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Toward design of a practical methodology for stereocontrolled synthesis of χ-constrained pyroglutamic acids and related compounds. Virtually complete control of simple diastereoselectivity in the Michael addition reactions of glycine Ni(II) complexes with *N*-(enoyl)oxazolidinones

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Abstract

A Ni(II) complex of the Schiff base of glycine with *o*-[*N*-α-picolylamino]benzophenone or -acetophenone as a nucleophilic glycine equivalent, and *N-trans*-enoyloxazolidinones, as a derivative of an α,β-unsaturated carboxylic acid, were found to be the substrates of choice in the corresponding Michael addition reactions. The reactions proceed at room temperature in the presence of catalytic amounts of DBU to afford quantitatively a virtually diastereocomplete formation of the corresponding addition products with (2*R**,3*R**) or (2*R**,3*S**) relative configuration, depending on the nature of the starting *N*-enoyloxazolidinones. Acidic decomposition of the products followed by treatment of the reaction mixture with NH_4OH gives rise to the corresponding diastereomerically pure 3-substituted pyroglutamic acids.

Keywords: amino acids; amino acid derivatives; asymmetric synthesis; addition reactions; nickel; mechanism.

Sterically constrained, tailor-made amino acids are of paramount importance in the de novo design of peptides with a pre-supposed pattern of biological and biophysical properties, and ultimately for the development of a new generation of highly selective and potent peptide-based drugs.[1] Systematic studies into the chemical–physical basis for peptide-mediated biological information transfer, as a function of the topographical properties and three-dimensional structures of peptide molecules, critically need readily available and structurally varied amino acid analogues in optically pure form and on multi-gram scales. Our current efforts in this field are focusing on the stereocontrolled synthesis of χ-constrained pyroglutamic acids which, apart from their own promising applications to peptide design, are key compounds for a whole family of corresponding glutamic acids, glutamines and prolines, all of which

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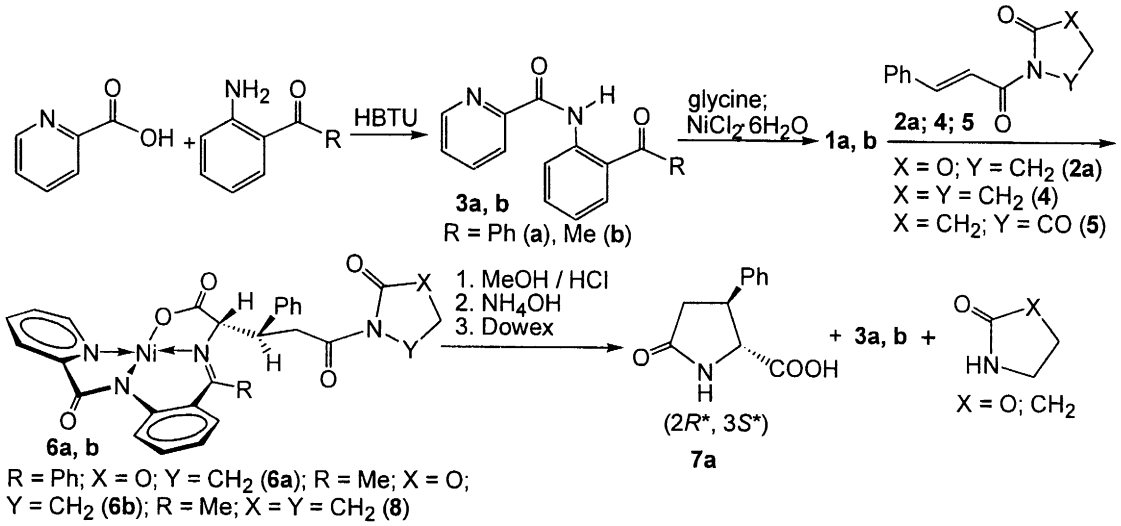
are extremely important structural units for rational modification of the conformational and topographical features of peptide and peptidomimetic molecules.[2]

Michael addition reactions between a nucleophilic glycine equivalent and an α,β-unsaturated carboxylic acid derivative have been shown to be a generalized approach to 3-substituted glutamic/pyroglutamic acids.[3] Although some of the diastereoselective Michael addition reactions reported in the literature excel in chemical yields and a degree of induced stereocontrol, their synthetic value is often compromised by incomplete diastereoselectivity, lack of generality, and problematic applicability for large-scale synthesis. Thus, we set ourselves a goal to develop a new protocol for Michael addition reactions which would be experimentally simple (room temperature reactions with no air/moisture sensitive reagents) and allowing for generalized access to the target amino acids with complete chemical yield and stereochemical control. In this Communication we report that the reactions between a Ni(II) complex of the Schiff bases of glycine **1a**,**b**, as a nucleophilic glycine equivalent, and *N-trans*-enoyloxazolidinones **2**, as derivatives of α,β-unsaturated carboxylic acids, meet the above requirements, and provide the basis for a highly practical approach to the target amino acids **7** (Scheme 1).



Scheme 1.

The origin of diastereoselectivity in Michael addition reactions, as a case of coupling of two unsymmetrically substituted trigonal centers, has been extensively studied.[2,3] Analysis of the literature data[2–4] reveals that the geometric and conformational homogeneity of an enolate derived from a glycine equivalent and an α,β-unsaturated carboxylic acid derivative, respectively, would have a major impact on the stereochemical outcome of the reaction. Thus, the best diastereoselectivity achieved so far in these type of Michael addition reactions has been reported by Seebach et al. who employed 2,6-di-*t*-butyl-4-methoxyphenyl esters as 'sterically protected but electronically effective' Michael acceptors.[3d] Unfortunately, the difficulties associated with the preparation of these derivatives and deprotection of the carboxylic function via Ce(IV) oxidation limits the synthetic value of the 2,6-di-*t*-butyl-4-methoxyphenyl esters, in particular, for large-scale preparations. Considering other α,β-unsaturated carboxylic acid derivative as candidates for an ideal Michael acceptor our attention was directed to the readily available and inexpensive *N-trans*-enoyloxazolidinones **2** (Scheme 1), which are thought to exist exclusively in the *s-trans* conformation by virtue of unfavorable electrostatic repulsive interactions between the two carbonyl groups.[5] As to the choice of a nucleophilic glycine equivalent, our major concern was its ability

to form geometrically homogeneous enolates on its own, without external chelating agents. The latter requirement could be met by a cyclic structure of a glycine equivalent. Among the literature data on various glycine derivatives we took note of the recent publication by Belokon et al. on a Ni(II)-complex of the Schiff base of alanine with *o*-[*N*-α-picolylamino]benzaldehyde.[6] Following also our own experience in the chemistry of Ni(II)-complexes of amino acids,[3] we designed and synthesized Ni(II)-complexes of Schiff bases of glycine with *o*-[*N*-α-picolylamino]benzophenone and -acetophenone **1a**,**b** (Scheme 1). Our first examination of the reaction between the complex **1a** and *N*-(*trans*-cinnamoyl)oxazolidinone **2a** gave unexpectedly excellent results. The reaction, catalyzed by 15 mol% DBU, was completed at rt in 50 min affording the diastereomerically pure product **6a** in quantitative chemical yield (Table 1, entry 1). The stereochemical outcome of the reaction was found to be kinetically controlled, as a resubmission of pure product **6a** to the original reaction conditions did not give starting compounds **1a** and **2a** in detectable amounts (^{1}H NMR, 500 MHz). Compound **6a** was isolated simply by pouring the reaction mixture into water followed by a filtration of the crystalline material. Without any purification, complex **6a** was decomposed to give the (2*R**,3*S**)-configured pyroglutamic acid **7a** along with quantitative recovery of ligand **3**.[7] Inspired by this outcome, we studied the addition reactions between Ni(II)-complexes **1a**,**b** and *N*-cinnamoyl derivatives of 3-oxazolidin-2-one **2a**, pyrrolidin-2-one **4** and succinimide **5**, to find the best combination of nucleophile/electrophile, and to get some insight into the origins of stereogenesis in these reactions (Table 1). Thus, under the same conditions, reaction of oxazolidinone **2a** with the acetophenone derived complex **1b** occurred at a substantially higher reaction rate (entry 2) furnishing the corresponding (2*R**,3*S**)-diastereomer as the sole product in quantitative chemical yield. On the other hand, reaction of the pyrrolidin-2-one derived electrophile **4** with complex **1b** had a decreased rate of reaction, but afforded the product **8** with the same excellent stereochemical outcome (entry 3). Surprisingly, the reaction between complexes **1a**,**b** and the succinimide derivative **5** did not take place at all, even under forcing conditions (entry 4). These results suggested that both complexes **1a** and **1b** provide virtually complete diastereoselectivity in the reactions with *N*-cinnamoyl derivative **2a**. In terms of reactivity, **1b** should be superior to **1a**, which could be rationalized by assuming that **1b** has a less sterically shielded glycine moiety. However, the observed reactivity in the reactions of complex **1b** with 3-oxazolidin-2-one **2a**, pyrrolidin-2-one **4** and succinimide **5** is quite intriguing, because the electrophilicity of the C,C double bond of these compounds increases in the same order.

Table 1
The additions of oxazolidinones **2a**, **4**, **5** with Ni(II)-complexes **1a**,**b**[a]

entry	**1a**,**b**	**2a**, **4**, **5**	time, min
1	**1a**	**2a**	50
2	**1b**	**2a**	20
3	**1b**	**4**	35
4	**1b**	**5**	NR

[a] All reactions were conducted under same conditions: 15 mole % of DBU, in DMF, rt, ratio of **1a**,**b**/**2a**,**4**,**5** 1/1.
According to ^{1}H-NMR analysis of the crude mixtures, in all reactions but entry **4** only one diastereomer was formed in quantitative chemical yield.

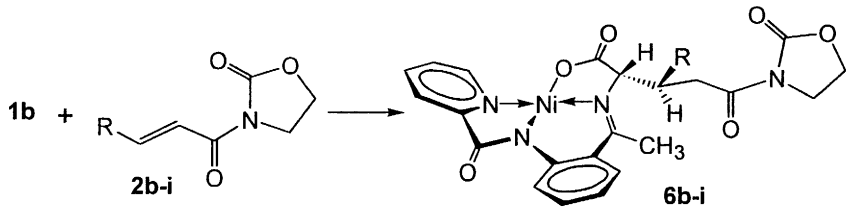
Having selected complex **1b** and the oxazolidinones **2** as the best glycine and α,β-unsaturated

carboxylic acid derivatives, respectively, we studied the generality of this reaction. We investigated additions between **1b** and a series of *N*-(enoyl)-3-oxazolidin-2-one derivatives **2** (Scheme 2, Table 2) bearing in the β-position a phenyl ring with electron withdrawing (CF_3, **2b**) and electron donating groups (OMe, **2c**), and with bulky β-**2d** and α-naphthyl **2e**, and electron rich (*N*-Mts-β-indolyl, **2f**) and electron deficient (C_6F_5, **2g**) aromatic rings, as well as alkyl substituents Me **2h** and *n*-Pr **2i**. To our satisfaction, all reactions, occurred under the same conditions at rt, and gave rise to only one diastereomer in quantitative yield regardless of the steric or electronic nature of the substituent of the starting oxazolidinone **2b–i**. However, the nature of the substituent had a substantial effect on the reaction rate. Thus, the addition of the trifluoromethyl-containing **2b** (Table 2, entry 1) and pentafluorophenyl derivatives **2g** (entry 6) with complex **1b** occurred almost instantly, while the reactions of compounds **2c** and **2f**, bearing electron donating substituents, were markedly slower (entries 2 and 5). Increase in the steric bulk of the subsituent also decreased the reaction rates, which was observed in both the aromatic (entries 3 and 4) and aliphatic series (entries 7 and 8).

Table 2
The additions of **2b–i** with **1b**[a]

entry	**2b-i**	time, min
1	**2b**	5
2	**2c**	120
3	**2d**	25
4	**2e**	90
5	**2f**	150
6	**2g**	6
7	**2h**	10
8	**2i**	150

[a] All reactions were conducted under same conditions: 15 mole % of DBU, in DMF, rt, ratio of **1b**/**2b-i** 1/1.1. According to ^{1}H-NMR analysis of the crude mixtures, in all reactions only one diastereomer was formed in quantitative chemical yield.



R = 4-CF_3-C_6H_4 (**b**); 4-MeO-C_6H_4 (**c**); β-Naphthyl (**d**); α-Naphthyl (**e**); *N*-Mts-β-indolyl (**f**); C_6F_5 (**g**); Me (**h**); *n*-Pr (**i**)

Scheme 2.

In conclusion, we have found a unique combination of nucleophilic glycine and α,β-unsaturated carboxylic acid derivatives allowing the corresponding Michael addition reactions to proceed at room temperatures in the presence of a catalytic amount of organic non-chelating base with virtually complete

diastereoselectivity and quantitative chemical yield. Moreover, the reactions showed extraordinary generality, suggesting an intriguing transition state for the stereoselective step, which is currently under investigation. Taking into account that both the Ni(II)-complexes **1** and the *N*-(enoyl)-3-oxazolidin-2-ones **2** can easily be prepared in chiral versions, or a chiral base could be used in the place of DBU, the discovered process provides a realistic basis for a truly practical entry into a large family of β-substituted and stereochemically defined amino acids of synthetic and biomedicinal importance.

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7. To a stirred suspension of complex **1b** (1.64 g, 4.64 mmole) and oxazolidinone **2a** (1.01 g, 4.64 mmole) in DMF (18 mL), DBU (0.107 g, 0.696 mmole) was added at ambient temperature. The progress of the reaction was monitored by TLC and upon completion the reaction mixture was poured into water (200 mL). The resultant crystalline product was filtered and washed thoroughly with water. The product **6b** (2.63 g, 4.6 mmole) was dried in the air, dissolved in methanol (60 mL) and added to a 1/1 mixture (120 mL) of 3 *N* HCl and water at 70°C. After the decomposition of the complex was completed (disappearance of the orange color) the mixture was evaporated and treated with conc. ammonia and extracted with $CHCl_3$ to give ligand **3b** (1.07 g, 96% yield). The aqueous phase was evaporated and the solid residue was washed with acetone to remove 2-oxazolidinone (0.4 g, 99% yield). The resultant product was dissolved in water and loaded on Dowex ion-exchange resin column, which was washed with H_2O:EtOH (2:1). The acidic fraction which emerged from the column was collected and evaporated to afford (2*R**,3*S**)-3-phenylpyroglutamic acid **7a** (0.85 g, 90% yield). The product was recrystallized from THF/hexanes to give the analytically pure sample of **7a**.