **41**/**42**, major products **48** or **49** were obtained with at least 95% de and excellent chemical yields. In both aliphatic and aromatic series, the stereochemical outcome was shown to be kinetically controlled, affording products with relative topicity like.



R = Me; Et; n-Pr; i-Pr; Bn; Ph; b-naphthyl; 4-MeO-C_6H_4; 3-MeO-C_6H_4; N-Mts-b-indolyl; 4-CF_3-C_6H_4

Scheme 10. Michael additions between achiral Ni(II) complex **47** and chiral acceptors **41** and **42**.

To demonstrate the synthetic efficiency of this method, >25 g of enantiomerically pure β-phenyl pyroglutamic acid (2S, 3R)-**45** was prepared in >85% total yield in less than 14 hours. In this case, the crystalline product **49** of the addition between **47** and (R)-**42** was isolated simply by filtration after pouring the reaction mixture into water. Without additional purification, product **49** was disassembled to afford the target amino acid **46**.

The relatively broad substrate generality, excellent chemical yields and diastereoselectivity, combined with the simplicity of the experimental procedures, render the present method synthetically superior to the literature method for preparing various 3-substituted pyroglutamic acids and related amino acids.

Apparent success of these Ni(II) complexes in the asymmetric Michael addition reactions stimulatedinterest in the developing of new types of chiral as well as achiral Ni(II) complexes [108–111]. Figure 4 presents just a few most prospective types.

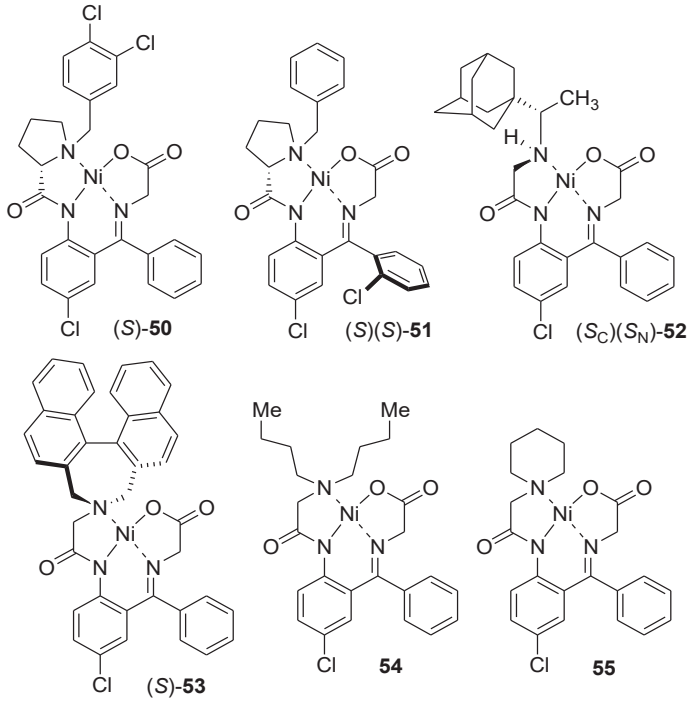
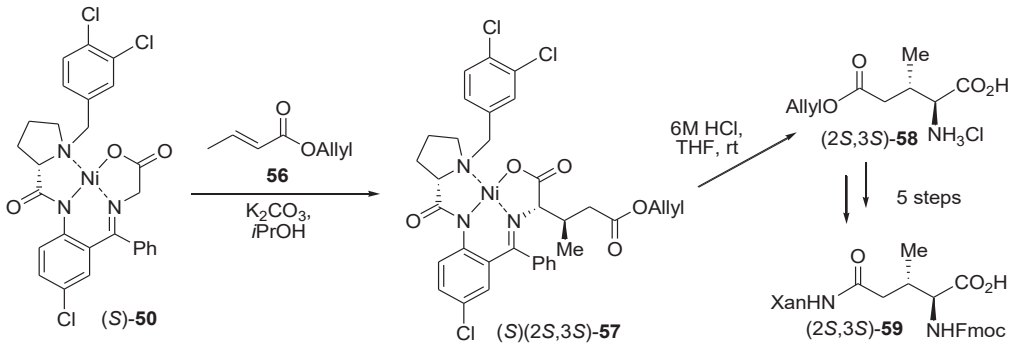


Fig. 4. New generation of chiral and achiral Ni(II) complexes.

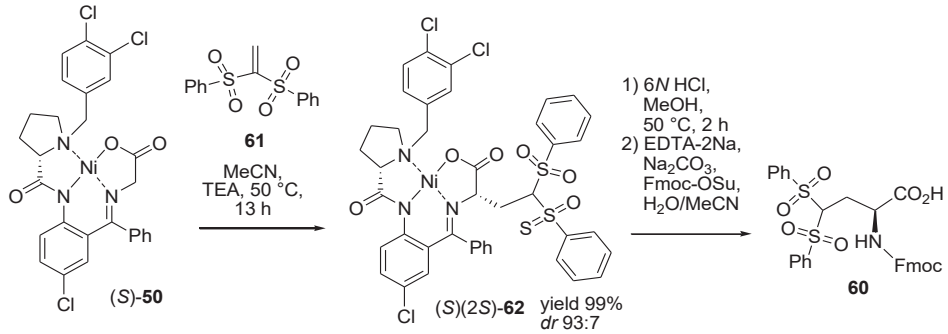
For example, chlorinated Ni(II) complex **50**, available in both enantiomeric forms [112] possesses exceptional stereocontrolling properties [113,114] due to electrostatic interactions between electron-rich benzophenone phenyl and electron-deficientchlorine-containing rings [115].Thus, complex (*S*)-**50** was successfully used in Michael addition for the synthesis of (2*S*, 3*S*)-3-methylglutamine, the key compound used in the total synthesis of cytotoxic marine peptides callipeltin O and Q [116]. As presented in Scheme 11, glycine Ni(II) complex **50** was reacted with Michael acceptor **51** under specially designed conditions to keep intact the allyl ester moiety [117].

The acidic disassembly of the major diastereomeric product (*S*)(2*S*3*S*)-**57** was also performed under strictly controlled conditions using THF as a solvent. Allyl ester hydrochloride **58** was subsequently transformed into the target properly protected for peptide synthesis glutamine derivative **59** in five steps.

It was demonstrated that the substitution of phenylalanine in endogenous peptides with a bulkier and more lipophilic *β*-phenylphenylalanine (diphenylalanine, DPA) usually leads to improved binding to the apolar site of the targeted receptors. In particular, DPA-modified peptides were found to possess enhanced biological profiles in the series of thrombin inhibitors [118], angiotensin-converting enzyme (ACE) inhibitors [119], HIV protease inhibitors [120], pain-related norepinephrine transporter inhibitors [121], *μ* and *δ* opioid receptors [122]. In this regard, 2-amino-4,4-bis-(phenylsulfonyl)butanoic acid **60** (Scheme 12) is one of the promising structures featuring enhanced steric bulk and lipophilicity. Chiral Schiff base complex **50** was selected for preparation of this amino acids via Michael addition using specially designed vinyl–disulfonyl Michael acceptor **61** [123, 124].



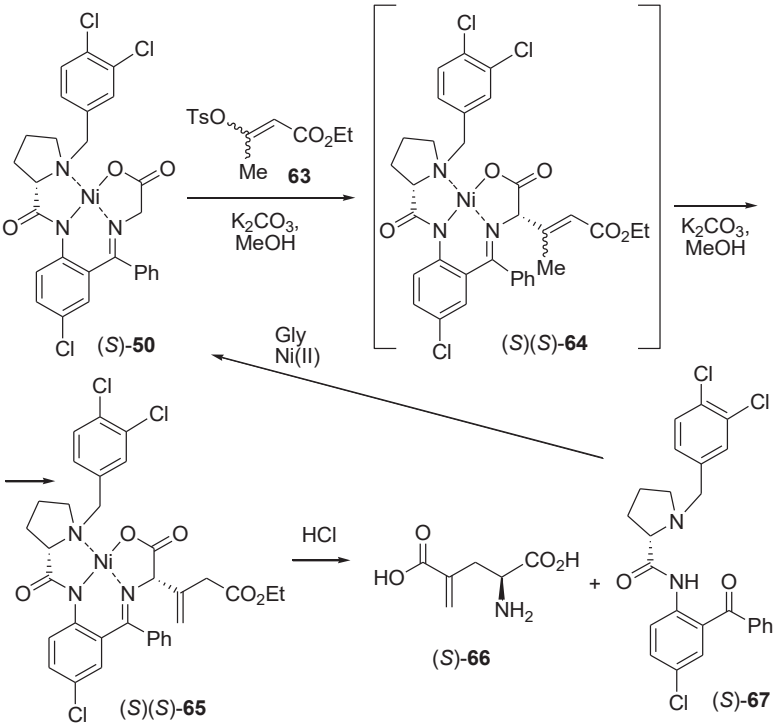
Scheme 11. Synthesis of properly protected (2*S*,3*S*)-3-methylglutamine**59** using rationally designed chlorinated Ni(II)-complex (*S*)-**50**.



Scheme 12. Asymmetric synthesis of sterically bulky and lipophilic 2-amino-4,4-bis-(phenylsulfonyl)butanoic acid (*S*)-**60**.

It was found that due to the high electrophilicity of reagent**61**, the corresponding Michael addition with chiral glycine complex **50** can be efficiently conducted using triethylamine as base. Optimization of the reaction conditions allowed for preparation of the diastereomeric products with an excellent yield (99%) and excellent diastereoselectivity (93/7). The major product **62** was transformed into the corresponding Fmoc derivative of 2-amino-4,4-bis-(phenylsulfonyl)butanoic acid **60** under standard conditions.

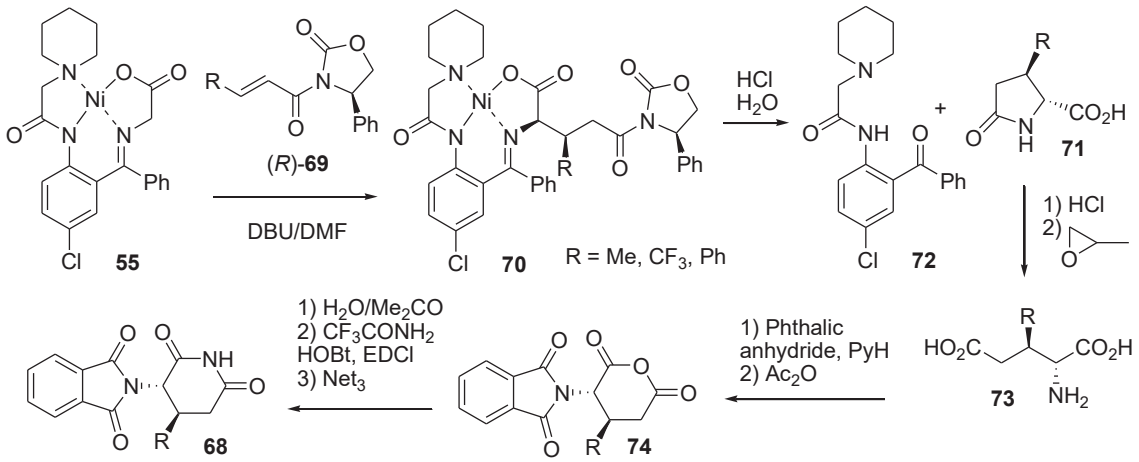
Rather unexpected resultswere reported for the Michael addition between chiral glycine Ni(II) complex **50** and Michael acceptor **63** bearing a tosylate leaving group (Scheme 13) [125]. The original goal of this research was preparation of addition product **64** containing the corresponding β-methyl-unsaturated amino acid moiety. However, quite surprisingly, compound **65** was isolated as the major reaction product. (S)-3-Methyleneglutamic acid **66** was previously unknown in enantiomerically pure form. One can assume that the target addition product **64** underwent base-catalyzed isomerization to **65**. Major product (S)(S)-**65** was isolated in diastereomerically pure form and disassembled to release the unsaturated amino acid (S)-**66** along with the chiral ligand (S)-**67**, which was recycled and reused for preparation of new portions of starting chiral glycine Schiff base Ni(II) complex (S)-**50**.



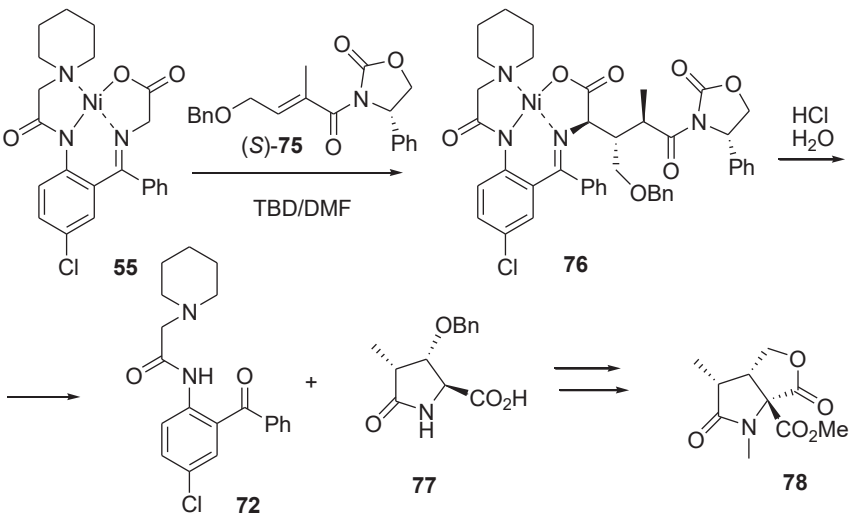
Scheme 13. Asymmetric synthesis of (S)-3-methyleneglutamic acid **66** via Michael addition reaction.

Achiral complex **55** was selected for preparation of 4-substituted configurationally stable thalidomide derivatives **68** (Scheme 14) [126,127]. As illustrated in Scheme 14, key step in the multistep synthesis of the thalidomide derivatives is Michael addition reaction of achiral glycine Schiff base derivatives **55** with chiral (*R*)- or (*S*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidine-2-one **69** were conducted in DMF using DBU as a base.The resultant addition products **70** were isolated as individual diastereoisomers in quantitative chemical yields. Products **70** can be easily hydrolyzed under mild conditions and, upon a workup procedure, transformed to the pyroglutamic acids **71** along with recovery of ligand **72** which can be used for preparation of the starting complex **55**. Hydrolysis of pyroglutamic acids **71** with 3N HCl at reflux afforded 3-substituted glutamic acids **73** in high chemical yield.

The next step, transformation of acid **73** to N-phthaloyl anhydrides **74**, was an important step as it was expected that during this process the corresponding alpha-stereogenic carbon would undergo epimerization setting up the trans-configuration in the final products **74** [128]. Indeed the transformation of acids **73** to N-phthaloyl anhydrides **74**, occurred as expected furnishing a single diastereomers **74** in up to 70% (two steps)yield. The final transformation of enantio- and diastereomerically pure **74** to the target 4-substituted thalidomides **68**, was conducted in two major steps under the standard conditions [129]. After hydrolysis of anhydrate **74** with water in acetone, the corresponding intermediates were smooth lytrans formed to **68** using trifluoroacetamide as a source of nitrogen. The target products **68** were isolated in good yields (~70% for two steps) as single diastereomers.



Scheme 14. Asymmetric synthesis of 4-substituted thalidomide derivatives via Michael addition reactions.



Scheme 15. Asymmetric synthesis of 3,4-disubstituted pyroglutamic acid **77** via Michael addition reaction of achiral N(II) complex **55**.

With the goal of developing a new approach for preparing analogs of oxazolomycin family products **78** (Scheme 15), the reaction of achiral Ni(II) complex **55** with disubstituted chiral Michael acceptor **75** was considered a key step, allowing the formation of the structural frame as well as the three required stereogenic centers.Interestingly, the reaction of **55** with **75** conducted in DMF/DBU did not proceed at all, resulting in complete recovery of the starting material. Eventually, after numerous attempts to find the right conditions, 1,5,7-triazabicyclo [4.4.0] dec-5-ene (TBD), slightly more basic than DBU, was found to catalyze the reaction, affording a mixture of the Michael addition products. It was determined

that the reaction mixture consisted of six diastereomers obtained in a ratio of 68:8:7:7:7:3. The major product was separated by silica gel column chromatography to give **76** in 62% isolated yield [130].

Under standard acidic conditions, the major diastereomer **76** was disassembled to release the target pyroglutamic acid **77** along with the reusable tridentate ligand **72**. Key amino acid **77** was then transformed into oxazolomycin analog **78** using literature procedures.

Application of this Ni(II) complex methodology is not limited to glutamic acids and can be extended to preparing various other derivatives using, to mention just a few, alkyl halide alkylations [131–133], aldol [134–136], Mannich [113, 137] addition reactionsand DKR [138, 139].

CONCLUSIONS. This review has sought to emphasize the key synthetic and methodological concepts developed to control both simple and facial stereoselectivity in Michael addition reactions involving nucleophilic glycine equivalents and α, β-unsaturated carboxylic acid derivatives. While some methods discussed hold historical significance, others present practical, generalized, and synthetically efficient solutions. However, various synthetic and stereochemical challenges remain, particularly in reactions involving α-, α, β-bis-, and β, β-bis-substituted α,β-unsaturated carboxylic acid derivatives. As the importance of sterically constrained glutamic/pyroglutamic acids and related amino acids continues to grow, Michael addition reactions–offering the most straightforward and generalized approach to this family of amino acids – will remain a fascinating and challenging area in the field of asymmetric synthesis.

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АСИМЕТРИЧНИЙ СИНТЕЗ ХІРО-ОБМЕЖЕНИХ ГЛУТАМІНОВИХ КИСЛОТ І СПОРІДНЕНИХ СПОЛУК ЗА ДОПОМОГОЮ РЕАКЦІЙ МІХАЕЛЯ

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Реакції Міхаеля, що включають нуклеофільні еквіваленти гліцинута α, β-ненасичені похідні карбонових кислот, пропонують короткий та узагальнений методологічний підхід до синтезу сімейства амінокислот з хі-обмеженням, що містять п'ять атомів вуглецю. Ціамінокислоти відіграють вирішальну роль у дизайні нових пептидів та в з'ясуванні тривимірної структури пептидів/білків та їхніх біологічних функцій/активності. У цьому огляді узагальнено значні синтетичні та методологічні досягнення у зазначеній галузі на сьогодні. Кожен розглянутий метод включає оцінку синтетичних можливостей і обмежень, практичності та ефективності процедур і механістичне обґрунтування спостережуваних стереохімічних переваг.

Ключові слова: асиметричний синтез, реакції Міхаеля, еквіваленти гліцину, металокомплекси, шіфові основи, конформації, стеричне обмеження, глутамінова кислота, піроглутамінова кислота, пролін.

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