ORGANIC LETTERS

2000
Vol. 2, No. 6
747−750

(*S*)- or (*R*)-3-(*E*-Enoyl)-4-phenyl-1,3-oxazolidin-2-ones: Ideal Michael Acceptors To Afford a Virtually Complete Control of Simple and Face Diastereoselectivity in Addition Reactions with Glycine Derivatives

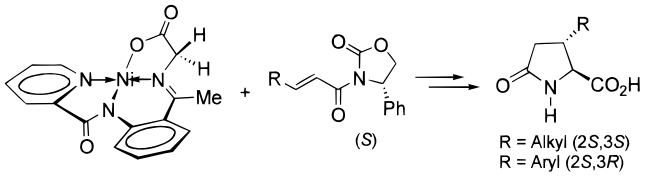
Vadim A. Soloshonok,*,† Chaozhong Cai, and Victor J. Hruby*,‡

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

hruby@mail.arizona.edu

Received December 14, 1999

ABSTRACT



Enantiomerically pure (*S*)- or (*R*)-3-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones were found to serve as ideal Michael acceptors in addition reactions with achiral Ni(II) complexes of glycine Schiff bases. Virtually complete control of simple and face diastereoselectivity, observed in these reactions, combined with quantitative chemical yields renders this methodology synthetically superior to the previous methods.

The asymmetric Michael addition is among the most powerful reactions in synthetic organic chemistry.[1] In particular, the additions between glycine equivalents and α,β-unsaturated carboxylic acid derivatives, which provide the most straightforward and generalized approach to β-substituted glutamic and pyroglutamic acids, glutamines, and prolines, have been extensively studied over the past 15 years.[2,3] Analysis of the relevant literature[2−4] reveals that thus far only one strategy to control the stereochemical outcome in these reactions has been explored. In this approach additions of various chiral glycine equivalents with α,β-unsaturated carboxylic acid derivatives were studied and, in some cases,

† Vadim A. Soloshonok: Department of Chemistry, The University of Arizona, 1306 East University, Tucson, AZ 85721. Fax: (520) 621-4964. e-mail: vadym@u.arizona.edu.

‡ Regents Professor Victor J. Hruby: Department of Chemistry, The University of Arizona, 1306 East University, Tucson, AZ 85721. Fax: (520) 621-8407. e-mail: hruby@mail.arizona.edu.

(1) (a) Oare, D. A.; Heathcock, C. H. *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1990; Vol. 19, pp 227−407. (b) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132.

(2) For reviews, see: (a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (b) Ohfune, Y. *Acc. Chem. Res.* **1992**, *25*, 360. (c) Williams, R. M. *Synthesis of Optically Active* α*-Amino Acids*; Pergamon Press: Oxford, 1989.

(3) For leading papers, see: (a) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron: Asymmetry* **1999**, *10*, 4265. (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) Antolini, L.; Forni, A.; Moretti, I.; Prati, F. *Tetrahedron: Asymmetry* **1996**, *7*, 3309. (e) Gestmann, D.; Laurent, A. J.; Laurent, E. G. *J. Fluorine Chem.* **1996**, *80*, 27. (f) Hartzoulakis, B.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2525. (g) Suzuki, K.; Seebach, D. *Liebigs Ann. Chem.* **1992**, 51. (h) Belokon, Yu. 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. (i) El Achqar, A.; Boumzebra, M.; Roumestant, M.-L.; Viallefont, P. *Tetrahedron* **1988**, *44*, 5319. (j) Pettig, D.; Schöllkopf, U. *Synthesis* **1988**, 173. (k) Schöllkopf, U.; Pettig, D.; Schulze, D.; Klinge, M.; Egert, E.; Benecke, B.; Noltemeyer, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1194. (l) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, 44, 5277. (m) Hartwig, W.; Born, L. *J. Org. Chem.* **1987**, *52*, 4352. (n) Minowa, N.; Hirayama, M.; Fukatsu, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1761. (o) Belokon, Yu. N.; Bulychev, A. G.; Ryzhov, M. G.; Vitt, S. V.; Batsanov, A. S.; Struchkov, Yu. T.; Bakhmutov, V. I.; Belikov, V. M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1865. (p) Schöllkopf, U.; Pettig, D.; Busse, U. *Synthesis* **1986**, 737.

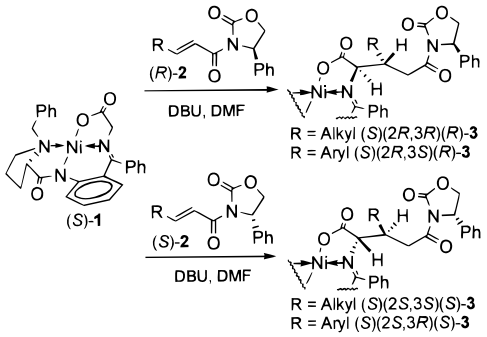
10.1021/ol990402f CCC: $19.00
Published on Web 02/24/2000

reasonably high levels of asymmetric induction at both the α- and β-positions of the resultant glutamic acid derivatives were obtained.[2−4] Surprisingly, the alternative strategy, an application of chiral derivatives of α,β-unsaturated carboxylic acids in the reactions with achiral glycine equivalents, remains virtually unexplored so far.[5] We wish to report that the enantiomerically pure 3-(*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 Ni(II) complexes of glycine Schiff bases. Extraordinarily high chemical and optical yields, combined with the extreme simplicity of the experimental procedure, render this new strategy synthetically superior over the previously reported approaches.

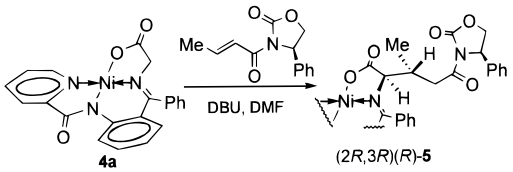
Recently we discovered that the Ni(II) complex of the chiral Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)-amino]benzophenone **1** and chiral 3-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **2** (Scheme 1) represent a unique combination of nucleophilic glycine equivalent and Michael acceptor, respectively, to afford virtually complete control of simple and face diastereoselectivity in the corresponding addition reactions.[6] A distinguishing feature of these reactions, as compared with the previously reported methods, is that they proceeded at room temperature in the presence of catalytic amounts of DBU, giving rise to the sole diastereomeric products in quantitative chemical yield. However, a most unexpected observation was the fact that the stereochemical outcome in these reactions was overwhelmingly controlled by the chirality of Michael acceptor **2**. Thus, the additions of (*S*)-**1** with (*S*)-**2** gave rise to (*S*)-(2*S*,3*S*)-**3** (R = Alk) while application of (*R*)-**2** furnished (*S*)-(2*R*,3*R*)-**3** (R = Alk) derivatives. The slower reaction rates in the former case were the only noticeable effect of complex (*S*)-**1** chirality on the addition process. Since DBU, used as a base in our reactions, cannot be considered as a chelating agent, such a powerful stereocontrolling effect of the 4-phenyl-1,3-oxazolidin-2-one moiety on the Michael acceptors **2** was rather surprising.[7] In addition to our interest in the origin of stereoselectivity in these reactions,[10] the results obtained offered a pleasant bonus of further improving of synthetic efficacy of our method by employing achiral Ni(II) complexes in place of chiral (*S*)-**1**.

First we studied the reaction between the Ni(II) complex of the Schiff base of glycine with *o*-[*N*-α-pycolylamino]-benzophenone **4a**, the achiral analogue of (*S*)-**1**, and (*R*)-3-(*E*-crotonyl)-4-phenyl-1,3-oxazolidin-2-one (**2a**) (Scheme 2).

Scheme 1



Scheme 2



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 diastereomer, **5**, by NMR (500 MHz) in quantitative chemical yield (Table 1, entry 1). Despite the excellent diastereoselectivity obtained, the reaction rate was unsatisfactory slow,[11] as compared with the 5 min reaction of chiral (*S*)-**1** with **2a**.[6] Therefore, we examined, under the same reaction conditions, the addition

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

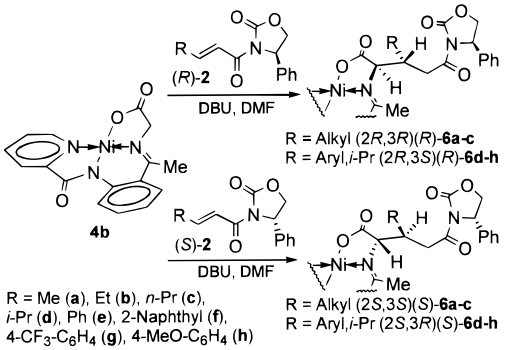
				products **5**, **6a**−**h**		
entry	**4a**,**b**	**2a**−**h**	time	yield,[b] %	de,[c] %	config[d]
1	**a**	(*R*)-**a**	50 min	99	>98	(2*R*,3*R*)-**5**
2	**b**	(*R*)-**a**	20 min	99	>94	(2*R*,3*R*)-**6a**
3	**b**	(*S*)-**a**	20 min	99	>94	(2*S*,3*S*)-**6a**
4	**b**	(*R*)-**b**	20 min	99	>94	(2*R*,3*R*)-**6b**
5	**b**	(*R*)-**c**	20 min	99	>94	(2*R*,3*R*)-**6c**
6	**b**	(*R*)-**d**	4 h[e]	15[f]	>99[g]	(2*R*,3*R*)-**6d**
7	**b**	(*R*)-**e**	10 min	98	>94	(2*R*,3*S*)-**6e**
8	**b**	(*R*)-**f**	10 min	96	>94	(2*R*,3*S*)-**6f**
9	**b**	(*S*)-**g**	5 min	98	>94	(2*S*,3*R*)-**6g**
10	**b**	(*S*)-**h**	30 min	99	>94	(2*S*,3*R*)-**6h**

[a] All reactions were run in DMF in the presence of 15 mol % of DBU at ambient temperature. Ratio **4a**,**b**/(*S*)-or (*R*)-**2** 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 **5** and **6a**−**h**, as well as by comparison of the optical rotation of the corresponding pyroglutamic acids **9** isolated from the corresponding complexes with literature data; see also the text. [e] Less then 30% conversion of the starting materials. [f] Isolated yield (column chromatography) of the diastereomerically pure compound. [g] 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 using NMR analysis of the crude reaction mixture. See also text.

(4) Seebach, D.; Hoffman, M. *Eur. J. Org. Chem.* **1998**, 1337.
(5) (a) Shibuya, A.; Kurishita, M.; Ago, C.; Taguchi, T. *Tetrahedron* **1996**, *52*, 271. A correction for the absolute configuration of products reported in the paper was subsequently made: (b) Shibuya, A.; Sato, A.; Taguchi, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1979. (c) Ezquerra, J.; Pedregal, C.; Merino, I.; Flórez, J.; Barluenga, J.; García-Granda, S.; Llorca, M.-A. *J. Org. Chem.* **1999**, *64*, 6554.
(6) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Angew. Chem., Int. Ed.*, in press.

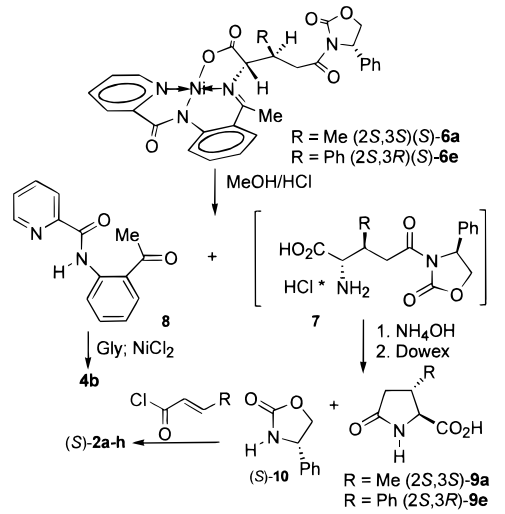
between oxazolidinone (*R*)-**2a** and a Ni(II) complex of the Schiff base of glycine with *o*-[*N*-α-pycolylamino]acetophenone **4b** (Scheme 3). To our satisfaction, the reaction

Scheme 3



occurred at a substantially higher rate (20 min) with the same perfect stereochemical outcome: the only diastereomeric product **6a** was obtained (entry 2). These results suggest that the substituent at the ketimine carbon in complexes **4a**,**b** (Ph or Me, respectively) influences only the reaction rate, while both simple and face selectivity in the addition reaction are controlled by the Michael acceptor used. To assign the absolute stereochemistry of products **5** and **6a**, we decomposed these complexes to afford pyroglutamic acid **9**, along with a 95−97% recovery of ligand **8**, and the chiral auxiliary **10** (Scheme 4). Comparison of the spectroscopic and

Scheme 4



chiroptical properties of acid **9** with the literature data revealed its (2*R*,3*R*) absolute configuration. Application of the (*S*)-configured 3-(*E*-crotonyl)-4-phenyl-3-oxazolidin-2-one (**2a**) in the addition with complex **4b** mirrored the results obtained in the reaction of (*R*)-**2a**, giving rise to only the diastereomeric product (2*S*,3*S*)-**6a**, in quantitative chemical yield (entry 3). The crude compound (2*S*,3*S*)-**6a** was decomposed without any purification to afford the corresponding enantiomerically pure pyroglutamic acid (2*S*,3*S*)-**9**. Synthesis of (2*S*,3*S*)-**9** was performed on a 10 g scale, demonstrating the preparative efficiency of the method.[12] Finally, to find out the origin of the observed stereochemical outcome, we subjected the diastereomerically pure product (2*R*,3*R*)-**6a** to the original reaction conditions, except that 50 mol % of DBU was used. Analysis of the reaction mixture (4 days) revealed some trace amounts of starting complexes **4b** as well as up to 2% of decomposition products, and compound (2*R*,3*R*)-**6a** 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. Since the acetophenone-derived complex **4b**, designed and introduced for the first time by our group,[13] was found to be superior over the benzophenone derivative **4a**, we used the former glycine complex in the rest of the study. First we investigated the addition reactions between the Ni(II) complex **4b** and (*R*)-3-(*E*-enoyl)-4-phenyl-3-oxazolidin-2-ones **2b**−**d** bearing an alkyl substituent R on the C,C double bond using the standard reaction conditions: DMF solution, 15 mol % of DBU, ambient temperature (Scheme 2). Under these conditions, ethyl- and *n*-propyl-containing oxazolidin-2-ones (*R*)-**2b** and (*R*)-**2c** readily reacted with complex **4b** to afford the corresponding diastereomers (2*R*,3*R*)-**6b** and (2*R*,3*R*)-**6c**, respectively, as major reaction products in excellent isolated yield (Table 1, entries 4 and 5). NMR (500 MHz) analysis of the crude reaction mixture revealed that two more diastereoisomers, or byprod-

(7) Despite the fact that chiral 4-substituted 1,3-oxazolidin-2-ones represent a group of one of the most studied and useful auxiliaries in organic chemistry,[8] their use in controling the face selectivity of Michael acceptors in the DBU-catalyzed reactions under study was not straightforward. To the best of our knowledge, a successful application of chiral oxazolidines in asymmetric synthesis requires the use of a chelating agent to ensure a stereocontrolling effect of the substituent at the C-4 stereogenic carbon of the oxazolidine ring. In particular, *N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones (**2**) exist exclusively in the *s-cis* conformation[9] 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.

(8) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23.

(9) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(10) The corresponding mechanistic studies are currently in progress.

(11) The reactions of complex **4a** with more sterically demanding Michael acceptors **2**, such as *N*-cinnamyl derivative **2e**, containing a phenyl group, require even longer reaction times and thus were accompanied by formation of some byproducts.

(12) A solution of diastereomerically pure complex (2*S*,3*S*)(*S*)-**6a** (15 mmol) in MeOH (50 mL) was slowly added with stirring to a mixture of aqueous 3 N HCl and MeOH (90 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 concentrated NH_4OH and extracted with $CHCl_3$ (3 × 100 mL). The $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated in vacuo to afford a 1:1 mixture (99%) of ligand **8** and chiral auxiliary (*S*)-**10**. The aqueous solution was evaporated in vacuo, dissolved in a minimum amount of water, and loaded on cation-exchange resin Dowex 50 × 2 100. The column was washed with water, and the acidic fraction was collected to give, after evaporation in vacuo, pyroglutamic acid (2*S*,3*S*)-**9a** (96%). An analytically pure sample of the product was obtained by crystallization of the compound from THF/*n*-hexane.

(13) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41(2)*, 135.

ucts,[14] were present in the mixture but in amounts not greater than 2−3%. In contrast, the addition of complex **4b** with oxazolidin-2-one (*R*)-**2d**, containing the bulky isopropyl group, proceeded at a very slow rate (entry 6). 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 **6d** in 15% yield (flash chromatography), these results suggest that the present method could not be extended to substrates containing tertiary alkyl R groups.

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 and naphthyl groups **2e** and **2f**, as well as derivatives bearing a phenyl ring with electron-withdrawing and electron-donating **2g** and **2h** substituents. The addition of Ni(II) complex **4b** with *N*-cinnamyl derivative (*R*)-**2e** (entry 7) occurred at a high reaction rate, similar to the rates observed in the aliphatic series (entries 2−5), giving rise to the corresponding product **6e** in excellent chemical yield and diastereomeric purity. Analysis of the crude reaction mixture (NMR) showed that the content of the major diastereomer **6e** was at least 97%, while three other theoretically possible diastereomeric products and/or byproducts[14] were formed in an amount not greater than 3%. To determine the absolute configuration of product **6e**, it was decomposed using our standard procedure to afford the corresponding pyroglutamic acid **9e** which gave spectral and chiroptical properties consistent with its (2*R*,3*S*) absolute stereochemistry.[15] These data allowed us to conclude that in both the aliphatic and aromatic series 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*.[17]

The addition of complex **4b** with 2-naphthyl derivative (*R*)-**2f** (entry 8) occurred unexpectedly at the same rate as that for the reaction of the phenyl-containing (*R*)-**2e** (entry 7 vs 8), despite the fact that the 2-naphthyl group might be considered to be more sterically demanding than the phenyl group. On the other hand, substrate (*S*)-**2g**, with enhanced electrophilicity of the C,C double bond due to the electron-withdrawing effect of the trifluoromethyl group, reacted almost instantly with complex **4b**, affording the product diastereomer (2*S*,3*R*)-**6g** in excellent chemical yield and optical purity (entry 9). In this case the reaction went to completion even when a 1/1 ratio of the starting compounds was used. As expected, the addition of the methoxy-containing derivative (*S*)-**2h** with complex **4b** occurred at a substantially lower reaction rate but with the same synthetically excellent stereochemical outcome (entry 10). These data clearly suggest that the pattern of the substitution (steric or electronic) on the phenyl ring in Michael acceptors **2e**−**h** influences only the rate of the addition and does not affect the stereochemical outcome of the reaction. As one can see from Table 1, in all cases studied, the major diastereomers (2*R*,3*S*)-**6e**,**f** or (2*S*,3*R*)-**6g**,**h** were obtained in excellent chemical yields and in, at least, 94% diastereomeric excess (entries 7−10).

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 the previous methods, most notably in terms of generality and synthetic efficiency. Excellent chemical yields and diastereoselectivity, 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. The full scope of the method and mechanism of these Michael addition reactions are currently under study.

Acknowledgment. The work was supported by the grants from U.S. Public Health Service and the National Institute of Drug Abuse (DA 06284, DA 04248, and DK 17420). The views expressed are those of the authors and not necessarily those of the USPHS.

Supporting Information Available: Experimental procedures and characterization of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990402F

(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 diastereoisomers or to byproducts.

(15) The (2*R*,3*S*) absolute stereochemistry for the 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) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.