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# Virtually Complete Control of Simple and Face Diastereoselectivity in the Michael Addition Reactions between Achiral Equivalents of a Nucleophilic Glycine and (*S*)- or (*R*)-3-(*E*-Enoyl)-4-phenyl-1,3-oxazolidin-2-ones: Practical Method for Preparation of *β*-Substituted Pyroglutamic Acids and Prolines

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This study demonstrates a new strategy for controlling the stereochemical outcome of the Michael addition reactions between nucleophilic glycine equivalents and α,*β*-unsaturated carboxylic acid derivatives: The addition reactions between achiral Ni(II)-complex of the Schiff base of glycine with *o*-[*N*-α-pycolylamino]acetophenone and (*S*)- or (*R*)-3-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones were shown to occur at room temperature in the presence of nonchelating organic bases and, most notably, with very high stereoselectivity at both newly formed stereogenic centers. Thus, the chiral 4-phenyl-1,3-oxazolidin-2-one moiety was found to control efficiently both face diastereoselectivities of the glycine derived enolate and the C,C double bond of the Michael acceptor. The new strategy developed in this work is methodologically superior to previous methods, most notably in terms of generality and synthetic efficiency. Excellent chemical yields and diastereoselectivities, combined with the simplicity of the experimental procedures, render the present method of immediate use for preparing various 3-substituted pyroglutamic acids and related amino acids (glutamic acids, glutamines, prolines, etc.) available via conventional transformations of the former.

## Introduction

The asymmetric synthesis of natural and tailor-made α-amino acids[1−3] has enjoyed continuous and vigorous research activity for at least 25 years. A number of synthetically efficient approaches allowing for highly stereoselective synthesis of various amino acids and their derivatives on laboratory and industrial scales have been developed.[2] However, the growing demand for new and structurally varied amino acids to address current biological and medicinal problems, as well as the increasing requirements for synthetic efficiency of modern synthetic organic chemistry, requires the development of more practical and general methods.[3] In particular, addition reactions between glycine equivalents and α,*β*-unsatur-

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(1) For previous papers from these groups related to the synthesis of stereochemically defined *C*-substituted glutamic acids and their derivatives see: (a) Soloshonok, V. A.; Avilov, D. V.; Kukhar', V. P.; Meervelt, L. V.; Mischenko, N. *Tetrahedron Lett*. **1997**, *38*, 4903. (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Mischenko, N. *Tetrahedron* **1999**, *55*, 12031. (c) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V. *Tetrahedron* **1999**, *55*, 12045. (d) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron*: *Asymmetry* **1999**, *10*, 4265. (e) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett*. **2000**, *41*, 135. (f) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Angew. Chem., Int. Ed*. **2000**, *39*, 2172. (g) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Org. Lett*. **2000**, *2*, 747. (h) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Yamazaki, T. *J. Org. Chem*. **2000**, *20*, 6688. (i) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett*. **2000**, *41*, 9645. (j) Cai, C.; Soloshonok, V. A.; Hruby, V. J. *J. Org Chem*. **2001**, *66*, 1339−1350. (k) Soloshonok, V. A.; Ueki, H.; Jiang, C.; Cai, C.; Hruby, V. J. *Helv. Chim. Acta* **2002**, *85*, 3616−3623.

(2) For general reviews on asymmetric synthesis of α-amino acids via homologation of chiral equivalents of electrophilic or nucleophilic glycine see: (a) Williams, R. M. In *Synthesis of Optically Active α-Amino Acids*; Baldwin, J. E., Ed.; Organic Chemistry Series; Pergamon Press: Oxford, UK, 1989. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539−1650. (c) Cativiela, C.; Diaz-De-Villegas, M. D. *Tetrahedron*: *Asymmetry* **1998**, *9*, 3517. (d) Cativiela, C.; Diaz-De-Villegas, M. D. *Tetrahedron*: *Asymmetry* **2000**, *11*, 645. For selected recent reviews, see: (e) Calmes, M.; Daunis, J. *Amino Acids* **1999**, *16*, 215−250. (f) Bouifraden, S.; Drouot, C.; El Hadrami, M.; Guenoun, F.; Lecointe, L.; Mai, N.; Paris, M.; Pothion, C.; Sadoune, M.; Sauvagnat, B.; Amblard, M.; Aubagnac, J. L.; Calmes, M.; Chevallet, P.; Daunis, J.; Enjal-bal, C.; Fehrentz, J. A.; Lamaty, F.; Lavergne, J. P.; Lazaro, R.; Rolland, V.; Roumestant, M. L.; Viallefont, P.; Vidal, Y.; Martinez, J. *Amino Acids* **1999**, *16*, 345−379. (g) Sutherland, A.; Willis, C. L. *Nat. Prod. Rep*. **2000**, *17*, 621−631. (h) Beller, M.; Eckert, M. *Angew. Chem., Int. Ed*. **2000**, *39*, 1010−1027. (i) Kawabata, T.; Fuji, K. *Synth. Org. Chem. Jpn*. **2000**, *58*, 1095−1099. (j) Kazmaier, U.; Maier, S.; Zumpe, F. L. *Synlett* **2000**, 1523−1535. (k) Yao, S. L.; Saaby, S.; Hazell, R. G.; Jorgensen, K. A. *Chem. Eur. J*. **2000**, *6*, 2435−2448. (l) Abellan, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Najera, C.; Sansano, J. M. *Eur. J. Org. Chem*. **2000**, 2689−2697. (m) Rutjes, F. P. J. T.; Wolf, L. B.; Schoemaker, H. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4197−4212. (n) Shioiri, T.; Hamada, Y. *Synlett* **2001**, 184−201. (o) Soloshonok, V. A. *Curr. Org. Chem*. **2002**, *6*, 341.

(3) For the recent collection of leading papers on asymmetric synthesis of amino acids, see: *Asymmetric Synthesis of Novel Sterically Constrained Amino Acids*, Tetrahedron Symposia-in-Print, No. 88: Hruby, V. J., Soloshonok, V. A., Guest Eds. *Tetrahedron* **2001**, *57*, No. 30.

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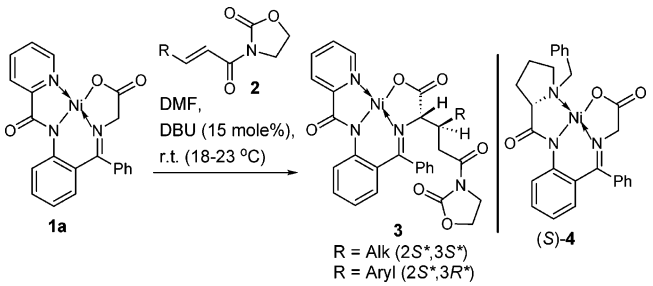
ated carboxylic acid derivatives, which provide the most straightforward and general approach to *β*-substituted glutamic and pyroglutamic acids, glutamines, and prolines, have been extensively studied over the past 15 years.[1,2o,4] Analysis of the relevant literature[1−4] reveals that thus far only one strategy to control the stereochemical outcome in these reactions has been explored. In this approach, addition reactions of various chiral glycine equivalents with α,*β*-unsaturated carboxylic acid derivatives were studied and, in some cases, reasonably high levels of asymmetric induction at both α- and *β*-positions of the resultant glutamic acid derivatives were obtained. Surprisingly, the alternative strategy, application of chiral derivatives of α,*β*-unsaturated carboxylic acids in reactions with achiral glycine equivalents, remains virtually unexplored so far.[4a] In this paper we report in full[1g] that enantiomerically pure *N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones serve as ideal chiral Michael acceptors to afford virtually complete control of simple and face diastereoselectivity in the corresponding addition reactions with achiral Ni(II)-complexes of glycine Schiff bases. The high chemical and optical yields achieved under the operationally convenient conditions,[5] combined with the quantitative recovery of both the chiral auxiliary and the glycine Schiff base precursor, render this new strategy truly practical and synthetically superior over previously reported approaches.[2,4]

## Results and Discussion

Recently we have discovered that the inexpensive and readily available *N*-(*E*-enoyl)-1,3-oxazolidin-2-ones **2** (Scheme 1), featuring conformational homogeneity and enhanced electrophilicity of the C,C double bond, serve as ideal Michael acceptors in the corresponding addition reactions with an achiral equivalent of nucleophilic glycine **1a**.[1e,g] The synthetically advantageous characteristics of these reactions over the literature methods[4] are that they occur at operationally convenient conditions,[5] such as, *room temperature* in the presence of *nonchelating organic bases*, and with *virtually complete* simple diastereoselectivity (>98% de). Our first attempt to realize

**SCHEME 1**




the asymmetric version of this reaction by employing a Ni(II)-complex of the chiral Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone **4** (Scheme 1), though successful, did not give the desired result.[1d,j] Specifically, the problem we met was generally poor *si*/*re* face stereocontrol of the complex (*S*)-**4** derived enolate, while the face selectivity of the Michael acceptors **2** was perfect giving rise only to the corresponding diastereomeric products resulting from the transition states (TSs)[1d,j] with the approach geometry *like*.[6] Therefore, we decided to explore an alternative approach, the additions of the achiral Ni(II)-complex of glycine with chiral 4-substituted *N*-(*E*-enoyl)oxazolidin-2-ones.

**Achiral Equivalents of Nucleophilic Glycine.** Picolinic acid derived Ni(II)-complex **1a** has emerged as a new type of highly efficient achiral nucleophilic glycine equivalent.[1e,h,7−9] Its synthetically superior qualities over the conventional esters of benzophenone-derived glycine Schiff base have been convincingly demonstrated, including the chemical stability and predictable formation of the corresponding (*Z*)-geometrically homogeneous enolates,[1e,h] a feature of paramount importance for highly diastereoselective/enantioselective homologation of the glycine moiety in **1a**. Thus, we recently reported the first practical synthesis of symmetrically α,α-dialkyl-substituted amino acids,[7] including 2-aminoindane-2-carboxylic acid,[8] using complex **1a** as a stable, yet highly reactive glycine equivalent. Recently, Belokon's group has described successful catalytic asymmetric alkylation of the glycine equivalent **1a** under phase-transfer conditions.[9] As reported by us, the Ni(II)-complex **1a**, as well as its various analogues, can be readily prepared on a >100 g scale (Scheme 2) under operationally convenient conditions and with inexpensive reagents.[10]

**Chiral Michael Acceptors.** Chiral, 4-substituted oxazolidin-2-ones are readily available and well-studied chiral auxiliaries. As shown by the pioneering work of Evans et al., the 4-substituted oxazolidin-2-one moiety has a remarkable stereocontrolling power in alkylation,[11a] acylation,[11b] aldol condensation,[11c] and Diels−Alder

(4) For some representative papers, see: (a) Ezquerra, J.; Pedregal, C.; Merino, I.; Flórez, J.; Barluenga, J.; García-Granda, S.; Llorca, M.-A. *J. Org. Chem.* **1999**, *64*, 6554. (b) Seebach, D.; Hoffman, M. *Eur. J. Org. Chem.* **1998**, 1337. (c) Antolini, L.; Forni, A.; Moretti, I.; Prati, F. *Tetrahedron*: *Asymmetry* **1996**, *7*, 3309. (d) Gestmann, D.; Laurent, A. J.; Laurent, E. G. *J. Fluorine Chem.* **1996**, *80*, 27. (e) Hartzoulakis, B.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2525. (f) Suzuki, K.; Seebach, D. *Liebigs Ann. Chem.* **1992**, 51. (g) Belokon', Y. N.; Bulychev, A. G.; Pavlov, V. A.; Fedorova, E. B.; Tsyryapkin, V. A.; Bakhmutov, V. I.; Belikov, V. M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2075. (h) El Achqar, A.; Boumzebra, M.; Roumestant, M.-L.; Viallefont, P. *Tetrahedron* **1988**, *44*, 5319. (i) Pettig, D.; Schöllkopf, U. *Synthesis* **1988**, 173. (j) Schöllkopf, U.; Pettig, D.; Schulze, D.; Klinge, M.; Egert, E.; Benecke, B.; Noltemeyer, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1194. (k) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277. (l) Hartwig, W.; Born, L. *J. Org. Chem.* **1987**, *52*, 4352. (m) Minowa, N.; Hirayama, M.; Fukatsu, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1761. (n) Belokon', Y. N.; Bulychev, A. G.; Ryzhov, M. G.; Vitt, S. V.; Batsanov, A. S.; Struchkov, Y. T.; Bakhmutov, V. I.; Belikov, V. M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1865. (o) Schöllkopf, U.; Pettig, D.; Busse, U. *Synthesis* **1986**, 737.

(5) A conception of the "Atom Economy" introduced by Professor Barry M. Trost has found quick and unanimous understanding, support, and appreciation in the chemistry community as a philosophical guideline for the development of organic synthesis in the 21st century. On the other hand, in the current literature one can notice another trend developing as a paradigm for the synthetic methodology of the future, which is simplicity of experimental conditions, or as we prefer to call it, operationally convenient reaction conditions.

(6) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.

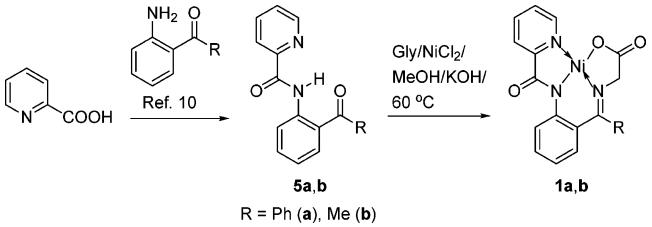
(7) (a) Ellis, T. K.; Martin, C. H.; Ueki, H.; Soloshonok, V. A. *Tetrahedron Lett.* **2003**, *4*, 1063−1066. (b) Ellis, T. K.; Martin, C. H.; Tsai, G. M.; Ueki, H.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 6208−6214.

(8) Ellis, T. K.; Hochla, V. M.; Soloshonok, V. A. *J. Org. Chem.* **2003**, *68*, 4973−4976.

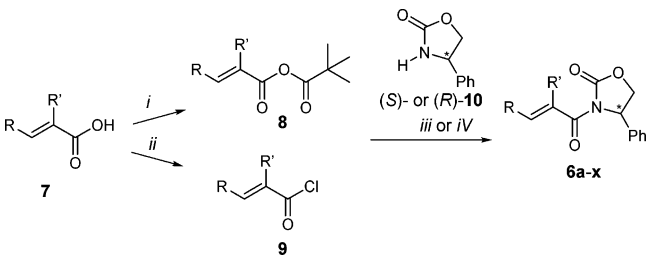
(9) Belokon, Yu. N.; Bespalova, N. B.; Churkina, T. D.; Cisarova, I.; Ezernitskaya, M. G.; Harutyunyan, S. R.; Hrdina, R.; Kagan, H. B.; Kocovsky, P.; Kochetkov, K. A.; Larionov, O. V.; Lyssenko, K. A.; North, M.; Polasek, M.; Peregudov, A. S.; Prisyazhnyuk, V. V.; Vyskocil, S. *J. Am. Chem. Soc.* **2003**, *125*, 12860−12871.

(10) Ellis, T. K.; Martin, C. H.; Ueki, H.; Soloshonok, V. A. *Eur. J. Org. Chem.* **2003**, 1954−1957.

**SCHEME 2**



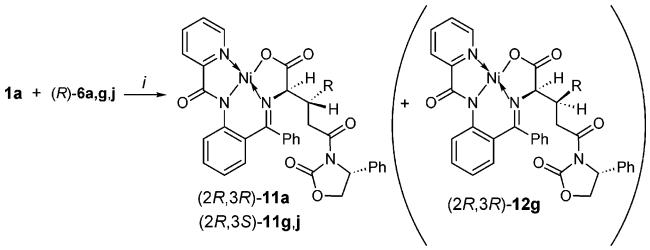

**SCHEME 3** [a,b]




[a] Reagents and conditions. (i) $Me_3CCOCl$; (ii) $SOCl_2$; (iii) *n*-BuLi; (iv) TEA/LiCl; THF; rt. [b]Key: R = Me, R′ = H (**a**); R = Et, R′ = H (**b**); R = *n*-Pr, R′ = H (**c**); R = *i*-Pr, R′ = H (**d**); R = Bn, R′ = H (**e**); R = R′ = Me (**f**); R = Ph, R′ = H (**g**), R = 2-naphthyl, R′ = H (**h**); R = 4-MeO-$C_6H_4$, R′ = H (**i**); R = 3-MeO-$C_6H_4$; R′ = H (**j**); R = 2-MeO-$C_6H_4$; R′ = H (**k**); R = 4-$CF_3$-$C_6H_4$; R′ = H (***l***); R = 3-$CF_3$-$C_6H_4$; R′ = H (**m**); R = 2-$CF_3$-$C_6H_4$; R′ = H (**n**); R = 4-$NO_2$-$C_6H_4$; R′ = H (**o**); R = *N*-Mts-*β*-indolyl, R′ = H (**p**); R = 4-F-$C_6H_4$; R′ = H (**q**); R = 3,5-$F_2$-$C_6H_3$; R′ = H (**r**); R = 2,6-$F_2$-$C_6H_3$; R′ = H (**s**); R = 4-Cl-$C_6H_4$; R′ = H (**t**); R = 3,4-$Cl_2$-$C_6H_3$; R′ = H (**u**); R = 4-Br-$C_6H_4$; R′ = H (**v**); R = Ph, R′ = Me (**w**); R = R′ = Ph (**x**).

reactions.[11d] However, the use of 4-substituted oxazolidin-2-ones to control the face selectivity of the corresponding *N*-enoyl derivatives as Michael acceptors in the DBU-catalyzed reactions under study was not straightforward. To the best of our knowledge, a successful application of chiral oxazolidin-2-ones in asymmetric synthesis requires the use of a chelating agent to ensure the stereocontrolling effect of the substituent at the C-4 stereogenic carbon of the oxazolidine ring. In particular, *N*-(*E*-enoyl)-4-substituted-1,3-oxazolidin-2-ones exist exclusively in the *s-cis* conformation[11d] with the phenyl on the oxazolidine ring being pointed away from the C,C double bond to exercise effective control of the face selectivity of the latter. For instance, as demonstrated by Williams et al., in the addition reactions between *N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **6** (Scheme 3) used in this study and organomettalic reagents, application of Cu(II)-derived chelating reagents was absolutely essential to achieve high stereochemical outcome.[12] According to standard procedures,[1k,11] we synthesized (Scheme 3) a series of (*S*)- and (*R*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **6a**−**x** to conduct a systematic study of the steric and electronic effects of the substituents and their position on the enoyl moiety on the stereochemical outcome of the corresponding addition reactions with complex **1a**.

**SCHEME 4** [a,b]




[a] Reagents and conditions: (i) DMF, DBU (15 mol %), rt (18−23 °C). [b]R = Me (**a**), Ph (**g**), 3-MeO-$C_6H_4$ (**j**).

**Reactions between Benzophenone-Derived Complex 1a and Chiral Michael Acceptors 6.** First we studied the reaction between Ni(II)-complex **1a** and (*R*)-*N*-(*E*-crotonyl)-4-phenyl-1,3-oxazolidin-2-one (**6a**) (Scheme 4). The reaction, conducted at room temperature in DMF in the presence of 15 mol % of DBU, was completed in 50 min giving rise to only one detectable (NMR, 500 MHz) diastereomer **11a** in quantitative chemical yield (Table 1, entry 1). The reactions of phenyl and *m*-methoxyphenyl-containing Michael acceptors **6g**,**j** were notably less successful in terms of both reactivity and the stereochemical outcome. Thus, the addition between **6g** and **1a** occurred at a low rate giving rise to a mixture of two diastereomeric products **11g** and **12g** in a ratio of 9/1, respectively (entry 2). The *m*-methoxyphenyl derivative **6j** reacted with complex **1a** faster, however, with the same incomplete diastereoselectivity (entry 3). Increasing the concentration of the base substantially accelerated the reaction rate, but had no effect on the stereochemical outcome (entry 4). The excellent-to-moderate diastereoselectivity obtained in the reaction of complex **1a** with crotonyl-**6a** and cinnamoyl-containing Michael acceptors **6g**,**j** was rather encouraging, since in contrast to our expectations (vise contra), the 4-phenyloxazolidin-2-one moiety was found to be effective in controlling both the face diastereoselectivities of the complex **1a** derived enolate and the C,C double bond of the corresponding Michael acceptors. However, the incomplete stereochemical outcome in the reactions of **1a** with **6g**,**j**, along with the generally low reaction rates, suggested that the current version, employing complex **1a**, is still imperfect. Therefore, we considered substitution of the ketimine phenyl in **1a** by a methyl group. Taking into account that the total steric bulk[13] of a phenyl group is much larger than that of a methyl, we expected that the substitution of the methyl for the phenyl would increase the reaction rates of the corresponding addition reactions. The synthesis of the methyl-containing complex **1b** has been performed as shown in the Scheme 2, starting with inexpensive *o*-picolinic acid and *o*-aminoacetophenone.

**Reactions between Acetophenone-Derived Complex 1b and Alkyl-Containing Chiral Michael Acceptors.** First we examined the addition between the methyl-containing complex **1b** and oxazolidin-2-one (*R*)-**6a** (Scheme 5), conducted under standard reaction condi-

(11) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154. (c) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (d) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (e) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23. See also: (f) Nicolás, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766. (g) Li, G.; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 2561.

(12) Williams, D. R.; Kissel, W. S.; Li, J. J. *Tetrahedron Lett.* **1998**, *39*, 8593.

(13) One should be aware that the total steric bulk of a substituent and its stereocontrolling steric bulk are not the same; for example, see: (a) Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Ishikawa, K.; Nagashima N.; Hayashi, T. *J. Org. Chem.* **1997**, *62*, 3470. See also: (b) MacPhee, J. A.; Panaye, A.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 3553. (c) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

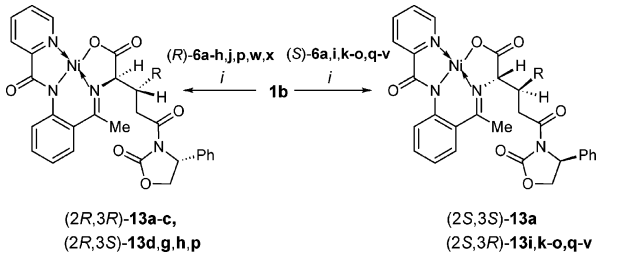
**TABLE 1. Addition Reactions of Ni(II)-Complexes 1a,b with (*S*)- or (*R*)-*N*-(*E*-Enoyl)-4-phenyl-3-oxazolidin-2-ones 6a−x[a]**

| | | | | products **11a,g,j, 13a-d,g-v** | | |
|---|---|---|---|---|---|---|
| entry | **1a,b** | **6a−x** | time | yield,[b] % | de,[c] % | config[d] |
| 1 | **a** | (*R*)-**a** | 50 min | 99 | >98 | (2*R*,3*R*)-**11a** |
| 2 | **a** | (*R*)-**g** | 2.5 h | 95 | 80 | (2*R*,3*S*)-**11g** |
| 3 | **a** | (*R*)-**j** | 1 hr | 99 | 80 | (2*R*,3*S*)-**11j** |
| 4 | **a** | (*R*)-**g** | 30 min[e] | 98 | 80 | (2*R*,3*S*)-**11g** |
| 5 | **b** | (*R*)-**a** | 20 min | 99 | >98 | (2*R*,3*R*)-**13a** |
| 6 | **b** | (*S*)-**a** | 20 min | 99 | >98 | (2*S*,3*S*)-**13a** |
| 7 | **b** | (*R*)-**b** | 20 min | 99 | >94 | (2*R*,3*R*)-**13b** |
| 8 | **b** | (*R*)-**c** | 20 min | 99 | >94 | (2*R*,3*R*)-**13c** |
| 9 | **b** | (*R*)-**d** | 4 hr[f] | 15[g] | >99[h] | (2*R*,3*S*)-**13d** |
| 10 | **b** | (*R*)-**e** | 12 h | | no reaction | |
| 11 | **b** | (*R*)-**f** | 12 h | | no reaction | |
| 12 | **b** | (*R*)-**g** | 10 min | 98 | >94 | (2*R*,3*S*)-**13g** |
| 13 | **b** | (*R*)-**h** | 10 min | 96 | >94 | (2*R*,3*S*)-**13h** |
| 14 | **b** | (*S*)-**i** | 30 min | 99 | >94 | (2*S*,3*R*)-**13i** |
| 15 | **b** | (*R*)-**j** | 35 min | 96 | >94 | (2*R*,3*S*)-**13j** |
| 16 | **b** | (*S*)-**k** | 24 h | 98 | >98 | (2*S*,3*R*)-**13k** |
| 17 | **b** | (*S*)-***l*** | 1 min | 98 | >94 | (2*S*,3*R*)-**13l** |
| 18 | **b** | (*S*)-**m** | 2 min | 99 | >94 | (2*S*,3*R*)-**13m** |
| 19 | **b** | (*S*)-**n** | 1.5 h | 95 | >98 | (2*S*,3*R*)-**13n** |
| 20 | **b** | (*S*)-**o** | 1 min | 99 | >94 | (2*S*,3*R*)-**13o** |
| 21 | **b** | (*R*)-**p** | 40 min | 96 | >94 | (2*R*,3*S*)-**13p** |
| 22 | **b** | (*S*)-**q** | 5 min | 96 | >94 | (2*S*,3*R*)-**13q** |
| 23 | **b** | (*S*)-**r** | 1 min | 99 | >94 | (2*S*,3*R*)-**13r** |
| 24 | **b** | (*S*)-**s** | 6 h | 93 | >98 | (2*S*,3*R*)-**13s** |
| 25 | **b** | (*S*)-**t** | 5 min | 97 | >94 | (2*S*,3*R*)-**13t** |
| 26 | **b** | (*S*)-**u** | 1 min | 99 | >94 | (2*S*,3*R*)-**13u** |
| 27 | **b** | (*S*)-**v** | 5 min | 96 | >94 | (2*S*,3*R*)-**13v** |
| 28 | **b** | (*R*)-**w** | 12 h | | no reaction | |
| 29 | **b** | (*R*)-**x** | 12 h | | no reaction | |

[a] All reactions were run in DMF in the presence of 15 mol % of DBU at ambient temperature. Ratio **1a**,**b**/(*S*)- or (*R*)-**6** = 1/1.05−1.1. [b] Isolated yield of crude product. [c] Determined by NMR (500 MHz) analysis of the crude reaction mixtures. [d] The absolute configuration of the products was determined on the basis of chiroptical properties of the Ni-complexes **11** and **13**, as well as by comparison of the optical rotation of the corresponding pyroglutamic acids **15** isolated from the corresponding complexes with literature data; see also text. [e] 30 mol % of DBU was used. [f] Less than 30% conversion of the starting materials. [g] Isolated yield (column chromatography) of the diastereomerically pure compound. [h] Diastereo- and enantiomerically pure compound isolated by chromatography of the reaction mixture. Since the reaction was incomplete and accompanied by formation of some byproducts, the original stereochemical outcome could not be determined by using NMR analysis of the crude reaction mixture. See also text.

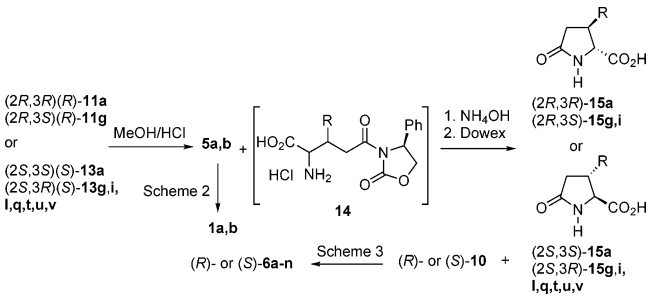
tions. To our satisfaction, the reaction occurred at a substantially higher rate (20 min) with the same perfect stereochemical outcome, as the only diastereomeric product obtained was **13a** (entry 5 vs entry 1). This result suggested that, as we assumed, the substituent at the ketimine carbon in complexes **1a**,**b** (Ph or Me, respectively) influences only the reaction rate, while both simple and face selectivity in the addition reaction are effectively controlled by the Michael acceptor used. Application of the (*S*)-configured *N*-(*E*-crotonyl)-4-phenyl-3-oxazolidin-2-one (**6a**) in the addition with complex **1b** mirrored the results obtained in the reaction of the (*R*)-**6a** giving rise to only the diastereomeric product (2*S*,3*S*)-**13a**, in quantitative chemical yield (entry 6). The crude compound (2*S*,3*S*)-**13a** was decomposed without any purification to afford the corresponding enantiomerically pure pyroglutamic acid (2*S*,3*S*)-**15a** (Scheme 6). Synthesis of (2*S*,3*S*)-**15a** was performed on a 10-g scale demonstrating the preparative efficiency of the method. Finally, to find out the origin of the observed stereochemical outcome,

**SCHEME 5**[a,b]




[a] Reagents and conditions: (i) DMF, DBU (15 mol %), rt (18−23 °C). [b]Key: R = Me, R′ = H (**a**); R = Et, R′ = H (**b**); R = *n*-Pr, R′ = H (**c**); R = *i*-Pr, R′ = H (**d**); R = Bn, R′ = H (**e**); R = R′ = Me (**f**); R = Ph, R′ = H (**g**), R = α-naphthyl, R′ = H (**h**); R = 4-MeO-$C_6H_4$, R′ = H (**i**); R = 3-MeO-$C_6H_4$; R′ = H (**j**); R = 2-MeO-$C_6H_4$; R′ = H (**k**); R = 4-$CF_3$-$C_6H_4$; R′ = H (***l***); R = 3-$CF_3$-$C_6H_4$; R′ = H (**m**); R = 2-$CF_3$-$C_6H_4$; R′ = H (**n**); R = 4-$NO_2$-$C_6H_4$; R′ = H (**o**); R = *N*-Mts-*β*-indolyl, R′ = H (**p**); R = 4-F-$C_6H_4$; R′ = H (**q**); R = 3,5-$F_2$-$C_6H_3$; R′ = H (**r**); R = 2,6-$F_2$-$C_6H_3$; R′ = H (**s**); R = 4-Cl-$C_6H_4$; R′ = H (**t**); R = 3,4-$Cl_2$-$C_6H$; R′ = H (**u**); R = 4-Br-$C_6H_4$; R′ = H (**v**); R = Ph, R′ = Me (**w**); R = R′ = Ph (**x**).

**SCHEME 6**




we subjected the diastereomerically pure product (2*R*,3*R*)-**13a** to the original reaction conditions, except that 50 mol % of DBU was used. Analysis of the reaction mixture (4 days) revealed up to 2% of decomposition products, but the compound (2*R*,3*R*)-**13a** was isolated in 95% chemical yield and was stereochemically intact. The data obtained allow us to conclude that the addition reaction under study is virtually irreversible and the observed stereochemical outcome is likely kinetically controlled.

With these results in hand we studied next the generality of the method employing achiral complex **1b**. First we investigated the addition reactions between the Ni(II)-complex **1b** and (*R*)-3-(*E*-enoyl)-4-phenyl-3-oxazolidin-2-ones **6b−d** bearing an alkyl substituent R on the C,C double bond using the standard reaction conditions: DMF solution, 15 mol % of DBU, and ambient temperature (Scheme 1). Under these conditions, ethyl (*R*)-**6b** and *n*-propyl (*R*)-**6c**-containing oxazolidin-2-ones readily reacted with complex **1b** to afford the corresponding diastereomers (2*R*,3*R*)-**13b** and (2*R*,3*R*)-**13c**, respectively, as major reaction products in excellent isolated yields (Table 1, entries 7 and 8). NMR (500 MHz) analysis of the crude reaction mixture revealed that some byproducts or other diastereomers were present in the mixture but in amounts not greater than 2−3%.[14] In contrast, the addition of complex **1b** with oxazolidin-2-one (*R*)-**6d**, containing the bulky isopropyl group, proceeded at a very slow rate (entry 9). After 4 h of reaction, conversion of the starting materials was not higher than 30% and substantial amounts of byproducts were detected by TLC.

Though we isolated the target product (2*R*,3*S*)-**13d**[15] in 15% yield (flash chromatography), these results suggest that the present method could not be extended to substrates containing tertiary alkyl R groups. Unfortunately our attempts to react complex **1b** with benzyl-containing **6e** (entry 10) and bis-methyl-containing **6f** (entry 11), albeit for different reasons,[17] added to the limitations of the method.

**Reactions between Acetophenone-Derived Complex 1b and Aryl-Containing Chiral Michael Acceptors.** To examine the applicability of the method to aromatic series, which would lead to the synthesis of the corresponding 3-aryl-substituted amino acids, we chose substrates containing classical phenyl **6g** and naphthyl **6h** groups; derivatives bearing a phenyl ring with electron-donating (OMe) **6i**−**k** and electron-withdrawing ($CF_3$, $NO_2$) **6*l***−**o** groups in *p*-, *m*- and *o*-positions; and compounds with the electron-rich indolyl moiety **6p** as well as a series of mono- and difluoro- **6q**−**s**, -chloro- **6t**,**u**, and -bromo-substituted cinnamic acid derivatives **6v**. We also synthesized bis-substituted aromatic derivatives **6w**,**x** to explore the possibility of preparing *β*,*γ*-disubstituted glutamic acids. The addition of Ni(II)-complex **1b** with *N*-cinnamyl derivative (*R*)-**6g** (entry 12) occurred at a high reaction rate, similar to the rates observed in the aliphatic series, giving rise to the corresponding product **13g** in excellent chemical yield and diastereomeric purity. Analysis of the crude reaction mixture (NMR) showed that the content of the major diastereomer **13g** was at least 97%, while three other theoretically possible diastereomeric products and/or byproducts were formed in an amount not greater than 3%.[14] The addition of complex **1b** with the naphthyl derivative (*R*)-**6h** (entry 13) occurred unexpectedly at the same rate as the reaction of the phenyl-containing (*R*)-**6g** (entry 13 vs entry 12), despite the fact that the naphthyl group might be considered as more sterically demanding then the phenyl group. As expected, the addition of the methoxy-containing derivatives (*S*)-**6i**,**k** and (*R*)-**6j** with complex **1b** occurred at lower reaction rates, as a consequence of the electron-releasing effect of the methoxy group, however, with the same synthetically excellent stereochemical outcome (entries 14−16). On the other hand, substrates (*S*)-**6*l***−**o**, with enhanced electrophilicity of the C,C double bond, due to the electron-withdrawing effect of trifluoromethyl or nitro group, reacted with complex **1b** at very high rates affording the diastereomerically pure products (2*S*,3*R*)-**13*l***−**o** in excellent chemical yields and optical purities (entries 17−20). In these cases the reaction went to completion even when a 1/1 ratio of the starting compounds was used. By contrast the indolyl derivative (*R*)-**6p** reacted with complex **1b** rather slowly (40 min). However, the product (2*R*,3*S*)-**13p** was isolated as a sole reaction product in high chemical yield (entry 21). In a series of reactions of mono- and dihalo-substituted derivatives (*S*)-**6q**−**v** with **1b**, we observed a similar pattern of reactivity (entries 22−27). The monosubstituted compounds (*S*)-**6q**,**t**,**v** reacted with **1b** more slowly (entries 22, 25, and 27), as compared with the rates observed in the reactions of disubstituted (*S*)-**6r,s,u** (entries 23 and 26). The only exception was the reaction of ortho,ortho-disubstituted compound (*S*)-**6s** requiring about 6 h for completion (entry 24). Unfortunately, all attempts to involve the bis-substituted derivatives **6w**,**x** in the addition reactions with complex **1b**, under the standard or forcing reaction conditions, were unsuccessful (entries 28 and 29). These results, along with the negative outcome of the bismethyl derivative **6f** (entry 11), suggested that α-substitution on the starting Michael acceptors, apart from the electronic effects, might create some sterically unfavorable interactions interfering with the addition process.

These data clearly suggest that the pattern of the substitution (steric or electronic) on the phenyl ring in Michael acceptors **6g**−**v** influences dramatically the rate of the addition and slightly affects the stereochemical outcome of the reaction. As one can see from Table 1, in all cases studied, the major diastereomers (2*R*,3*S*)-**13g**,**h**,**j**,**p** or (2*S*,3*R*)-**13i**,**k**−**o**,**q**−**v** were obtained in excellent chemical yields and in, at least, 94% diastereomeric excess.

**Stereochemical Assignments.** The absolute configurations of the 3-(3′,4′dichlorophenyl)- and -(4-trifluoromethylphenyl)glutamic acid residues in the products **13u**,***l*** were determined as (2*S*,3*R*) by X-ray analysis (see the Supporting Information). In four other cases the products **11a**, **11g**, **13a**, and **13g**, which were obtained by using the (*R*)-configured Michael acceptors **6a**,**g**, were decomposed (Scheme 6) to yield the corresponding pyroglutamic acids. The absolute configuration of the acids was assigned as (2*R*,3*R*)-**15a** and (2*R*,3*S*)-**15g** by comparison of the NMR data and optical rotation of acids **15a**,**g** with the literature data. The stereochemistry of all of the other products was assigned by analogy based on the similarity of the spectral and optical properties of the products.

These data allowed us to conclude that in both aliphatic and aromatic series using complex **1a** or **1b**, the sense of stereochemical preferences is the same, giving rise almost exclusively to the products (with combination of the trigonal centers) with relative topicity *like*.[6]

**Mechanistic Considerations.** Considering the relative stereochemistry of the addition products in the reactions between achiral complexes **1a**,**b** and achiral 1,3-oxazolidin-2-one Michael acceptors **2** (Scheme 1), the chiral complex (*S*)-**4**, and achiral **2**,[1h] as well as the reactions under study (Scheme 5), between the achiral glycine complexes **1a**,**b** and chiral Michael acceptors **6**, we can assume that all these reactions occur via similar transition states (TSs) in which the approach geometry of the corresponding trigonal centers has the relative topicity *like*.[6] Therefore, based on the mechanistic conclusions made in our previous work, we can construct TS **A** (Figure 1) to account for the stereochemical outcome observed in the present study. Thus, TS **A**, in which the *β*-substituent (R) of Michael acceptors **6** and the ketimine group (R″ = Ph or Me) are in a close proximity to each

(14) Due to the minute integral intensity of some peaks found in the NMR spectra of the crude reaction mixtures it was impossible to conclude whether they belong to another diastereoisomer or to byproducts.

(15) The (2*R*,3*S*) absolute stereochemistry for the isopropyl and aromatic derivatives is a consequence of the Cahn−Ingold−Prelog priorities (see ref 16) and is stereochemically equivalent to the (2*R*,3*R*) absolute configuration in the aliphatic series of compounds.

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

(17) While in the case of bis-methyl-containing **6f** derivative the presence of the α-substituent might create unfavorable steric interactions and decrease electrophilicity of the C,C double bond, the high C−H acidity of the benzylic methylene group in **6e** might be the cause of the unsuccessful results.

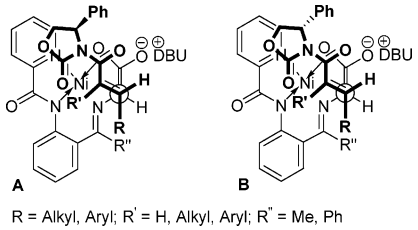
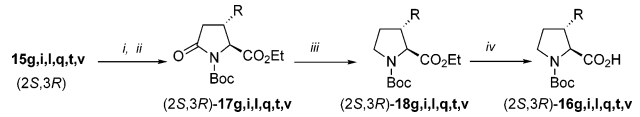



**FIGURE 1.** Possible TSs in the addition between **6a**,**b** and **11**.

other, can easily account for the noticeable difference in reactivity between **1a** (R″ = Ph) and **1b** (R″ = Me) as a result of the corresponding unfavorable steric interactions in the former case. As a consequence of these steric interactions, the observed higher stereoselectivity in the reactions of the aromatic Michael acceptors **6g**−**v** with complex **1b**, as compared with the additions with **1a**, also can be understood. Next, TS **A** perfectly accounts for the failure to accomplish the addition reactions between complex **1b** and bis-substituted Michael acceptors **6f**,**w**,**x**. As one can see, in TS **A** the α-substituent (R′) on the Michael acceptor is pointing directly to the Ni atom of complex **1b**, thus causing nonbonding, unfavorable steric interactions which might interfere with the formation of this TS. Apparently, when the R′ is an H, the latter can easily fit in the room provided by TS **A** and the corresponding addition reactions can proceed smoothly to completion.

Finally, the central question of this study—the unexpected stereocontrolling power of the 4-phenyl-1,3-oxazolidin-2-one chiral auxiliary on the Michael acceptors—can be fully rationalized by using TS **A**. In the TS **A**, which represents the interaction between complexes **1a**,**b** and the (*R*)-configured Michael acceptor, the phenyl at C-4 of the chiral oxazolidinone ring is pointed up, away from any possible steric interactions with the rest of substituents on both the Ni(II)-complex and the Michael acceptor. In this position the phenyl does not control directly the facial diastereoselectivity of the Michael acceptor's C,C double bond via a stereodiscrimination process but works as a topographical feature, making a difference in accessibility of the Michael acceptor plane sides by the plane of the Ni(II)-complex. Thus, in the case when the Michael acceptor is of opposite (*S*)-configuration, the hypothetical TS **B** (Figure 1) cannot be formed as the phenyl pointed down will interfere with the approaching Ni(II)-complex plane. Instead, the (*S*)-configured Michael acceptor will allow the Ni-complex to approach the opposite Michael acceptor's side to form a similar TS leading to the products with (2*S*,3*S*) (R = *n*-alkyl) absolute configuration. This mode of interaction, controlling the absolute configuration of the products, represents a topographical match or mismatch of two geometric figures and so we are inclined to call it topographically controlled face diastereoselectivity. Our results demonstrate that topographically controlled face diastereoselectivity, realized in the reactions under study, is a much more powerful way to achieve stereocontrol in asymmetric reactions, as compared with the usual stereodiscrimination process involving interactions between a stereocontrolling element with other substituents on the reacting molecules.

**SCHEME 7**[a]




[a] Reagents and conditions: (i) $SOCl_2$, EtOH; (ii) $(Boc)_2O$, DMAP, $CH_3CN$; (iii) (a) $Et_3LiBH$/THF, (b) $Et_3SiH/BF_3$-$OEt_2$; (iv) LiOH/THF.

**Elaboration of the Pyroglutamic Acids 15.** As mentioned above, simple decomposition of the addition products **11** or **13**, followed by $CHCl_3$ extraction and Dowex chromatography, allows for the simultaneous recovery of ligands **5a**,**b**, chiral auxiliary (*S*)- or (*R*)-**10**, and isolation of the target pyroglutamic acids **15** (Scheme 6). The latter could be easily obtained in the analytically and diastereo- and enantiomerically pure state simply by recrystallization from THF/hexanes, that renders our method not only synthetically efficient (virtually complete diastereoselectivity) but also operationally superior over previous approaches.[1−4] Previously we have demonstrated that acidic hydrolysis of the pyroglutamic acids **15** easily afforded the corresponding glutamic acids.[1h] In this study we report the preparation of *β*-substituted prolines **16** via reduction of pyroglutamic acids **15** (Scheme 7).

Transformation of **15** to their ethyl esters by reaction with thionyl chloride in ethanol,[18] followed by protection of the amide NH with *tert*-butoxycarbonyl (Boc) groups[19] produced the *N*-Boc-3-aryl pyroglutamates **17** in good yields (75−96%). To selectively reduce the amide carbonyl group to a methylene group, we first used $BH_3$·$Me_2S$ as a reducing agent.[20] In a typical case of ethyl (2*S*,3*R*)-*N*-Boc-3-phenylpyroglutamate **17a**, the reduction proceeded slowly at room temperature to completion in 4 days and afforded the *N*-Boc-3-phenylprolinate **18a**, along with significant amounts of a byproduct, (2*S*,3*R*)-*N*-Boc-3-phenyl-2-pyrrolidinemethanol. We found that the yield of **18a** can be improved from 39% at room temperature to 55% by refluxing for 2 h. Nevertheless, the low yields and the overreduction resulting in the formation of the corresponding alcohol prompted us to look for other conditions. Taking advantage of the work reported by Pedregal,[21] an efficient selective reduction from the *N*-Boc-protected pyroglutamates **17** to the corresponding ethyl 3-aryl prolinates **18** was achieved. The mechanism for selective reduction has been proposed by Rubio and co-workers.[22] First, partial reduction of the amides to hemiaminals was accomplished by treating with lithium triethyl borohydride (super-hydride) in THF at −78 °C. The resulting crude hemiaminals were then reduced to give the corresponding prolinates by treatment with triethylsilane and boron trifluoride etherate in dichloromethane at −78 °C. The Lewis acid ($BF_3$·$Et_2O$) is responsible for the generation of *N*-acylimium ion inter-

(18) Silverman, R. B.; Levy, M. A. *J. Org. Chem*. **1980**, *45*, 815.
(19) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem*. **1983**, *48*, 2424.
(20) Langlois, N.; Andriamialisoa, R. Z. *Tetrahedron Lett*. **1991**, *32*, 3057.
(21) Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M. C.; Ruano, J. L. G. *Tetrahedron Lett*. **1994**, *35*, 2053.
(22) Ezquerra, J.; Pedregal, C.; Yruretagoyena, B.; Rubio, A.; Carreño, M. C.; Escribano, A.; Ruano, J. L. G. *J. Org. Chem*. **1995**, *60*, 2925.

mediates that were reduced by triethylsilane. $^1$H NMR spectra of crude reduction products showed that the *N*-Boc group was removed by the action of an excess of Lewis acid. The resulting 3-aryl prolinates were protected again with the Boc group and led to (2*S*,3*R*)-*N*-Boc-3-aryl prolinates **18**, which facilitated purification by column chromatography on silica gel and can be directly used in peptide synthesis by Boc chemistry. Finally, basic hydrolysis of **18** by LiOH in THF−MeOH−$H_2O$ solution gave (2*S*,3*R*)-*N*-Boc-3-aryl prolines **16**.

In summary, we have demonstrated that the new strategy for controlling the stereochemical outcome of the asymmetric Michael addition reactions developed in this work is methodologically superior to previous methods, most notably in terms of generality and synthetic efficiency. Excellent chemical yields and diastereoselectivities, combined with the simplicity of the experimental procedures, render the present method of immediate use for preparing various 3-substituted pyroglutamic acids and related amino acids available via conventional transformations of the former.

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**Supporting Information Available:** Complete experimental details including the general experimental procedure and full characterization of all new compounds, $^1$H NMR and proton-decoupled $^{13}$C NMR spectra of new compounds, and X-ray data (in CIF format) for Ni(II) complex of the Schiff base of PABP and (2*S*,3*R*,4′*S*)-3-(*p*-trifluoromethylphenyl)-5-[3′-(4′-phenyl-2′-oxazolidinonyl)]glutamic acid (vs295m) and for the Ni(II) complex of the Schiff base of PAAP and (2*S*,3*R*,4′*S*)-3-(*m*,*p*-dichlorophenyl)-5-[3′-(4′-phenyl-2′-oxazolidinonyl)]glutamic acid (vs2102s). This material is available free of charge via the Internet at http://pubs.acs.org.

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