# Rational Design of Highly Diastereoselective, Organic Base-Catalyzed, Room-Temperature Michael Addition Reactions[1]

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Via the rational design of a single-preferred transition state, stabilized by electron donor−acceptor-type attractive interactions, structural and geometric requirements for the corresponding starting compounds have been determined. The Ni(II) complex of the Schiff base of glycine with *o*-[*N*-α-picolylamino]acetophenone, as a nucleophilic glycine equivalent, and *N*-(*trans*-enoyl)oxazolidin-2-ones, as derivatives of an α,*β*-unsaturated carboxylic acid, were found to be the substrates of choice featuring geometric/conformational homogeneity and high reactivity. The corresponding Michael addition reactions were found to proceed at room temperature in the presence of catalytic amounts of DBU to afford quantitatively the addition products with virtually complete diastereoselectivity. Acidic decomposition of the products followed by treatment of the reaction mixture with $NH_4OH$ gave rise to the diastereomerically pure 3-substituted pyroglutamic acids.

## Introduction

The Michael addition reaction is one of the most synthetically powerful and versatile ways to form a C,C bond.[2] Of particular interest for us are the reactions between *n*ucleophilic *g*lycine equivalents and α,*β*-*u*nsaturated *c*arboxylic *a*cid derivatives (NGUCA reactions), the most methodologically concise and generalized approach to the family of five-carbon-atom amino acids such as glutamic and pyroglutamic acids, glutamines, prolines, ornithines, and arginines.[3−5] All of these amino acids play a critical pharmacophore role in numerous natural peptides and therefore are a focus of current peptide research.[6] Following the introduction by our group of the local constraint paradigm for understanding peptide structure−activity relationship and in de novo peptide design,[7] we have needed a series of novel, stereochemically defined and *χ*-constrained[8] derivatives of glutamic/pyroglutamic acids to implement some of our current projects in the understanding of the chemical−physical basis of peptide-mediated biological information transfer.[9]

NGUCA reactions have been extensively studied by many research groups, and a plethora of original approaches have been developed to control both simple and face diastereoselectivities of the additions.[3,10] Though some of these methods excel in chemical yields and a degree of stereocontrol, their synthetic value is often compromised by incomplete stereoselectivity, lack of generality, and most importantly, problematic applicability for large-scale preparations. Therefore, we set for

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ourselves a goal to develop a new protocol for Michael addition reactions which would be experimentally simple and allow for generalized access to the target amino acids with nearquantitative chemical yields and complete stereochemical control. In this paper, we describe in full[12] the basic, paramount steps toward this goal, the design of a starting nucleophilic glycine equivalent and α,β-unsaturated carboxylic acid derivatives which allow the corresponding addition reactions to proceed with *virtually complete* simple diastereoselectivity (>98% de) at *room temperature* in the presence of *nonchelating organic bases*.

## Results and Discussion

Analysis of the relevant literature reveals that, in all previously studied NGUCA reactions, application of lithium reagents as bases (*n*-BuLi) or additives (LiCl) was of critical importance to obtain synthetically useful stereochemical outcomes.[3,10] The well-defined mechanism of these addition reactions postulates the formation of highly organized transition states (TSs) in which the lithium cation plays a paramount role, chelating the glycine enolate oxygen and nitrogen, as well as the oxygen of the Michael acceptor carbonyl group. Organic bases, for instance, triethylamine (TEA) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), are ineffective for playing the role of chelating agent. Therefore, not surprisingly, organic base-catalyzed and highly diastereoselective NGUCA reactions have not been reported so far.[3,10] Obviously, application of organic bases in NGUCA reactions would necessitate the development of a new and nontraditional way to provide the formation of highly organized TSs. Besides the role of chelated TSs, the importance of stereochemical discriminations between substituents on the starting nucleophilic glycine equivalent and on the α,β-unsaturated carboxylic acid derivatives was also well defined.[3,10] Surprisingly, a geometric/conformational homogeneity of the starting compounds, as one more important factor that can contribute to the origin of simple diastereoselectivity in the NGUCA reactions, has not received much attention in the literature.[3,10] Analysis of the stereochemical outcomes of reported NGUCA reactions suggests that the geometric/conformational properties of the starting compounds might be regarded as a critical factor in determining the diastereoselectivity of the reactions and, therefore, should be a central issue in design.

Considering the NGUCA reactions as a case of coupling of two unsymmetrically substituted trigonal centers, one can expect up to 18 TSs to be involved in determining the stereochemical outcome of the reaction. Such a large number of theoretically possible TSs is a result of the fact that both starting nucleophilic glycine equivalent, in its enolate form, and Michael acceptor can react in two geometric (cis vs trans) forms and in two conformations (s-cis vs s-trans), respectively. If we can control geometric homogeneity of the glycine enolate and conformational homogeneity of the Michael acceptor, then the number of possible TSs will be substantially reduced to only 6. Further reduction of the possible TSs, to only one out of six, is a much more formidable task. This problem might be solved by the right choice of substitution pattern on the starting nucleophilic glycine equivalent, and Michael acceptor, that will give preference to a single TS as a result of steric or electron donor−acceptor type attractive interactions. Apart from stereochemical considerations, our design of organic base-catalyzed, room-temperature reactions involves also the issue of reactivity, C−H acidity of the glycine methylene moiety and electrophilicity of the Michael acceptor C,C double bond. Thus, both starting nucleophilic glycine equivalent and Michael acceptor should possess high reactivity to be able to react in the presence of relatively weak organic bases. With this set of requirements for starting compounds, we started our design using available literature data and molecular modeling/calculations.

**Design of the Nucleophilic Glycine Equivalent.** A number of potential candidates for a nucleophilic glycine equivalent of choice was substantially narrowed by the requirements for geometric homogeneity and high C−H acidity. The latter could be provided by the presence of a strong electron-withdrawing Schiff base function, and the former by a cyclic structure of the glycine equivalent. Taking advantage of Professor Belokon's studies,[10h,o,13,14] as well as our extensive experience in the chemistry of Ni(II) complexes of α-amino acids,[1a,b,15,16] we designed and synthesized a new Ni(II) complex of glycine Schiff base derived from 2-aminoacetophenone **2** (Scheme 1). Preparation of complex **2** is very simple and can be easily performed on a multigram (50 g and more) scale. The glycine complex **2** is reasonably soluble in polar organic

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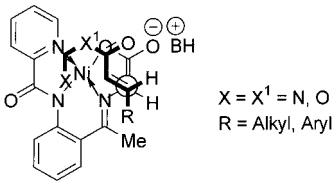
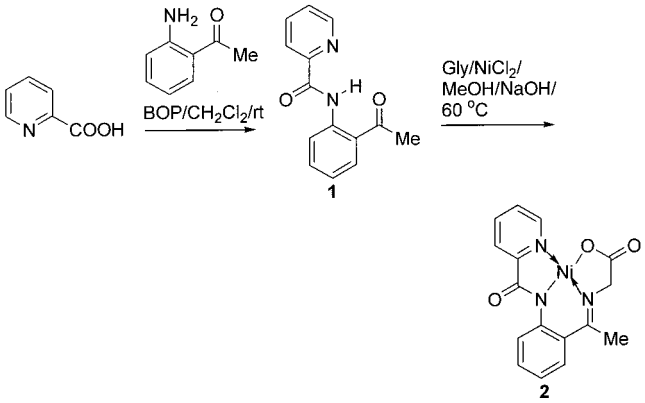



**Figure 1.** Design of the Michael acceptor.

**Scheme 1**




solvents, diamagnetic, and can be stored in crystalline form in the air for at least one year without any signs of partial decomposition. At room temperature and in the presence of TEA (slow) and DBU (fast), the methylene protons of complex **2** underwent complete deutero-exchange, suggesting that the corresponding enolate could be easily generated under mild conditions using these organic bases. Due to the cyclic structure of complex **2**, the corresponding enolate can be generated only in *cis*-form and thus, complex **2** perfectly meets the requirements for high reactivity and enolate geometric homogeneity.

**Design of the Michael Acceptor.** Apart from the required characteristics for high reactivity and geometric homogeneity, the structure of complex **2** possesses one more unique feature, the positively charged Ni(II) atom, a potential center to coordinate a negatively charged species. As discussed above, electron donor−acceptor-type attractive interactions, which provide a way to give thermodynamic preference for a single TS, could be realized involving the Ni atom in complex **2**.[17] To this end, we considered all possible TSs representing the interaction between complex **2** and various hypothetical Michael acceptors in their s-cis or s-trans conformations. As a result, we came up with a potential structure for the corresponding Michael acceptors shown in Figure 1. In our model, the carbonyl group of the Michael acceptor is located in close proximity to the enolate oxygen. That would allow the reactions to occur with a thermodynamically advantageous minimum charge separation.[10b,g] Next, the group $X^1$ should be oxygen or nitrogen to afford, upon hydrolysis, the corresponding glutamic/pyroglutamic acid. Finally, the group X, located under or above the Ni(II) ion, should contain an atom, for instance O or N, capable of electron donor−acceptor type attractive interactions

(17) Electron donor−acceptor type attractive interactions between the nickel (II) ion and fluorine atoms, were shown to be a critical factor controlling virtually complete diastereoselectivity in the aldol addition reaction between trifluoroacetone and Ni(II) complex of the Schiff bases of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (see ref 18).

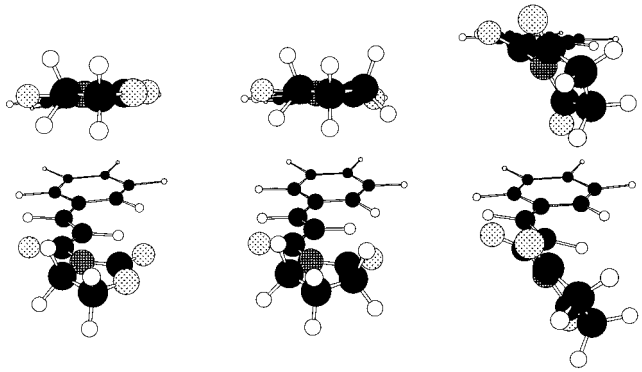
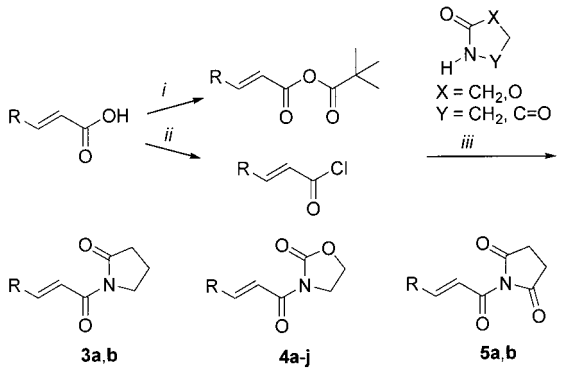


**Figure 2.** X-ray structures of compounds **3b**, **4b**, and **5b**.

**Scheme 2**[a]




[a] Key: (i) $Me_3CCOCl$; (ii) $SOCl_2$; (iii) *n*-BuLi. R = Me (a), Ph (b), *n*-Pr (c), *i*-Pr (d), *β*-naphthyl (e), α-naphthyl (f), 4-$CF_3$-$C_6H_4$ (g), 4-MeO-$C_6H_4$ (h), *N*-Mts-*β*-indolyl (i), $C_6F_5$ (j).

with the nickel. Using this pattern of structural features for the ideal Michael acceptor, and bearing in mind the requirement for high electrophilicity of the C,C double bond and conformational homogeneity, we considered numerous derivatives of α,*β*-unsaturated carboxylic acid derivatives. Finally, we identified a group of cyclic imides **3**−**5** shown in Scheme 2, as potential candidates for the ideal Michael acceptor. Our reasoning leading to compounds **3**−**5**, in particular **3** and **4**,[19] turned out to be very successful, and we were surprised to find out that these derivatives of α,*β*-unsaturated carboxylic acids have never been used as Michael acceptors in reactions with nucleophilic glycine equivalents.[3,10] Compounds **3**−**5** were readily prepared according to standard procedures, as depicted in Scheme 2. Single-crystal X-ray analyses of compounds **3b**, **4b,** and **5b** (Figure 2), revealed an important fact that all three imides exist exclusively in the *s*-cis conformation. However, while molecules of **3b** and **4b** are virtually flat, the succinimide derivative **5b** is twisted at the acyclic amide bond [torsion angle C2−N1−C8−C10 of 40.1(4)°]. The angle between the best planes through the five- and six-membered rings is 1.2(2)° (**3b**), 7.6(1)° (**4b**) and 60.2(2)° (**5b**). On the other hand, the five-membered rings in **3b** and **4b** have an envelope structure, while in **5b** this ring is planar [maximum

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(19) Apart from the perfect conformational/electronic properties of these compounds (see text), the ready availability of their chiral versions renders cyclic imides **3** and **4** particularly promising Michael acceptors.

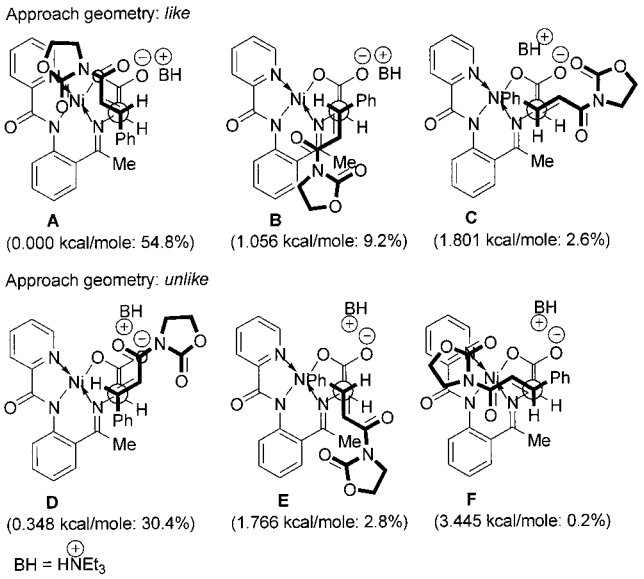


**Figure 3.** Possible TSs in the addition between **2** and **4b**.

deviation of 0.029(2) Å for atom N1]. Conformational *s*-cis homogeneity of compounds **3b**, **4b** and **5b** is a result of nonbonding steric repulsive interactions between the *β*-hydrogen of the C,C double bond and the carbonyl oxygen of the pyrrolidin-2-one (**3**), oxazolidin-2-one (**4**) or succinimide (**5**) ring, and electrostatic repulsive interactions between the oxygens of the carbonyl groups in **3b**, **4b,** and **5b**.[20] In addition to the conformational homogeneity of the α,*β*-unsaturated carboxylic moiety in compounds **3**−**5**, the electrophilicity of the C,C double bond in **3**-**5** is substantially enhanced, as compared with the corresponding esters. According to the p$K_a$ data (in DMSO),[21] the pyrrolidin-2-one (p$K_a$ = 24.1), oxazolidin-2-one (20.5), and succinimide (14.7) rings are substantially stronger electron-withdrawing substituents, as compared with alkoxy groups (MeOH, 27.9) and their enhancing effect on electrophilicity of the C,C double bond is comparable with that of a phenoxy group (18.0).[22] Thus, the Michael acceptors **3**−**5**, comparing with the cyclic imide moiety, meet the necessary requirements for conformational homogeneity and high reactivity of the C,C double bond.

**Mechanistic Considerations.** Since both starting compounds, glycine complex **2**, and Michael acceptors **3**−**5**, are geometrically/conformationally homogeneous, six theoretically possible TSs could be involved in determining the stereochemical outcome of the corresponding addition reactions. Figure 3 shows the model TSs **A**−**F** constructed for the reaction of glycine complex **2** with the cinnamoyl derived oxazolidin-2-one **4b**. According to the molecular mechanics calculations of these TSs, accounting only for steric but not electrostatic interactions (see the Experimental Section), TS **A** (0.000 kcal/mol, population 54.8%), in the series of the TSs with approach geometry *like*, and TS **D** (0.348 kcal/mol, 30.4%), in the series of TSs with approach geometry *unlike*, might be substantially favored over the rest of the TSs. TSs of type **A** and **D**, with the enolate oxygen and the carbonyl of Michael acceptor in close proximity to each other, are routinely used to account for the stereochemical outcome of the addition reactions between nucleophilic glycine equivalents and α,*β*-unsaturated carboxylic esters.[1a,b,10] In this case, the diastereoselectivity of the additions was shown to be a result of nonbonding stereochemical discriminations between the substituents on both starting compounds. Thus, if the stereochemical outcome of the addition reactions under study were governed exclusively by steric interactions, two diastereomeric products would be obtained in a ratio of roughly 1:2. This outcome stands in a good agreement with the 70:30 ratio of the corresponding (2*S*,3*R*)/(2*S*,3*S*)-diastereomers obtained in the DBU-catalyzed addition reactions between Ni(II)-complex of the Schiff bases of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone and the esters of cinnamic acid.[23] In contrast, according to our design, the preference for a single TS would not only be steric in origin, but also electron donor−acceptor type attractive interactions between, for example, the oxazolidin-2-one carbonyl group of **4b** and the Ni(II) atom of complex **2**, situated in close proximity to each other in TS **A** (Figure 3). If the designed interactions do take place, then TS **A** would be substantially thermodynamically favored relative to TS **D**, and the addition reactions might proceed with high diastereoselectivity. Interestingly, the calculations also suggested that for the reaction of complex **2** with succinimide derivative **5**, TS **A** cannot be formed due to the nonflat geometry of the latter. In contrast, the flat geometry of pyrrolidin-2-one derivatives **3**, similar to oxazolidin-2-one-containing **4**, allows minimization of steric interactions in both TS **A** and TS **D**.

**Michael Addition Reactions between Glycine Complex 2 and α,*β*-Unsaturated Carboxylic Acid Derivatives 3**−**5.** The choice of the solvent, as a medium for the addition reactions, turned out to be limited to aprotic solvents only. We found that when alcohols (for instance methanol) were used as a reaction medium, the oxazolidin-2-one derivative **4** easily underwent nucleophilic substitution of the oxazolidin-2-one moiety by the corresponding alkoxy group, generated in the presence of the base (for instance DBU). Chloroform, the best solvent for Ni(II)-complexes of type **2**, was found to be unsuitable, as the addition reactions did not proceed in this solvent, neither in the presence of TEA or DBU. Finally, *N*,*N*-dimethylformamide (DMF) was found to be a solvent of choice.

First we tried the reaction between complex **2** and *N*-(*trans*-crotonyl)pyrrolidin-2-one **3**. The addition did not occur in the presence of TEA at room temperature in DMF. Attempts to conduct the reaction at higher temperature (50 °C) resulted in partial decomposition of the starting compounds. In sharp contrast, DBU, even when used in catalytic amounts (15 mol %), was effective in catalyzing the reaction at room temperature (18−23 °C) which proceeded smoothly to completion in 2.5 h affording a single diastereomer **6** (Scheme 3) in quantitative chemical yield (Table 1, entry 1). Being satisfied and excited with the desired virtually complete diastereoselectivity and excellent chemical yield obtained in this reaction, we studied the additions of complex **2** with the two other designed Michael acceptors **4** and **5**. The reaction of **2** with *N*-(*trans*-crotonyl)oxazolidin-2-one

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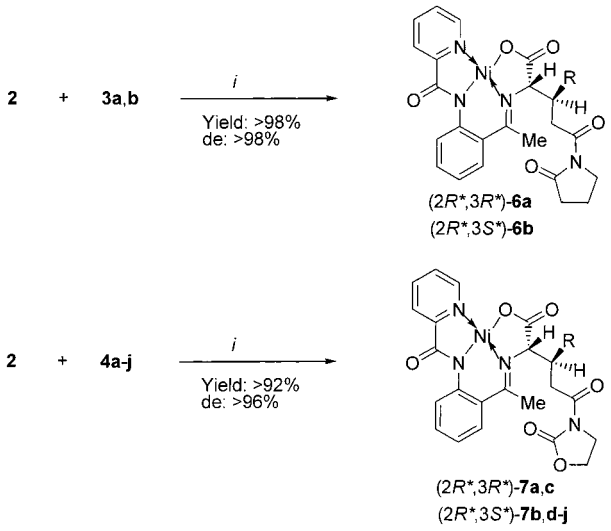
**Scheme 3**[a]




[a] Key: (i) DMF, DBU (15 mol %), rt (18−23 °). R = Me (a), Ph (b), *n*-Pr (c), *i*-Pr (d), *β*-naphthyl (e), α-naphthyl (f), 4-$CF_3$-$C_6H_4$ (g), 4-$MeOC_6H_4$ (h), *N*-Mts-*β*-indolyl (i), $C_6F_5$ (j).

**Table 1. Addition Reactions of Ni(II) Complexes 2 with Michael Acceptors 3a,b and 4a,b**[a]

| | | | products **6**, **7a,b** | | |
|---|---|---|---|---|---|
| entry | **3a,b/4a,b** | time | yield,[b] % | de,[c] % | config-on[d] |
| 1 | **3a** | 2.5 h | 98 | >98 | (2*R**,3*R**)-**6a** |
| 2 | **4a** | 10 min | 99 | >98 | (2*R**,3*R**)-**7a** |
| 3 | **3b** | 35 min | 99 | >98 | (2*R**,3*S**)-**6b** |
| 4 | **4b** | 20 min | 99 | >98 | (2*R**,3*S**)-**7b** |

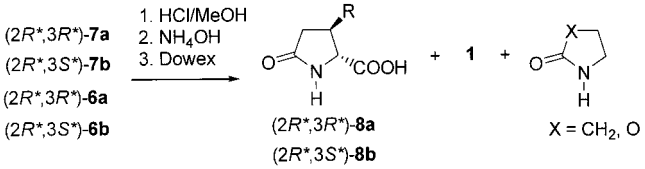
[a] All reactions were run in DMF in the presence of 15 mol % of DBU at ambient temperature. Ratio **2**/**3,4** 1/1.05−1.1. [b] Isolated yield of crude product. [c] Determined by NMR (500 MHz) analysis of the crude reaction mixtures. [d] Relative configuration of the products was determined by comparison of the spectral characteristics of the corresponding pyroglutamic acids **8**, isolated from complexes **6** and **7**, with the literature data; see also the text.

derivative **4a**, conducted under same conditions, occurred at a surprisingly high rate being completed in just 10 min. NMR analysis of the crude product revealed that only diastereomeric product **7a** was obtained in quantitative chemical yield (entry 2). In sharp contrast, the addition between complex **2** and succinimide derivative **5** did not proceed at all, even under forcing reaction conditions (1 mole DBU, 50 °C).

Next, we investigated a series of the reactions between glycine complex **2** and cinnamic acid derived Michael acceptors **3b**, **4b**, and **5b**, conducted under the same conditions (Scheme 3). Addition of complex **2** with pyrrolidin-2-one **3b** occurred at a substantially higher rate, as compared with the crotonyl derivative **3a** (entry 3 vs 1), giving rise quantitatively to a single diastereomer **6b**. In contrast, the reaction between complex **2** and oxazolidin-2-one **4b** proceeded slower, as compared with the methyl containing derivative **4a** (entry 4 vs 2), but faster than addition of **2** with **3b** (entry 4 vs 3). Similar to the failed addition between complex **2** and **5a**, the reaction of **2** with cinnamic acid derived **5b** also did not occur under the standard or forced conditions.

Taking into account that in a series of Michael acceptors **3**−**5**, the succinimide derivatives **5a**,**b** should be regarded as the most electrophilic, the negative outcome of their reactions with complex **2** was quite unexpected. The only plausible rationale that can be provided at this

**Scheme 4**




stage might be based on, as revealed by X-ray analysis (Figure 2), the nonplanar geometry of derivatives **5a**,**b**. This phenomenon might be general in nature,[24] raising an interesting issue of topographically controlled reactivity.

Resubmission of pure products **6a**,**b** and **7a**,**b** to the original reaction conditions did not give the starting compounds in detectable amounts ($^1$H NMR, 500 MHz). These results suggested that the reactions are rather irreversible and thus, the stereochemical outcome of the successful reactions between complex **2** and derivatives **3a**,**b**, **4a**,**b** is most likely kinetically controlled. Taking advantage of the fact that the data for the diastereomerically pure *β*-methyl- and *β*-phenyl-substituted pyroglutamic acids are available from the literature, we decided to decompose products **6a**,**b** and **7a**,**b** to afford the corresponding pyroglutamic acids and thus, to determine the relative configuration of the products. To this end we performed preparative (3−5 g) synthesis of **6a**,**b** and **7a**,**b** which were isolated simply by pouring the reaction mixtures into water followed by a filtration of the crystalline materials. Without any purification, complexes **6a**,**b** and **7a**,**b** were decomposed to give pyroglutamic acids **8a**,**b** along with quantitative recovery of ligand **1** and the corresponding pyrrolidin-2-one or oxazolidin-2-one (see the Experimental Section) (Scheme 4). Comparison of the spectral characteristics, in particular the α-H/*β*-H coupling constants, of the obtained acids **8a**,**b** with the literature values revealed a (2*R**,3*R**)-configuration for **8a** and (2*R**,3*S**) for **8b**.[25] These data indicate that all successful additions between glycine complex **2** and Michael acceptors **3a**,**b** and **4a**,**b** might proceed exclusively through TS **A** (Figure 3), suggesting a complete success of our design.

With these excellent results in hand we next studied the generality of the method. Since the oxazolinin-2-one derived Michael acceptors **4a**,**b** were found to be superior, in terms of reactivity, over the pyrrolidin-2-one derivatives **3a**,**b** (Table 1, entry 2 vs 1, 4 vs 3), we synthesized a series of the corresponding *N*-(enoyl)oxazolidin-2-one derivatives **4c**−**j** (Scheme 2). To investigate the steric and electronic effects of the substituents on the stereochemical outcome of the addition reactions, we studied the reactions of glycine complex **2** with Michael acceptors bearing in the *β*-position various groups differing in steric bulk and electronic nature as well. Thus, in the aliphatic series, besides the methyl-substituted derivative **4a**, we studied also the reactions of Michael acceptors with *n*-Pr

(24) Taking into account that the particular planar geometry of the Ni(II) complex **2** could be a reason for the failure of the additions with **5a**,**b**, we studied the reactions of the acyclic and more flexible *N*-(diphenylmethylene)glycine ethyl ester with **5a**,**b** (DMF, rt, DBU). The results were the same; no trace of the addition products was found. As one can assume, the planar geometry, like for instance in the case of **3** and **4**, is the critical topographic requirement for TS of type **A** or **B** (Figure 4) to be formed.

(25) The (2*R**,3*S**) relative stereochemistry for the aromatic (R = Ph) derivatives is a consequence of the Cahn−Ingold−Prelog priority (see ref 26) and is stereochemically equivalent to the (2*R**,3*R**) configuration in the aliphatic (R = Me) series of compounds.

**Table 2. Addition Reactions of Ni(II) Complexes 2 with *N*-(*E*-Enoyl)oxazolidin-2-ones 4c−j[a]**

| | | | products **7c−j** | | |
|---|---|---|---|---|---|
| entry | **4c−j** | time | yield,[b] % | de,[c] % | config-on[d] |
| 1 | **c** | 2.5 h | 94 | >96 | (2*R**,3*R**) |
| 2 | **d** | 22 h | *e* | *e* | (2*R**,3*S**) |
| 3 | **e** | 25 min | 95 | >98 | (2*R**,3*S**) |
| 4 | **f** | 1.5 h | 96 | >96 | (2*R**,3*S**) |
| 5 | **g** | 5 min | >96 | >98 | (2*R**,3*S**) |
| 6 | **h** | 2 h | 92 | >96 | (2*R**,3*S**) |
| 7 | **i** | 2.5 h | 92 | >96 | (2*R**,3*S**) |
| 8 | **j** | 2 min | >96 | >98 | (2*R**,3*S**) |

[a] All reactions were run in DMF in the presence of 15 mol % of DBU at ambient temperature. Ratio **2**/**4** 1/1.05−1.1. [b] Isolated yield of crude product. [c] Determined by NMR (500 MHz) analysis of the crude reaction mixtures. [d] Relative configuration of the products was determined by comparison of the spectral characteristics of the corresponding pyroglutamic acids **8**, isolated from complexes **6a**,**b** and **7a**,**b**, with the literature data; The relative configuration of products **7c−j** was assigned by analogy; see also the text. [e] Less then 36% conversion of the starting materials. Formation of only one diastereomeric product was observed, however.

**4c** and *i*-Pr **4d** groups. In the aromatic series we chose the derivatives containing bulky *β*-**4e** and α-naphthyl groups **4f**, a phenyl ring with electron withdrawing ($CF_3$, **4g**) and electron donating groups (MeO, **4h**), electron rich (*N*-Mts-*β*-indolyl, **4i**) and electron deficient ($C_6F_5$, **4j**) aromatic rings as well.

All reactions, conducted under the same conditions (DMF, 15 mol % of DBU, r.t.), gave rise to only one diastereomer[27] in excellent yields regardless of the steric or electronic nature of the substituent of the starting oxazolidin-2-one **4c−j** (Scheme 3, Table 2). However, the nature of the substituent had a substantial effect on the reaction rate. Thus, the addition of the *n*-Pr derivative **4c** occurred at a noticeably slower rate (Table 2, entry 1) as compared with the reaction of the methyl containing derivative (Table 1, entry 2). However, the resultant product was obtained in diastereomerically pure form and with excellent chemical yield. The addition of more sterically bulky *i*-Pr derivative **4d** exposed some limitations of the method. Thus after 22 h of the reaction between complex **2** and oxazolidin-2-one **4d**, we observed less than 36% conversion of the starting materials (Table 2, entry 2). Attempts to run the reaction at higher temperature or in the presence of the equimolar amount of DBU resulted in increasing decomposition of the starting compounds. Apparently the present method could not be extended to substrates containing tertiary alkyl R groups. In the aromatic series the *β*-naphthyl derivative **4e** reacted with complex **2** at a rate comparable with that of the phenyl containing Michael acceptor **4b** (Table 2, entry 3 vs Table 1, entry 4), while the α-naphthyl **4f** addition was remarkably slower (Table 2, entry 4). These data suggest that synthesis of *o*-phenyl substituted derivatives by this method could have some limitations, while preparation of compounds containing *m*-mono- or *m*,*p*-disubstituted phenyl rings would meet no synthetic problems. Effects of the electronic properties of the substituents on the reaction rate also were found to be pronounced like the steric effects. Thus, the reactions of the derivatives containing the electron-withdrawing trifluoromethyl group on the phenyl **4g** and the electron-deficient pentafluorophenyl ring **4j** occurred almost instantly (Table 2, entries 5, 8), affording the single diastereomeric products **7g**,**j** in quantitative chemical yield. In contrast, the additions of less electrophilic derivatives bearing the electron-donating methoxy group on the phenyl **4h** and the electron-rich *β*-indolyl group **4i** proceeded at substantially slower rates (Table 2, entries 6, 7).

In conclusion, via the rational design described in this paper, we have found a unique combination of nucleophilic glycine and α,*β*-unsaturated carboxylic acid derivatives allowing us to develop for the first time Michael addition reactions proceeding with virtually complete diastereoselectivity and excellent chemical yield at room temperatures in the presence of a catalytic amounts of organic nonchelating base. Since both the Ni(II)-complexes **2** and the *N*-(enoyl)oxazolidin-2-ones **4** can be prepared easily in chiral versions, or a chiral base can could be used in the place of DBU, the discovered process provides a realistic basis for a highly practical and general entry into a large family of *β*-substituted and stereochemically defined amino acids of synthetic and biomedical importance. Future work to realize this process in an asymmetric sense is currently in progress and will be reported in due course.

## Experimental Section

**General Methods.** $^1$H, $^{13}$C, and $^{19}$F NMR (299.94 MHz), recorded using TMS, $CDCl_3$ and $CCl_3F$ as internal standards, and High Resolution Mass Spectra (HRMS) were performed on facilities available at the Department of Chemistry, University of Arizona. Melting points (mp) are uncorrected and were obtained in open capillaries. All reagents and solvents, unless otherwise stated, are commercially available and were used as received. All new compounds were characterized by $^1$H, $^{13}$C, $^{19}$F NMR and HRMS.

**X-ray Diffraction Studies.** Crystals of compounds **3b**, **4b,** and **5b** were grown from acetone. All data were collected at 16 °C on a diffractometer available at K. U. Leuven − Department of Chemistry, with graphite-monochromated Mo Kα radiation ($\lambda$ = 0.710 73 Å) in the $\omega$-scan mode ($2\theta_{max}$ = 50°). The data were corrected for Lorentz and polarization effects. The lattice parameters were calculated by least-squares refinements of 35 (**3b**), 25 (**4b**), and 30 (**5b**) reflections. The structures were solved by direct methods and refined by full-matrix least-squares techniques on $F^2$ (SHELXTL-PC)[28] to an R1 value of 0.0528 ($wR_2$ = 0.1646) for **3b**, 0.0509 ($wR_2$ = 0.1195) for **4b** and of 0.0418 ($wR_2$ = 0.0983) for **5b**. These final R1 values are based on the reflections with $F > 4\sigma(F)$, $wR_2$ values on all data. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed at calculated positions with fixed isotropic temperature factors (1.2 times $U_{eq}$ of the carrying atom), except for **5b** where the C−H distances were also free to refine. The figures were drawn with PLATON.[29]

Crystal data for **3b**: $C_{13}H_{13}NO_2$, $M_r$ = 215.24, orthorhombic, space group *Pbca* (No. 61), lattice parameters: $a$ = 11.733(2) Å, $b$ = 8.113(2) Å, $c$ = 24.004(5) Å, $Z$ = 8, $V$ = 2284.9(8) Å$^3$, $D_c$ = 1.251 g/cm$^3$, $\mu$(Mo Kα) = 0.085 mm$^{-1}$, $F$(000) = 912, transparent blocks, crystal size: 0.2 × 0.2 × 0.35 mm, 2651 reflections collected, 2002 unique reflections, $R$(int) = 0.031, 1211 observed reflections ($F > 4\sigma(F)$).

(26) Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.

(27) Analysis of the crude reaction mixture (NMR) showed that the content of the major diastereomer **7c−j** was at least 97%, while the second diastereomer and/or byproducts was/were formed in an amount not greater than 3%.

(28) Sheldrick, G. M. (**1998**) SHELXTL-Plus. Program for the Solution and Refinement of Crystal Structures. Bruker Analytical X-ray Systems, Madison, WI.

(29) Spek, A. L. *Acta Crystallogr.* **1990**, *A46*, C-34.

Crystal data for **4b**: $C_{12}H_{11}NO_3$, $M_r = 217.22$, monoclinic, space group $P2_1/c$ (No. 14), lattice parameters: $a = 9.450(2)$ Å, $b = 6.568(1)$ Å, $c = 17.012(3)$ Å, $\beta = 97.42(1)°$, $Z = 4$, $V = 1047.1(3)$ Å$^3$, $D_c = 1.378$ g/cm$^3$, $\mu$(Mo K$\alpha$) = 0.100 mm$^{-1}$, $F(000) = 456$, transparent blocks, crystal size: $0.2 \times 0.3 \times 0.35$ mm, 2608 reflections collected, 1843 unique reflections, $R$(int) = 0.037, 1069 observed reflections ($F > 4\sigma(F)$).

Crystal data for **5b**: $C_{13}H_{11}NO_3$, $M_r = 229.23$, orthorhombic, space group $P2_12_12_1$ (No. 19), lattice parameters: $a = 5.948(2)$ Å, $b = 7.722(3)$ Å, $c = 24.858(4)$ Å, $Z = 4$, $V = 1141.7(6)$ Å$^3$, $D_c = 1.334$ g/cm$^3$, $\mu$(Mo K$\alpha$) = 0.096 mm$^{-1}$, $F(000) = 480$, transparent plates, crystal size: $0.15 \times 0.3 \times 0.4$ mm, 1722 reflections collected, 1539 unique reflections, $R$(int) = 0.032, 1149 observed reflections ($F > 4\sigma(F)$).

Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, and can be obtained on request from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

**Molecular Mechanics Calculations.** The TS models, using the already optimized **4b** and complex **2** and $Me_3N$, were constructed by (1) fixing the distance between the reaction centers C═*C* [enolate derived from **2** (d)]···*C*═C [Michael acceptor (a)] at 2.20 Å, (2) initially setting the angles of *C*═*C* (d)···*C*═C (a) and C═*C* (d)···*C*═*C* (a) both at 90 degrees, (3) changing the dihedral angle *C*═*C* (d)···*C*═*C* (a) to 0, 120, or 240°. This method when considering the two faces matching (*like* and *unlike*) eventually furnished six independent conformers. After optimization, the population percentage was obtained from the Boltzmann distribution equation at 25 °C considering their energy differences. Molecular mechanics calculations were performed by the Mechanics software implemented in the CAChe WorkSystem version 4.1.1.

***o*-[*N*-(α-Picolyl)amino]acetophenone (PAAP) 1.** Into a solution of 2-aminoacetophone (4.1 g, 30 mmol) and picolinic acid (3.7 g, 30 mmol) in dry $CH_2Cl_2$ (60 mL) was added triethylamine (8.4 mL, 60 mmol) with stirring, followed by benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (14.6 g, 33 mmol). The reaction mixture was stirred at room temperature overnight. After completion, the reaction was quenched by adding 1 *N* HCl (30 mL) and stirred for another 30 min. The organic phase was separated, washed with $H_2O$, saturated $NaHCO_3$ solution, and brine and dried over anhydrous $MgSO_4$ overnight. Removal of solvents gave a crude product (6.7 g, 95%) as an off-white solid, which was used in the next reaction without further purification. An analytic sample was purified by silica gel chromatography (EtOAc−hexanes: 4/6, v/v) for characterization: mp 112.0−112.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.73 (3H, s), 7.16−7.21 (1H, m), 7.47−7.51 (1H, m), 7.60−7.66 (1H, m), 7.90 (1H, dt, $J = 1.7$ Hz, 8.7 Hz), 7.97 (1H, dd, $J = 1.5$ Hz, 7.8 Hz), 8.29 (1H, d, $J = 8.1$ Hz), 8.80−8.82 (1H, m), 9.03 (1H, dd, $J = 1.0$ Hz, 8.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 28.6, 121.1, 122.7, 123.1, 126.4, 131.7, 134.9, 137.3, 140.2, 148.7, 150.4, 163.9, 202.2.

**Ni(II) Complex of Glycine Schiff Base with *o*-[*N*-(α-Picolyl)amino]acetophenone (PAAP) 2.** Into a suspension of *o*-[*N*-(α-picolyl)amino]acetophenone (PAAP) (4.8 g, 20 mmol), glycine (7.5 g, 100 mmol), and $NiCl_2 \times 6H_2O$ (9.5 g, 40 mmol) in methanol (100 mL) was added a suspension of NaOH (5.6 g, 40 mmol) in methanol (40 mL) at 60 °C. After being stirred at 60 °C for 4 h and at room temperature overnight, the reaction mixture was poured into a solution of ice−water (100 mL) and glacial acetic acid (10 mL) and stirred for a 10 min. The solid was filtered off, washed with hexanes, and dried in vacuo to afford the desired product (6.5 g, 95%): mp >290.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.43 (3H, s), 4.20 (2H, s), 6.99−7.04 (1H, m), 7.32−7.43 (2H, m), 7.62−7.65 (1H, m), 7.81−7.83 (1H, m), 7.93−7.98 (1H, m), 8.18−8.20 (1H, m), 8.70 (1H, d, $J = 8.4$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 19.1, 60.6, 121.9, 124.0, 124.5, 126.4, 126.9, 130.1, 132.7, 140.5, 142.1, 147.1, 153.3, 169.9, 170.6, 177.1; HRMS(FAB) $[M + H]^+$ calcd for $C_{16}H_{14}N_3NiO_3$ 354.0389, found 354.0386.

**General Procedure for Preparation of the *N*-(Enoyl)-pyrrolidin-2-ones 3a,b, *N*-(Enoyl)oxazolidin-2-ones 4a−j, and *N*-(Enoyl)succinimides 5a,b. Method A.** Into a cooled solution of the corresponding α,β-unsaturated carboxylic acid (1.1 equiv) in dried THF (5 mL/1 mmol of acid) were added triethylamine (1.2 equiv) and pivaloyl chloride (1.1 equiv) at −78 °C under Ar atmosphere. The resulting mixture was stirred at −78 °C for 15 min, at 0 °C for 1 h, and recooled at −78 °C. To the above solution was added a precooled lithiated oxazolidin-2-one or pyrrolidin-2-one or succinimide suspension solution prepared by adding *n*-butyllithium (1 equiv) into a solution of oxazolidin-2-one or pyrrolidin-2-one or succinimide (1 equiv) in dried THF (5 mL/1 mmol of oxazolidinone) at −78 °C. The resulting reaction was stirred at −78 °C for 2 h and room temperature overnight. The reaction was quenched by adding saturated $NH_4Cl$ solution and the solvent was removed by rotary evaporation. The residue was extracted with EtOAc, washed with dilute $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After filtration and evaporation, the crude product was purified by column chromatography (silica gel) if it was a liquid or recrystallization from EtOAc otherwise.

**Method B.** Into a boiling mixture of acid (1 equiv) in $CH_2Cl_2$ (1 mL/1 mmol of acid) was added dropwise a solution of $SOCl_2$ (2 equiv) in $CH_2Cl_2$. The reaction mixture was refluxed for 2 h (until a clear solution formed). The solvent and remaining $SOCl_2$ was removed by reduced pressure distillation. After cooling to room temperature, the resulting carbonyl chloride was dissolved in dried THF (1 mL/mmole of acid) and transferred a precooled lithiated oxazolidin-2-one or pyrrolidin-2-one or succinimide suspension solution, which was prepared in advance by adding *n*-butyllithium (1 equiv) into a solution of oxazolidin-2-one or pyrrolidin-2-one or succinimide (1 equiv) in dried THF (5 mL/mmole of oxazolidinone) at −78 °C. The resulting reaction was stirred at −78 °C for 2 h and room-temperature overnight. The reaction was quenched by adding saturated aqueous $NH_4Cl$ solution and the solvent was removed by rotary evaporation. The residue was extracted with EtOAc, washed with dilute $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. After filtration and evaporation, the crude product was purified by column chromatography (silica gel) if it was a liquid or recrystallization from EtOAc and hexanes otherwise.

***N*-(*trans*-Crotonyl)pyrrolidin-2-one 3a** (method B): yield 91%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.95 (3H, dd, $J = 1.2$ Hz, 6.4 Hz), 1.99−2.09 (2H, m), 2.62, 3.86 (4H, AB, $J = 8.1$ Hz), 7.07−7.29 (2H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 17.2, 18.4, 33.9, 45.7, 123.6, 145.8, 166.1, 175.5.

***N*-(*trans*-Cinnamoyl)pyrrolidin-2-one 3b** (method B): yield 80%; mp 101.0−102.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.08 (2H, tt, $J = 6.8$ Hz, 7.2 Hz), 2.66 (2H, t, $J = 6.8$ Hz), 3.93 (2H, t, $J = 7.2$ Hz), 7.38−7.41 (3H, m), 7.61−7.64 (2H, m), 7.84, 7.95 (2H, AB, $J = 15.9$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 17.2, 34.0, 45.9, 119.0, 128.5, 128.8, 130.3, 134.9, 145.5, 166.3, 175.7.

***N*-(*trans*-Crotonyl)oxazolidin-2-one 4a** (method A): yield 65%; mp 42.0−43.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.97 (3H, dd, $J = 0.7$ Hz, 5.4 Hz), 4.07, 4.43 (4H, AB, $J = 8.1$ Hz), 7.12−7.29 (2H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.5, 42.6, 62.0, 121.4, 146.8, 153.5, 165.1.

***N*-(*trans*-Cinnamoyl)oxazolidin-2-one 4b** (method A): yield 66%; mp 151.0−151.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.15, 4.47 (4H, AB, $J = 8.0$ Hz), 7.40−7.42 (3H, m), 7.62−7.65 (2H, m), 7.87, 7.93 (2H, AB, $J = 15.9$ Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 42.8, 62.1, 116.5, 128.7, 128.9, 130.7, 134.5, 146.3, 153.6, 165.4.

***N*-(*trans*-2′-Hexenoyl)oxazolidin-2-one 4c** (method A): yield 53%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 0.95 (3H, t, $J = 7.3$ Hz), 1.50 (2H, tq, $J = 7.3$ Hz), 2.23−2.30 (2H, m), 4.07, 4.43 (4H, AB, $J = 8.1$ Hz), 7.12−7.27 (2H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 13.7, 21.3, 34.6, 42.7, 62.0, 120.0, 151.6, 153.5, 165.3.

***N*-(4′-Methyl-*trans*-2′-pentenoyl)oxazolidin-2-one 4d** (method A): yield 67%; oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.10 (6H, d, $J = 6.8$ Hz), 2.48−2.63 (1H, m), 4.07, 4.43 (4H, AB, $J = 8.0$ Hz), 7.09−7.29 (2H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.2, 31.4, 42.7, 62.0, 117.3, 153.5, 157.7, 165.6.

***N*-[3′-(2″-Naphthyl)-*trans*-propenoyl]oxazolidin-2-one 4e** (method B): yield 86%; mp 212.5−213.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.17, 4.48 (4H, AB, $J = 8.0$ Hz), 7.51−7.54 (2H, m), 7.77−7.90 (4H, m), 8.02−8.04 (3H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 42.9, 62.1, 116.6, 124.0, 126.3, 126.7, 127.4, 127.8, 128.7, 130.7, 132.0, 133.2, 134.4, 146.4, 153.7, 165.4.

***N*-[3′-(1″-Naphthyl)-*trans*-propenoyl]oxazolidin-2-one 4f** (method B): yield 78%; mp 156.0−157.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.19, 4.49 (4H, AB, $J$ = 8.0 Hz), 7.49−7.62 (3H, m), 7.88−7.94 (3H, m), 8.01, 8.73 (2H, AB, $J$ = 15.9 Hz), 8.25 (1H, d, $J$ = 8.1 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 42.9, 62.1, 118.9, 123.3, 125.5, 125.7, 126.2, 126.9, 128.8, 131.0, 131.6, 133.7, 143.0, 153.6, 165.4.

***N*-(*trans*-4′-Trifluoromethylcinnamoyl)oxazolidin-2-one 4g** (method B): yield 82%; mp 182.5−183.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.16, 4.49 (4H, AB, $J$ = 8.0 Hz), 7.65, 7.72 (4H, AB, $J$ = 8.4 Hz), 7.85, 7.98 (2H, AB, $J$ = 15.6 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −64.0 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 42.8, 62.2, 119.0, 123.5 (q, $J$ = 274.0 Hz), 125.8 (q, $J$ = 4.0 Hz), 128.7, 131.5, (q, $J$ = 32.2 Hz), 137.8, 144.2, 153.6, 164.9; HRMS(FAB) [M + H]$^+$ calcd for $C_{13}H_{11}F_3NO_3$ 286.0691, found 286.0692.

***N*-(*trans*-4′-Methoxycinnamoyl)oxazolidin-2-one 4h** (method B): yield 86%; mp 151.5−152.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.85 (3H, s), 4.13, 4.45 (4H, AB, $J$ = 8.0 Hz), 6.91, 7.58 (4H, AB, $J$ = 8.8 Hz), 7.77, 7.85 (2H, AB, $J$ = 15.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 42.8, 55.4, 62.0, 114.0, 114.3, 127.3, 130.4, 146.1, 153.6, 161.7, 165.6; HRMS(FAB) [M + H]$^+$ calcd for $C_{13}H_{14}NO_4$ 248.0923, found 248.0919.

***N*-[3′-[3″(1″-Mesitylenesulfonyl)indolyl]]-*trans*-propenoyl]oxazolidin-2-one 4i** (method B): yield 73%; mp 250.0−251.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.30 (3H, s), 2.54 (6H, s), 4.17, 4.48 (4H, AB, $J$ = 8.0 Hz), 6.97 (2H, S), 7.25−7.36 (3H, m), 7.96−8.00 (2H, m), 7.99, 8.07 (2H, AB, $J$ = 15.9 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.1, 22.7, 42.8, 62.1, 112.6, 115.8, 116.4, 121.3, 124.0, 125.2, 127.4, 130.6, 132.1, 132.6, 135.5, 137.6, 140.3, 144.6, 153.8, 165.5. HRMS(FAB) [M + H]$^+$ calcd for $C_{23}H_{23}N_2O_5S$ 439.1328, found 439.1326.

***N*-(*trans*-2′,3′,4′,5′,6′-Pentafluorocinnamoyl)oxazolidin-2-one 4j** (method B): yield 87%; mp 145.5−146.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.15, 4.50 (4H, AB, $J$ = 8.0 Hz), 7.78, 8.15 (2H, AB, $J$ = 15.9 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −162.6 (2F, m), −151.7 (1F, m), −139.9 (2F, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 42.7, 62.2, 124.5 (m), 129.1, 136.1 (m), 139.5 (m), 144.1 (m), 147.4 (m), 153.3, 164.6; HRMS(FAB) [M + H]$^+$ calcd for $C_{12}H_7F_5NO_3$ 308.0346, found 308.0345.

***N*-(*trans*-Crotonyl)succinimide 5a** (method B): yield 86%; mp 108.0−109.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.00 (3H, dd, $J$ = 1.7 Hz, 7.1 Hz), 2.82 (4H, s), 6.42 (1H, qd, $J$ = 1.7 Hz, 15.4 Hz), 7.25 (1H, qd, $J$ = 7.1 Hz, 15.4 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.7, 28.6, 124.6, 150.1, 163.9, 174.5.

***N*-(*trans*-Cinnamoyl)succinimide 5b** (method B): yield 84%; mp 119.0−120.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.87 (4H, s), 7.03, 7.92 (2H, AB, $J$ = 15.6 Hz), 7.38−7.46 (3H, m), 7.59−7.63 (2H, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 28.7, 119.2, 128.9, 129.0, 131.5, 133.9, 148.7, 164.2, 174.5.

**General Procedure for the Reactions of Glycine Ni(II) complex 2 with *N*-Enoylpyrrolidin-2-ones 3a,b or -oxazolidin-2-ones 4a−j**. To a suspension of Ni(II) complex **2** (0.177 g, 0.500 mmol) in DMF (3.0 mL) was added *N*-enoylpyrrolidin-2-ones **3a**, **3b** or -oxazolidin-2-ones **4a**−**j** (0.525 mmol). After stirring the mixture for 10 min at ambient temperature, DBU (0.01 mL, 0.07 mmol) was added. The reaction was monitored by TLC. After completion, the reaction mixture was poured into $H_2O$ (60 mL). The resultant crystalline product was filtered and washed thoroughly with $H_2O$ and dried in vacuo. An analytical sample was purified by chromatography on silica gel with $CHCl_3$ and acetone (1:1, v/v) as eluent. Yields and stereochemical outcomes of the reactions are given in Tables 1 and 2.

**Ni(II) complex of the Schiff case of PAAP with (2*S**,3*S**)-3-methyl-5-pyrrolidinonylglutamic acid 6a**: mp 232.0−233.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.01−2.14 (5H, m), 2.50−2.62 (3H, m), 2.80 (3H, s), 2.95, 3.73 (2H, ABX, $J$ = 3.7 Hz, 10.3 Hz, 19.0 Hz), 3.78−3.84 (2H, m), 4.62 (1H, d, $J$ = 4.2 Hz), 7.00−7.05 (1H, m), 7.35−7.44 (2H, m), 7.74−8.00 (3H, m), 8.19 (1H, d, $J$ = 5.4 Hz), 8.82 (1H, d, $J$ = 8.7 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 16.9, 17.1, 18.9, 33.5, 33.6, 40.0, 45.3, 72.9, 121.8, 123.8, 123.9, 126.8, 130.4, 132.6, 140.3, 141.9, 146.9, 153.3, 169.5, 170.4, 173.4, 175.2, 177.6; HRMS(FAB) [M + H]$^+$ calcd for $C_{24}H_{25}N_4NiO_5$ 507.1178, found 507.1171.

**Ni(II) complex of the Schiff base of PAAP with (2*S**,3*R**)-3-phenyl-5-pyrrolidinonylglutamic acid 6b:** mp 266.0−266.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.04−2.11 (2H, m), 2.58−2.65 (2H, m), 2.88 (3H, s), 3.43 (1H, part of ABX, $J$ = 2.7 Hz, 19.3 Hz), 3.74−3.95 (3H, m), 4.40 (1H, part of ABX, $J$ = 11.2 Hz, 19.3 Hz), 4.72 (1H, d, $J$ = 4.1 Hz), 6.70−6.75 (1H, m), 7.00−7.36 (5H, m), 7.47−7.54 (3H, m), 7.69−7.75 (2H, m), 7.83−7.89 (1H, m), 8.55 (1H, d, $J$ = 8.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 17.2, 18.3, 33.5, 38.0, 45.2, 45.4, 74.4, 121.7, 123.3, 123.8, 126.0, 127.3, 127.5, 128.0, 130.2, 130.5, 132.5, 139.2, 139.5, 141.9, 146.6, 153.3, 168.6, 168.9, 173.4, 175.1, 176.7; HRMS-(FAB) [M + H]$^+$ calcd for $C_{29}H_{27}N_4NiO_5$ 569.1335, found 569.1357.

**Ni(II) complex of the Schiff base of PAAP with (2*S**,3*S**)-3-methyl-5-(2′-oxazolidinonyl)glutamic acid 7a**: mp 194.0−195.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.12 (3H, d, $J$ = 6.8 Hz), 2.48−2.60 (1H, m), 2.78 (3H, s), 2.98, 3.75 (2H, ABX, $J$ = 3.9 Hz, 10.3 Hz, 18.8 Hz), 3.99−4.07 (2H, m), 4.40−4.45 (2H, m), 4.62 (1H, d, $J$ = 3.9 Hz), 7.00−7.06 (1H, m), 7.35−7.45 (2H, m), 7.74−8.01 (3H, m), 8.19 (1H, d, $J$ = 4.6 Hz), 8.82 (1H, d, $J$ = 7.6 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 16.8, 18.9, 33.6, 38.5, 42.4, 62.0, 72.8, 121.8, 123.8, 123.9, 126.8, 130.4, 132.7, 140.4, 142.0, 146.9, 153.2, 153.3, 169.6, 170.5, 172.6, 177.5; HRMS-(FAB) [M + H]$^+$ calcd for $C_{23}H_{23}N_4NiO_6$ 509.0971, found 509.0974.

**Ni(II) complex of the Schiff base of PAAP with (2*S**,3*R**)-3-phenyl-5-(2′-oxazolidinonyl)glutamic acid 7b:** mp 261.5−262.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.85 (3H, s), 3.47 (1H, part of ABX, $J$ = 2.9 Hz, 19.0 Hz), 3.76 (1H, td, $J$ = 3.7 Hz, 11.2 Hz), 4.00−4.11 (2H, m), 4.37−4.49 (3H, m), 4.74 (1H, d, $J$ = 4.6 Hz), 6.72−6.77 (1H, m), 7.00−7.38 (5H, m), 7.46−7.56 (3H, m), 7.70−7.90 (3H, m), 8.56 (1H, d, $J$ = 8.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.2, 36.5, 42.4, 45.0, 62.1, 74.3, 121.7, 123.3, 123.9, 126.1, 127.3, 127.7, 128.1, 130.2, 130.5, 132.6, 138.7, 139.6, 142.0, 146.6, 153.2, 153.3, 168.6, 169.0, 172.6, 176.7; HRMS-(FAB) [M + H]$^+$ calcd for $C_{28}H_{25}N_4NiO_6$ 571.1128, found 571.1114.

**Ni(II) complex of the Schiff base of PAAP with (2*S**,3*S**)-3-*n*-propyl-5-(2′-oxazolidinonyl)glutamic acid 7c:** mp 189.0−190.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 0.94 (3H, t, $J$ = 7.2 Hz), 1.25−1.45 (1H, m), 1.58−1.72 (1H, m), 1.84−1.79 (1H, m), 2.35−2.43 (1H, m), 2.80 (3H, s), 3.11 (1H, part of ABX, $J$ = 2.7 Hz, 19.3 Hz), 3.65−3.77 (2H, m), 3.95−4.09 (2H, m), 4.39−4.44 (2H, m), 4.61 (1H, d, $J$ = 4.2 Hz), 7.01−7.06 (1H, m), 7.36−7.45 (2H, m), 7.76−8.01 (3H, m), 8.19 (1H, d, $J$ = 4.9 Hz), 8.84 (1H, d, $J$ = 8.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 14.0, 19.1, 20.7, 31.9, 35.1, 38.3, 42.4, 62.0, 72.2, 121.8, 123.9, 126.8, 126.9, 130.4, 132.7, 140.4, 142.0, 147.0, 153.2, 153.3, 169.6, 170.7, 173.3, 177.9; HRMS(FAB) [M + H]$^+$ calcd for $C_{25}H_{27}N_4NiO_6$ 537.1284, found 537.1299.

**Ni(II) complex of the Schiff base of PAAP with (2*S**,3*R**)-3-isopropyl-5-(2′-oxazolidinonyl)glutamic acid 7d:** mp 186.0−187.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.07 (3H, d, $J$ = 6.8 Hz), 1.20 (3H, d, $J$ = 6.8 Hz), 2.64−2.68 (1H, m), 2.89 (3H, s), 2.93, 3.68 (2H, ABX, $J$ = 1.5 Hz, 11.5 Hz, 19.3 Hz), 3.90−3.41 (6H, m), 4.50 (1H, d, $J$ = 6.1 Hz), 7.03 (1H, t, $J$ = 7.2 Hz), 7.35−7.45 (2H, m), 7.75−8.01 (3H, m), 8.16 (1H, d, $J$ = 5.4 Hz), 8.85 (1H, d, $J$ = 8.1 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 16.9, 19.0, 23.7, 26.9, 30.4, 42.5, 44.3, 62.0, 71.5, 121.9, 123.7, 124.0, 126.7, 126.9, 130.6, 132.8, 140.4, 142.0, 146.8, 153.3, 153.4, 169.7, 170.4, 173.5, 178.6; HRMS(FAB) [M + H]$^+$ calcd for $C_{25}H_{27}N_4NiO_6$ 537.1284, found 537.1293.

**Ni(II) complex of the Schiff base of PAAP with (2*S**,3*R**)-3-(2′-naphthyl)-5-(2′-oxazolidinonyl)glutamic acid 7e:** mp 287.0−288.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.92 (3H, s), 3.59 (1H, part of ABX, $J$ = 3.0 Hz, 18.9 Hz), 3.97 (1H, td, $J$ = 3.6 Hz, 11.2 Hz), 4.02−4.14 (2H, m), 4.44−4.59 (3H, m), 4.77 (1H, d, $J$ = 4.1 Hz), 6.79−6.83 (1H, m), 7.01−7.14 (1H, m), 7.16−7.38 (7H, m), 7.44−7.50 (1H, m), 7.56−7.76 (3H, m), 8.07 (1H, s), 8.55 (1H, d, $J$ = 8.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.2, 36.6, 42.5, 45.2, 62.2, 74.7, 121.7, 122.8, 123.9, 125.4, 125.6, 126.1, 127.4, 127.8, 128.3, 130.1, 132.7, 133.1, 136.5, 139.1, 142.2, 145.6, 152.1, 153.2, 167.1, 167.0, 172.6, 176.7; HRMS-(FAB) [M + H]$^+$ calcd for $C_{32}H_{27}N_4NiO_6$ 621.1284, found 621.1284.

**Ni(II) complex of the Schiff base of PAAP with (2*S**,3*R**)-3-(1′-naphthyl)-5-(2′-oxazolidinonyl)glutamic acid 7f:** mp 190.0−191.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.91 (3H, s), 3.68 (1H, part of ABX, $J$ = 2.9 Hz, 19.0 Hz), 4.02−4.12 (2H, m), 4.43−4.49 (2H, m), 4.63 (1H, part of ABX, $J$ = 10.5 Hz, 19.0 Hz), 4.85 (1H, d, $J$ = 4.4 Hz), 4.94 (1H, td, $J$ = 3.7 Hz, 10.5 Hz), 6.94−7.06 (2H, m), 7.18−7.30 (6H, m), 7.45−7.88 (6H, m), 8.41 (1H, d, $J$ = 8.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.3, 36.9, 37.3, 42.5, 62.1, 75.3, 121.7, 122.2, 123.1, 123.3, 125.3, 125.9, 126.1, 126.3, 126.8, 127.0, 127.9, 128.8, 130.0, 132.5, 133.5, 133.6, 135.5, 139.5, 142.0, 146.3, 153.0, 153.2, 167.6, 169.3, 172.7, 176.9; HRMS(FAB) $[M + H]^+$ calcd for $C_{32}H_{27}N_4NiO_6$ 621.1284, found 621.1275.

**Ni(II) complex of the Schiff base of PAAP with (2*S**,3*R**)-3-(4′-trifluoromethyl)phenyl-5-(2′-oxazolidinonyl)glutamic acid 7g**: mp 261.0−262.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.88 (3H, s), 3.45 (1H, part of ABX, $J$ = 3.2 Hz, 19.0 Hz), 3.80 (1H, td, $J$ = 3.7 Hz, 11.2 Hz), 3.98−4.13 (2H, m), 4.37−4.50 (3H, m), 4.74 (1H, d, $J$ = 4.2 Hz), 7.01−7.06 (1H, m), 7.22−7.27 (1H, m), 7.32−7.38 (1H, m), 7.44−7.54 (3H, m), 7.62−7.77 (4H, m), 7.84−7.90 (1H, m), 8.62 (1H, d, $J$ = 8.8 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −63.4 (3F, s); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.4, 36.3, 42.4, 44.9, 62.2, 73.9, 121.7, 123.7, 123.8, 125.0, 126.3, 126.9, 130.0, 130.3, 130.5, 131.0, 132.8, 140.2, 142.0, 142.9, 146.0, 152.6, 153.2, 168.7, 170.0, 172.0, 176.3; HRMS(FAB) $[M + H]^+$ calcd for $C_{29}H_{24}F_3N_4NiO_6$ 639.1001, found 639.0998.

**Ni(II) complex of the Schiff base of PAAP with (2*S**,3*R**)-3-(4′-methoxyl)phenyl-5-(2′-oxazolidinonyl)-glutamic acid 7h:** mp 269.0−269.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.84 (3H, m), 3.42 (1H, part of ABX, $J$ = 3.2 Hz, 19.0 Hz), 3.49 (3H, s), 3.73 (1H, td, $J$ = 3.8 Hz, 11.2 Hz), 3.97−4.12 (2H, m), 4.37 (1H, part of ABX, $J$ = 11.2 Hz, 19.0 Hz), 4 42−4.48 (2H, m), 4.71 (1H, d, $J$ = 4.4 Hz), 6.64 (2H, part of AB, $J$ = 8.8 Hz), 7.00−7.06 (1H, m), 7.27−7.39 (4H, m), 7.57−7.91 (4H, m), 8.53 (1H, d, $J$ = 8.5 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.2, 36.7, 42.4, 44.4, 54.6, 62.1, 74.4, 113.2, 121.7, 123.0, 123.8, 126.0, 127.4, 130.2, 130.7, 131.6, 132.5, 139.6, 141.9, 146.6, 153.1, 153.2, 159.1, 168.7, 172.6, 176.6; HRMS(FAB) $[M + H]^+$ calcd for $C_{29}H_{27}N_4NiO_7$ 601.1233, found 601.1248.

**Ni(II) complex of the Schiff base of PAAP with (2*S**,3*R**)-3-(*N*-mesitylenesulfonyl-3′-indolyl)-5-(2′-oxazolidinonyl)glutamic acid 7i:** mp 188.0−189.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.24 (3H, s), 2.46 (6H, s), 2.90 (3H, s), 3.49 (1H, part of ABX, $J$ = 3.9 Hz, 18.6 Hz), 3.99−4.17 (3H, m), 4.38−4.47 (3H, m), 4.75 (1H, d, $J$ = 3.9 Hz), 6.88 (2H, s), 6.94−7.03 (4H, m), 7.19−7.37 (3H, m), 7.48−7.55 (2H, m), 7.73−7.82 (3H, m), 8.66 (1H, d, $J$ = 7.8 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.4, 20.9, 22.6, 30.9, 36.4, 37.0, 42.4, 62.2, 74.5, 112.0, 118.2, 120.5, 121.4, 122.7, 123.4, 123.9, 124.7, 126.3, 126.6, 127.1, 130.1, 130.5, 132.3, 132.6, 132.8, 134.5, 139.3, 140.0, 142.3, 143.9, 145.9, 152.3, 153.2, 168.7, 169.4, 172.0, 177.0; HRMS(FAB) $[M + H]^+$ calcd for $C_{38}H_{36}N_5NiO_8S$ 792.1638, found 792.1664.

**Ni(II) complex of the Schiff base of PAAP with (2*S**,3*R**)-3-pentafluorophenyl-5-(2′-oxazolidinonyl)-glutamic acid 7j:** mp 224.0−225.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.82 (3H, s), 3.51 (1H, d, $J$ = 16.4 Hz), 4.01−4.13 (2H, m), 4.36−4.49 (4H, m), 4.69−4.71 (1H, m), 7.01−7.06 (1H, m), 7.32−7.45 (2H, m), 7.69−8.04 (4H, m), 8.60 (1H, d, $J$ = 8.5 Hz); $^{19}$F NMR ($CDCl_3$) $\delta$ −162.6 (1F, m), −161.8 (1F, m), −155.0 (1F, m), −140.1 (1F, m), −133.8 (1F, m); $^{13}$C NMR ($CDCl_3$) $\delta$ 18.2, 34.6, 35.2, 42.4, 62.3, 71.9, 122.0, 123.8, 124.0, 127.0, 130.2, 133.1, 140.6, 142.0, 146.5, 152.9, 153.1, 168.3, 171.1, 171.8, 176.0, the resonance of $C_6F_5$ carbons was obscured due to their low intensities; HRMS(FAB) $[M + H]^+$ calcd for $C_{28}H_{20}F_5N_4NiO_6$ 661.0656, found 661.0671.

**Decomposition of Complex 6a,b or 7a,b and Isolation of (2*S**,3*S**)-3-Methylpyroglutamic Acid 8a or (2*S**,3*R**)-3-Phenylpyroglutamic Acid 8b.** A solution of complex **6a**,**b** or **7a**,**b** (15.4 mmol) in MeOH (60 mL) was slowly added with stirring to a mixture of aqueous 3 N HCl and MeOH (120 mL, ratio 1/1) at 70 °C. Upon disappearance of the red color of the starting complex, the reaction mixture was evaporated in vacuo to dryness. Water (80 mL) was added, and the resultant mixture was treated with excess of $NH_4OH$ and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated in vacuo to afford free PAAP (3.63 g, 98%). The aqueous phase was evaporated and the solid residue was washed with acetone to remove pyrrolidin-2-one (1.18 g, 90% yield) or oxazolidin-2-one (1.21 g, 90% yield). The resultant product was dissolved in water and loaded on a Dowex 50 × 2 100 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 the corresponding pyroglutamic acids. The products were recrystallized from THF/hexanes to give analytically pure samples.

**(2*S**,3*S**)-3-Methylpyroglutamic acid (8a):** yield 88%; mp 108.0−109.0 °C; $^1$H NMR ($CD_3OD$) $\delta$ 1.28 (3H, d, $J$ = 6.6 Hz), 1.99 (1H, part of ABX, $J$ = 9.6 Hz, 19.8 Hz), 2.50−2.59 (2H, m), 3.82 (1H, d, $J$ = 4.8 Hz); $^{13}$C NMR ($CD_3OD$) $\delta$ 20.1, 34.8, 38.4, 63.1, 174.0, 178.3; HRMS(FAB) $[M + H]^+$ calcd for $C_6H_{10}NO_3$ 144.0661, found 144.0660.

**(2*S**,3*R**)-3-Phenylpyroglutamic acid (8b)**: yield 85%; mp 166.5−167.0 °C; $^1$H NMR ($CD_3COCD_3$) $\delta$ 2.35, 2.76 (2H, ABX, $J$ = 6.3 Hz, 9.3 Hz, 16.8 Hz), 2.88 (1H, br s), 3.72 (1H, m), 4.26 (1H, d, $J$ = 4.9 Hz), 7.21−7.43 (5H, m); $^{13}$C NMR ($CD_3COCD_3$) $\delta$ 38.7, 44.9, 63.1, 127.8, 127.9, 129.6, 143.9, 173.5, 176.4; HRMS(FAB) $[M + H]^+$ calcd for $C_{11}H_{12}NO_3$ 206.0817, found 206.0809.

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**Supporting Information Available:** Complete set of X-ray data for compounds **3b**, **4b**, and **5b**. Copies of $^1$H NMR spectra of compounds **6a**,**b**, **7a**−**j**, and **8a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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