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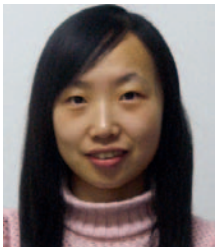
Application of Nickel(II) Complexes to the Efficient Synthesis of α- or β-Amino Acids

Jiang Wang, Lei Zhang, Hualiang Jiang, Kaixian Chen, and Hong Liu*

Abstract: Nonproteinogenic α- or β-amino acids have attracted tremendous attention, as they are widely utilized for biological, biochemical, pharmaceutical, and asymmetric chemical investigations. Recently, we developed a series of new strategies for preparing achiral and chiral nickel(II) complexes for the synthesis of amino acids. We applied these new methods utilizing chiral nickel(II) complexes for the asymmetric Mannich reaction to synthesize enantiopure α,β-diamino acids, the enantioselective tandem conjugate addition–elimination reaction to prepare glutamic acid derivatives, the Suzuki coupling reaction to yield β^2-amino acid derivatives, the asymmetric Mannich reaction to synthesize 3-aminoaspartate, the asymmetric Michael addition reaction to give β-substituted-α,γ-diaminobutyric acid derivatives, the asymmetric alkylation reaction to prepare linear ω-trifluoromethyl containing amino acids, and the asymmetric Michael addition reaction to synthesize *syn*-β-substituted tryptophans.

Keywords: Amino acids · C-alkylation reaction · Mannich reaction · Michael reaction · Nickel(II) complex · Suzuki reaction



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1. Introduction

Amino acids are key structural units of many natural products and have great significance for the synthesis of bioactive compounds. Non-protein amino acids have been extensively found in peptide antibiotics, antifungal dipeptides and other biologically active compounds (Fig. 1).[1] Based on their prominent biological activities, some compounds derived from amino acids have become novel classes of potential drugs with new clinical applications.

The nickel(II) complex of the chiral Schiff base of glycine has been widely used to synthesize enantiopure amino acids *via* aldol, Michael addition, Mannich reaction, and C-alkylation reactions. Notable merits of the nickel(II) complex's methods are: i) predictable stereochemical outcome and high level of enantio- and/or diastereoselectivity; ii) inexpensive cost-structure and ready availability of

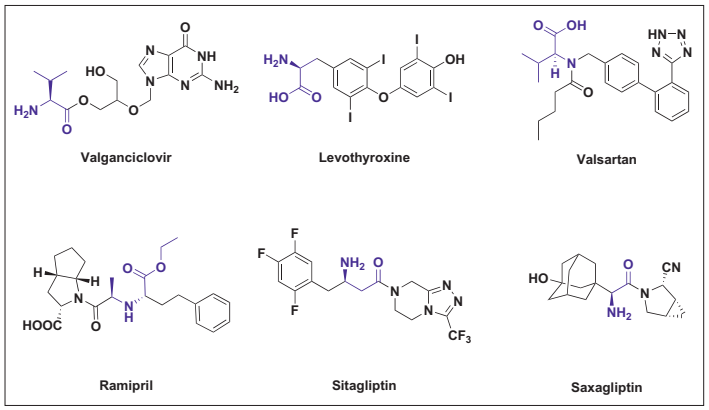
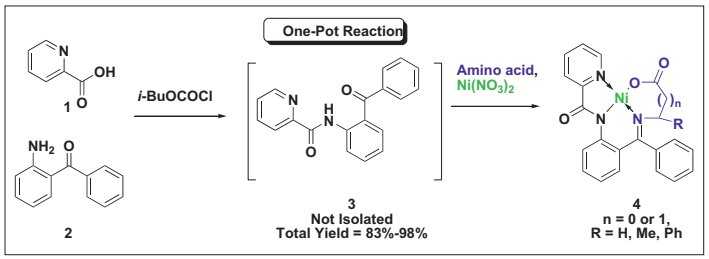


Fig. 1. Representative drugs containing amino acids.



Scheme 1. One-pot, large-scale synthesis of nickel(II) complexes derived from 2-[*N*-(α-picolyl)amino] benzophenone and α- or β-amino acids.

nickel(II) complexes; iii) operationally convenient reaction procedures; iv) high overall reaction yields and reproducibility; and v) easy and virtually complete recovery of chiral ligands, rivaling catalytic methods in terms of consumption of the stereocontrolling reagents. These unique features render this method an attractive strategy for practical synthesis of various α-amino acids, in particular, on relatively large scale.

The preparation of nickel(II) complexes and their practical synthesis of various α-amino acids are well-documented by Belokon's group[2–5] and Soloshonok's group.[6–10] However, Belokon's route, which employed excess $SOCl_2$ for the ligand preparation, not only led to incomplete transformation and generally low chemical yields but also led to laborious purification prior to its use for nickel(II) complex formation. Soloshonok's procedure improved the overall yield (up to 93%), but requires inconvenient inert atmosphere or protocol by introducing a general one-pot, two-step procedure to prepare both. We thus developed a one-pot, large-scale procedure to prepare the Belokon-Soloshonok nucleophilic glycine equivalent 2-[*N*-(α-picolyl)amino]benzophenone (PABP) derived nickel(II) complex [GlyNi(II) PABP] **4**.[11] This was accomplished by using isobutyl chloroformate to form PABP and then NaH/KOH as mixed bases to afford the corresponding complexes in a one-pot manner with up to an overall yield of 98% (Scheme 1). This method does not require the preparation of PABP as a separate step, works well with a variety of α- or β-amino acids, and does not need laborious purification. The potential of this method for preparation of β-amino acids derivatives, such as β-AlaNi(II)PABP and β-PheNi(II)PABP, has been demonstrated. In addition the method can be reproduced successfully on a >60 g scale, which confirms its efficiency and practicality.

2. Application of Nickel(II) Complexes to the Efficient Synthesis of Achiral β-Amino Acids

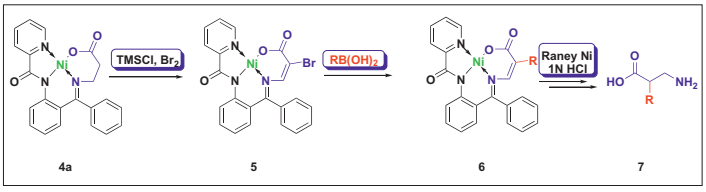
2.1 α-*Alkyl*-β-*Amino Acids*

α-Substituted β-amino acids have been widely used for the synthesis of enzyme inhibitors,[12] antiviral drugs,[13] and antibacterial drugs,[14] as well as in the treatment of inflammatory disease and pain.[15,16] We developed a new synthetic method using chlorotrimethylsilane as the activator to brominate the nickel(II) complex of the β-alanine Schiff's base [β-AlaNi(II)-PABA] for the preparation of α-aryl-/heteroaryl-substituted β-amino acids.[17] The procedure involves a Suzuki coupling reaction, followed by hydrogenation and hydrolysis (Scheme 2). A broad range of aryl and heteroaryl substituents may be employed under operationally simple and effective conditions. This is the first report of the application of the nickel(II) complex [β-AlaNi(II)-PABA], which represents an attractive route to afford α-aryl-/heteroaryl-substituted β-amino acids.

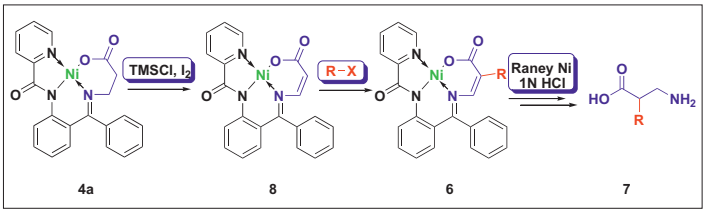
As a continuation of this work, we later successfully applied this nickel(II) complex to access α-alkyl-β-amino acids *via* alkylation with alkyl halides under operationally convenient conditions, without recourse to inert atmosphere, dry solvents, and low temperatures (Scheme 3).[18] The pivotal α-alkylated intermediate can be converted into the corresponding α-alkyl-β-amino acids *via* two steps with a wide range of substituents. Thus, the key advantages such as experimental simplicity and attractive cost structure could be realized. A broad range of benzyl substrates could be employed in the reaction.

2.2 α,α-*Disubstituted* β-*Alanines and* α,α-*Disubstituted Aldehydes*

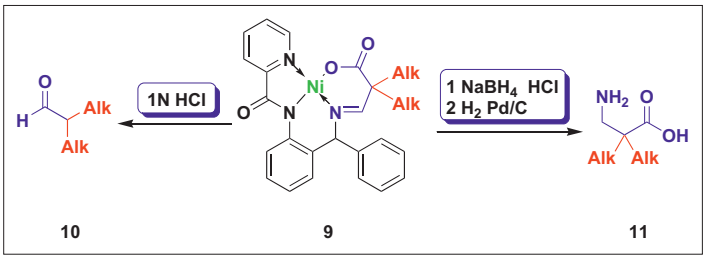
α,α-Dialkyl β-alanines are useful building blocks in potent pharmaceutical drugs and functional materials.[19–23] However, despite the substantial interest in these amino acids and their applications in drug design, there are few synthetic approaches for preparing these compounds, with most of them being rather impractical.[24–28] We have successfully synthesized dialkylated products of nickel(II) complexes of β-alanine Schiff base and developed a practical and highly efficient route to synthesize sterically constrained symmetrically α,α-disubstituted β-amino acids (Scheme 4).[29] In the course of our studies to prepare α,α-disubstituted β-alanines in this study, we unexpectedly obtained α,α-disubstituted aldehydes. The α,α-disubstituted aldehydes are commonly utilized in organic synthesis and medical chemistry, but there are few reports on the synthesis of these



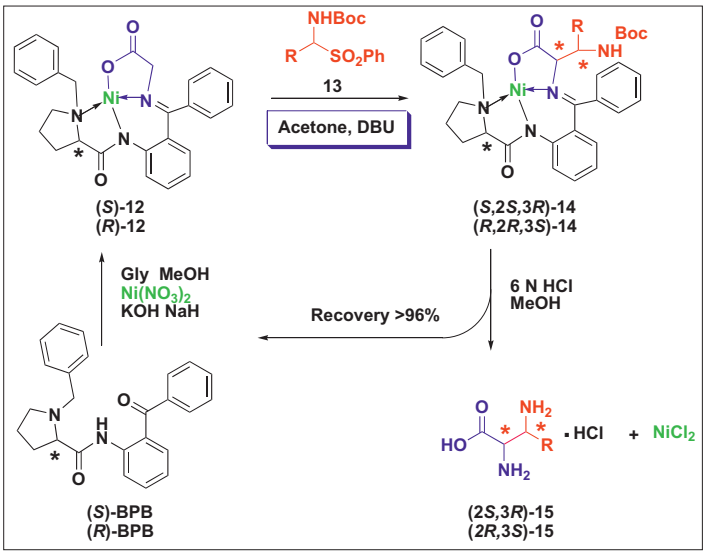
Scheme 2. Synthesis of α-substituted β-amino acids *via* a nickel (II) complex with boric acids.



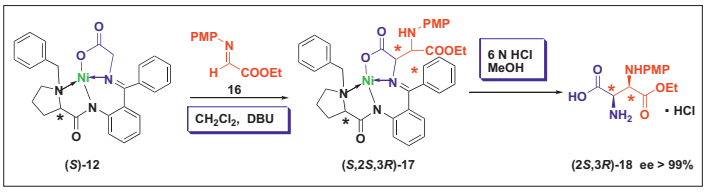
Scheme 3. Preparation of α-alkyl-β-amino acids *via* nickel(II) complex.



Scheme 4. Synthesis of α,α-disubstituted β-amino acids and α,α-disubstituted aldehydes *via* nickel(II) complex **9**.



Scheme 5. Stereoselective synthesis of enantioenriched α,β-diamino acids *via* a chiral nickel(II) complex **12** with sulfones **13**.



Scheme 6. Stereoselective synthesis of enantioenriched 3-aminoaspartate *via* a chiral nickel(II) complex **12** with α-imino ester **16**.

compounds. To our knowledge, this is the first example of a method to prepare aldehydes from β-AlaNi(II)-PABP. These dialkylation reactions were conducted under normal conditions not requiring inert atmosphere, dried solvents, and low temperatures, and thereby providing a simple experimental procedure and attractive cost structure.

3. Application of Nickel(II) Complexes to the Efficient Asymmetric Synthesis of Chiral Amino Acids

3.1 *Chiral α,β-Diamino Acids*

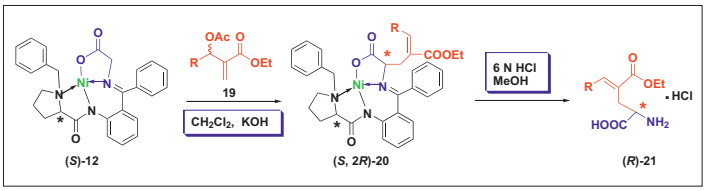
α,β-Diamino acids are versatile building blocks in organic synthesis and medicinal and peptide/peptidomimetic chemistry.[30–35] Furthermore, they are also useful in many applications, such as chiral auxiliaries and ligands for asymmetric synthesis.[36] Accordingly, the development of efficient methods in their preparation has been a mainstay in organic synthesis. We have developed a practical and highly efficient enantio- and diastereoselective route to *syn*-configured α,β-diamino acids using a direct asymmetric Mannich reaction (Scheme 5).[37] By a single operation, a new carbon–carbon bond and two adjacent stereogenic centers are created. This is a good example of highly stereoselective Mannich reactions with *in situ* generation of carbamate-protected imines by chiral nickel(II) complex. The robust and readily obtained Boc-α-amino sulfones with wide ranges of structural diversity can efficiently participate in the process with high enantio- and diastereoselectivity, thus significantly expanding the scope of the reactions. A broad range of aryl-, heteroaryl-, and alkyl-derived imines can all be employed under operationally simple and safe conditions. The absolute configuration of the Mannich product (*R*,2*R*,3*S*)-**14a** was determined by X-ray analysis. Theoretical calculations have been carried out to understand the reaction mechanism and the high enantio- and diastereoselectivity. As shown by the results of our quantum mechanics (QM) calculations, the high enantio- and diastereoselectivity came from the free energy difference among the four transition states, the states (*S*,2*S*,3*R*)-*syn*-TS, (*S*,2*R*,3*S*)-*syn*-TS, (*S*,2*S*,3*S*)-*anti*-TS, and (*S*,2*R*,3*R*)-*anti*-TS. This indicates that *anti*-TSs are less favorable than *syn*-TSs, due to the large steric repulsion between *tert*-butyl of imine and nickel(II)-enolate. Significantly, the process developed in this work is based on readily available and inexpensive starting materials and is operationally convenient.

Optically active α- and β-amino acids are fundamental building blocks for the preparation of molecules important for the pharmaceutical and agrochemical industries such as peptides, proteins, and other natural products. Among them, α,β-diamino acids are components of enzyme inhibitors, and their incorporation into peptides is used to modulate secondary and tertiary structural conformations. In particular, substituted 3-aminoaspartate derivatives as present in compounds like biotin, 3-fluoroaspartic acid and 5-fluorouracil exhibit various biological and medicinal activities. Consequently, the development of efficient methods for enantioselective 3-aminoaspartate is of interest. Some approaches to 3-aminoaspartate derivatives have been developed.[38–44] Although these methods are effective, some starting materials are not readily available or are difficult to prepare. There are no previous reports on the use of the chiral nickel(II) glycinate derivative **12** as a carbon nucleophile to react with the α-imino ester **16**. We developed a synthesis of a 3-aminoaspartate ester by a highly enantio- and diastereoselective Mannich reaction of a chiral nickel(II) complex of a Schiff base of glycine with an *N*-(*p*-methoxyphenyl)-protected α-imino ester in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene. These reactions proceed well at room temperature with dichloromethane as solvent and without the addition of any chiral catalyst (Scheme 6).[45] This procedure leads to the products with up to 99% diastereomeric excess and excellent yields. The method uses readily available starting materials and has economic and practical advantages over previous methods.

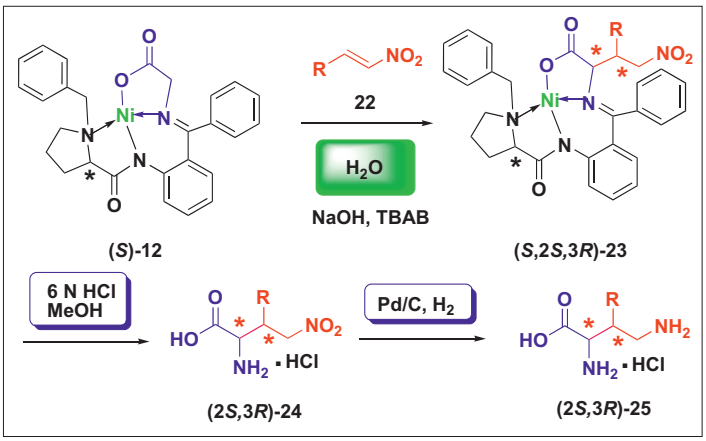
3.2 *Enantioenriched Glutamic Acid Derivatives*

Glutamic acid is the most abundant excitatory neurotransmitter in the mammalian nervous system. Its derivatives are used as fundamental building blocks for the synthesis of molecules that are important for the pharmaceutical and agrochemical industries, such as peptides, proteins, and other natural products.[46–48] In particular, glutamic acid derivatives are structural components of ligands for various types of glutamate receptors, which are potential therapeutic agents.[49,50] Asymmetric synthesis of glutamic acid derivatives is a difficult and challenging task. A number of potential methods have been developed for the synthesis of these compounds.[51,52] One of the most efficient methods for the

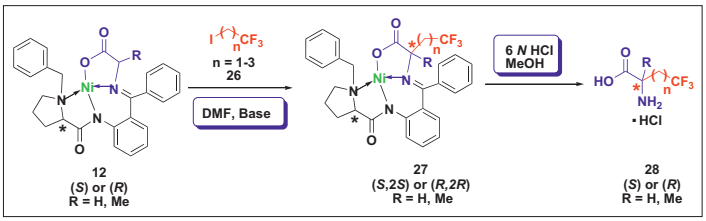
preparation of 3-substituted pyroglutamic acid derivatives is the 1,4-addition of glycine derivatives to α,β-unsaturated esters or amides.[53–57] Kobayashi *et al.* reported an effective method for the asymmetric 1,4-addition synthesis of 3-substituted glutamic acid derivatives in good enantiomeric excess.[58] O'Donnell *et al.* described the enantioselective synthesis of 4-substituted glutamic acid derivatives efficiently catalyzed by a chiral phase-transfer catalyst;[59] however, it requires long reaction times (30–48 h) and an expensive phase-transfer catalyst. However, no examples of the preparation of chainlike, 4-substituted glutamic acid derivatives by an asymmetric synthesis reaction have been reported. Various methodological and structural shortcomings of the literature approaches render these methods of limited synthetic application, in particular for the preparation of chainlike glutamic acid derivatives on a relatively large scale. On the other hand, Belokon and Soloshonok *et al.* developed an efficient, large-scale synthesis of the nickel(II) complex, which has made the starting materials readily available and inexpensive.[60–63] We thus developed a practically feasible method to asymmetrically synthesize enantiopure glutamic acid derivatives *via* diastereoselective conjugate addition–elimination of a chiral nickel(II) complex of glycine **12** with activated allylic acetates **19** (Scheme 7).[64] The reaction pathway was successfully controlled, and the desired formation of a carbon–carbon bond was exclusively obtained with high diastereoselectivity. A broad range of aryl- and heteroaryl-derived allylic acetates could be employed in this reaction under operationally convenient conditions, without the need for an inert atmosphere, dried solvents, and very low temperatures. Thus, the experimental procedure is very simple and cost-effective. Owing to the high chemical yields of the products of the conjugate addition–elimination reaction and the simplicity of the experimental procedure, this reaction can be employed for the multigram-scale preparation of glutamic acid derivatives.



Scheme 7. Stereoselective synthesis of enantioenriched glutamic acid derivatives *via* a chiral nickel(II) complex with allylic acetates.



Scheme 8. Asymmetric Michael reaction of a chiral nickel(II) glycinate and nitroalkenes.



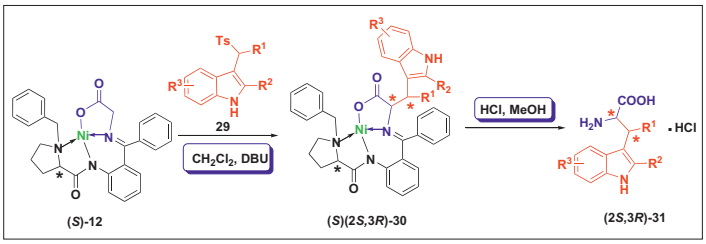
Scheme 9. Asymmetric synthesis of linear ω-trifluoromethyl containing amino acids *via* chiral nickel(II) complexes alkylation with alkyl halides.

3.3 *Chiral* β-*substituted* α,γ-*Diaminobutyric Acid*

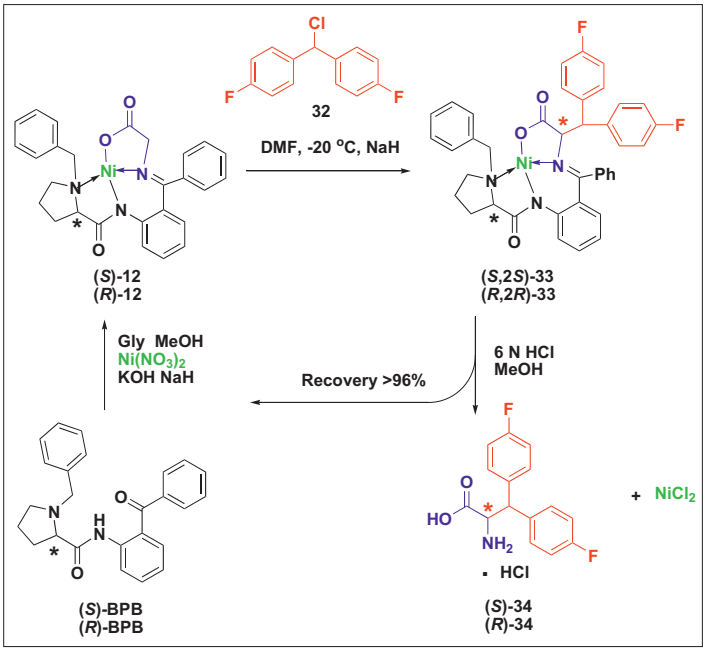
Water is preferred over organic solvents as a solvent due to its useful properties such as safety, nontoxicity, inflammability, low cost, and environmental friendliness. Therefore, organic reactions in aqueous media are receiving considerable attention in modern chemistry.[65–67] Chiral α,γ-diaminobutyric acids are frequently found in various bioactive compounds, such as miraziridine A, mureidomycin A, and synthetic inhibitors. Catalytic diastereoselective synthesis of these chiral building blocks mainly relies on asymmetric Michael addition reactions. Indeed, several examples of such reactions using chiral auxiliaries have been reported. However, all these reactions were performed in organic solvents. In this regard, we established the first asymmetric Michael addition reaction of chiral nickel(II) glycinate with nitroalkenes in pure water (Scheme 8).[68] In this process, the carbon–carbon bond and two stereogenic centers are efficiently created in a single reaction with a high control of the relative and absolute stereochemistry. The reactions were efficient when performed with electron-deficient, electron-rich, and sterically hindered nitroalkenes and provide functionalized Michael products with excellent diastereoselectivities. A broad range of aryl-, heteroaryl-, and alkyl-derived nitroalkenes can be employed under operationally simple and safe conditions.

3.4 Linear ω-Trifluoromethyl Containing Amino Acids

In the past decade, fluorine-containing analogs of natural compounds have become privileged targets in bioorganic and medicinal chemistry aimed at the rational design of potent and highly selective biologically active compounds.[69–73] Due to the special role of amino acids in various areas of health-related sciences, synthesis of fluorinated α- and β-amino acids has been of particular importance.[74,75] One particular type, linear ω-trifluoromethyl-containing α-amino acids, is of considerable interest for peptide design due to the strong steric and electrostatic requirements of the trifluoromethyl group. However, asymmetric synthesis of this type of amino acid rarely features operationally convenient synthetic methods based on readily available and inexpensive starting materials. We developed an asymmetric alkylation reaction between the nickel(II) complex of the Schiff base of glycine and alanine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino] benzophenone **12** and ω-trifluoromethyl alkyl iodides **26**, allowing for an efficient access to the enantiomerically pure, linear ω-trifluoromethyl-containing amino acid **28a** (R = H) as well as the previously unknown α-methyl derivative **28b** (R = Me) (Scheme 9).[76] The asymmetric alkylation reaction was performed at room temperature under operationally convenient conditions. The simplicity of the experimental procedures and high stereochemical outcome (yields up to 90% and diastereoselectivity up to 99%) of the presented method render these fluorinated amino acids readily available for systematic medicinal chemistry studies and *de novo* peptide design.



Scheme 10. Asymmetric synthesis of β-substituted tryptophans *via* Michael addition of a chiral nickel(II) complex with sulfonylindoles.



Scheme 11. Synthesis of (2*S*)-2-amino-3,3-bis(4-fluorophenyl) propanoic acid (*S*)-**34**.

3.5 *Optically Active Heterocyclic Amino Acids*

Optically active heterocyclic amino acids are very attractive motifs in organic synthesis because of their wide-ranging biological significance and high versatility as synthetic building blocks.[77–80] Likewise, β-substituted tryptophan analogs are important building blocks of many bioactive compounds and natural products, such as celogentin C, stephanotic acid, hemiasterlin, milnamide A, and other alkaloids. The development of efficient and practical catalysts for the asymmetric synthesis of β-substituted tryptophans is of considerable interest to both academia and industry. We also successfully applied the chiral nickel(II) complex of the Schiff base of glycine **12** with sulfonylindoles **29** to the enantio- and diastereoselective synthesis of *syn*-configured β-substituted toryptophans *via* the asymmetric Michael addition (Scheme 10).[81] A broad range of aryl-, heteroaryl-, and alkyl-derived sulfonylindoles could be employed under operationally simple and mild conditions. The resulting adducts were readily converted to *syn*-β-substituted tryptophans in 96% yield, indicating that the proposed method is a highly efficient route to chiral *syn*-β-substituted tryptophans.

4. Application of Nickel(II) Complexes to Synthesize Bioactive Compounds

DPP IV inhibitors are now of great importance in the treatment of type-2 diabetes.[82,83] The chiral amino acid (2*S*)-2-amino-3,3-bis(4-fluorophenyl) propanoic acid (*S*)-**34** is a key intermediate in the synthesis of denagliptin, a well-known DPP IV inhibitor as oral medication of type-2 diabetes being developed by Glaxo-SmithKline. A diastereoselective, cost-efficient synthetic procedure for (*S*)-**34** was developed by alkylating a nickel(II) glycine equivalent derived from (*S*)-2-[(*N*-benzylprolyl) amino] benzophenone [(*S*)-BPB] (Scheme 11).[84] The alkylated product was then decomposed to isolate the target amino acid (*S*)-**34** (*ee* >99%) and ligand (*S*)-BPB, which can be reused in subsequent reactions. The enantiomer (*R*)-**34** and racemate (*rac*)-**34** were synthesized from their corresponding nickel(II) glycine equivalents. Denagliptin diastereomers, derived from the key intermediates (*S*)-**34**, (*R*)-**34**, and (*rac*)-**34** were synthesized, and their dipeptidyl peptidase IV inhibitory activities were investigated. These findings are important in the design and synthesis of DPP IV inhibitors.

5. Conclusion

Synthesis of chiral amino acids *via* nickel(II) complexes features high selectivity, high yield, easy recovery of chiral ligands, low cost, and simple operation. Especially, chiral nickel(II) complex can act as a stereocontroller for the asymmetric synthesis of optically active amino acids. In recent years, we have developed several efficient and practical protocols for the asymmetric synthesis of α,β-diamino acid, 3-aminoaspartate, 4-substituted glutamic acid, ω-trifluoromethyl-containing amino acid, β-substituted tryptophans, and β-substituted-α, γ-diamino acids, as well

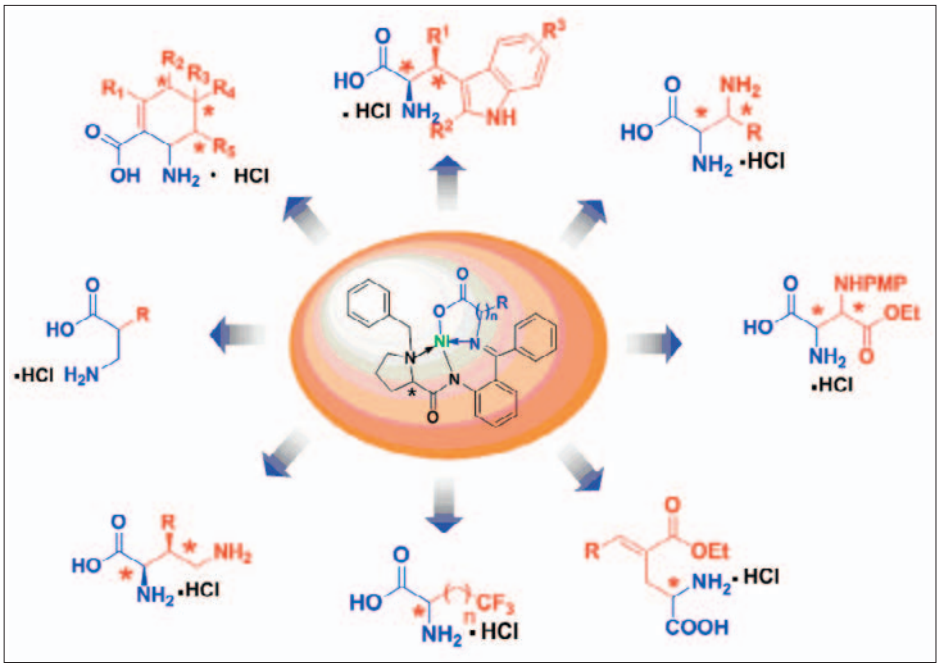


Fig. 2. Application of the nickel(II) complex to efficient synthesis of amino acids.

as the DPP IV inhibitor denagliptin *via* nickel(II) complexes (Fig. 2). Despite the considerable effort during the past years, more generally applicable and more efficient methods for stereoselective synthesis of diversified amino acids are still in high demand, and new progress is anticipated. Therefore, the search for cost-saving and mild chiral auxiliary reagents with high stereoselectivity is the most important direction of future development. More efforts are needed to focus on expanding the types of modified ligands, enhancing the reaction activity and scope, exploring reaction possibilities and application to synthesize natural products and bioactive molecules.

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