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Application of (*S*)- and (*R*)-methyl pyroglutamates as inexpensive, yet highly efficient chiral auxiliaries in the asymmetric Michael addition reactions

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Abstract—Methyl *N*-(*E*-enoyl)pyroglutamates, derived from inexpensive and readily available in both enantiomeric forms pyroglutamic acid were found to be an efficient Michael acceptors in the addition reactions with nucleophilic glycine equivalent allowing for an efficient practical asymmetric synthesis of β-substituted pyroglutamic acids and related compounds.

Synthesis of sterically constrained amino acids has attracted a great deal of attention in the past.[1] The interest toward these man-made amino acids is driven mostly by their application as a constrained structural unit in the de novo peptide design.[2] Of particular interest are β-substituted glutamic/pyroglutamic acids[3] as these compounds can be transformed to a family of the corresponding χ-constrained[4] five-carbon-atoms amino acids including glutamines, prolines, ornithines, and arginines.[5] The asymmetric synthesis of β-substituted pyroglutamic acids gains also an additional impetus considering practical synthetic applications of the natural pyroglutamic acid for preparing numerous stereochemically defined and biologically important compounds.[5]

Recently, we have developed organic base-catalyzed, room-temperature Michael addition reactions between nucleophilic glycine equivalents and α,β-unsaturated carboxylic acid derivatives[6,7] as an operationally convenient and generalized method for preparing β-substituted glutamic/pyroglutamic acids. In particular, we have demonstrated that *N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones (**1**) (Scheme 1) serve as ideal Michael acceptors in the addition reactions with various chiral and achiral equivalents of nucleophilic glycine, in particular the Ni(II)-complex **2**,[8] introduced by us, to afford the corresponding addition products **3** in high-to-quantitative chemical yields and with virtually complete diastereo- and enantioselectivity.[7c,h]

However, despite the fact that the Evans-type chiral auxiliary **5** can be efficiently recovered and reused by transformation to the starting Michael acceptor **1**,[9] its relatively high cost,[10] in particular for the large-scale preparations, poses a sensitive economic issue. Therefore, we decided to find a simple and economical alternative to the chiral auxiliary **5**, allowing at the same time to achieve the same, almost complete, level of stereochemical outcome provided by the Michael acceptors **1**. We now wish to report on the application of methyl pyroglutamate, as one of the most inexpensive, yet very efficient chiral auxiliaries in controlling the stereochemical outcome of the organic base-catalyzed Michael addition reactions.

Taking into account a close similarity between the structures of 1,3-oxazolidin-2-ones **5** and pyroglutamic acid **7a** (Fig. 1) it is not surprising that many research groups have been exploring the application of various compounds derived from pyroglutamic acid as Evans-type chiral auxiliaries for general asymmetric synthesis.[11]

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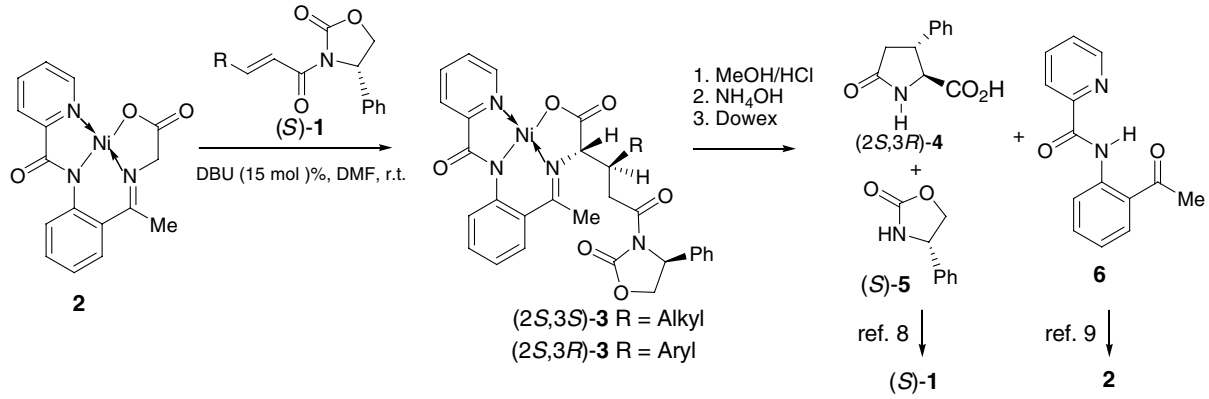


Scheme 1.

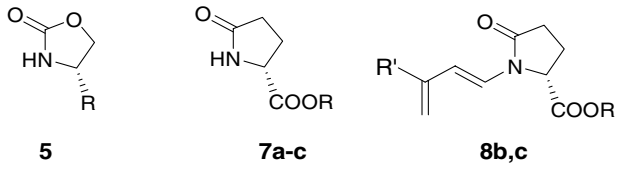


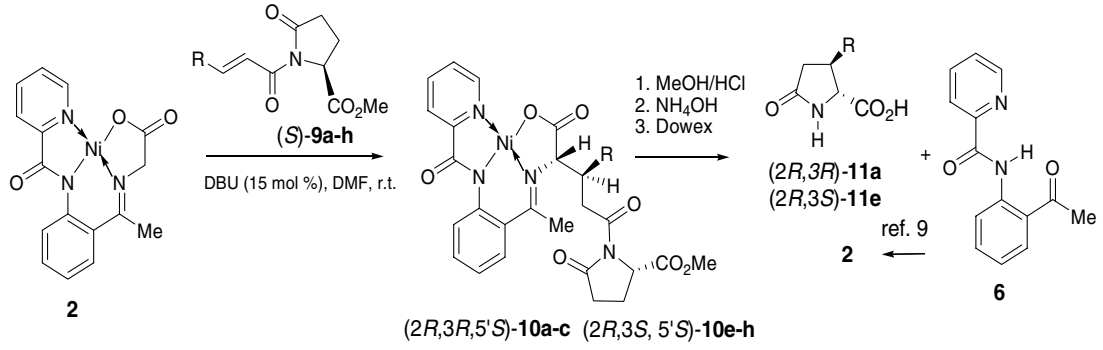
Figure 1. Reagents: (a) R = H; (b) Me; (c) Et.

However, most of the reported examples involve multistep modification of the pyroglutamic acid skeleton and therefore they lose the appeal of very inexpensive, readily available source of chirality. To the best of our knowledge, there are only three reports in the literature on application of methyl **7b** and ethyl **7c** pyroglutamates derived butadienes **8** in the Diels–Alder reactions.[12]

To explore an effectiveness of pyroglutamates as chiral auxiliaries in our Michael addition reactions, we prepared, according to the recently published procedure, a series of Michael acceptors **9** (Scheme 2) bearing various alkyl as well as aryl groups with electron-withdrawing and electron-releasing substituents. Our choice of the methyl ester **7b** was based on an expected simplicity of the NMR spectra over the corresponding products obtained form the ethyl ester **7c**. As an equivalent of nucleophilic glycine we chose the picolonic acid/*o*-(amino)acetophenone derived complex **2** as it was shown to provide the highest reaction rate and diastereoselectivity in the Michael addition reactions using *N*-(*E*-enoyl)-oxazolidinones **1**. All reactions were conducted at room temperature in a commercial-grade DMF using 15-mol% of DBU as a catalyst.

First we tried the reaction between crotonyl derived Michael acceptor (*S*)-**9a** and Ni(II)-complex **2**. To our delight the addition occurred at high reaction rate giving rise to a sole reaction product **10a** (Table 1, entry 1). Sterically bulkier ethyl (*S*)-**9b** and *n*-butyl (*S*)-**9c** containing derivatives reacted with complex **2** with a slightly slower rate however with the same complete diastereoselectivity as only one reaction product was detected by ^{1}H NMR of the crude reaction mixture (entries 2 and 3). Unfortunately, in the reaction of *i*-propyl containing Michael acceptor (*S*)-**9d** with Ni(II)-complex **2** no products were observed after 2 h of the reaction time (entry 4). Nevertheless, this outcome came without any surprise, as the corresponding *i*-propyl containing oxazol-idinone derived Michael acceptor also did not react with complex **2**.[7c,h] Application of (*R*)-configured Michael acceptor **9a** mirrored the result obtained with (*S*)-**9a** (entry 5).

In the aromatic series we first conducted the addition between cinnamoyl containing Michael acceptor (*S*)-**9e**



Scheme 2. Reagents: (a) R =Me; (b) Et; (c) *n*-Bu; (d) *i*-propyl; (e) Ph; (f) 4-OMe–C_6H_4; (g) 4-OMe–C_6H_4; (h) C_6H_5.

Table 1. Reactions between Michael acceptors **9a**–**h** and Ni(II)-complex **2**[a]

Entry	R	**9a**–**h**	*t* (min)	Yield, %[b]	% de of **10a**–**h**[d]
1	Me	(*S*)-**a**	25	96	>96[c]
2	Et	(*S*)-**b**	30	98	>96[c]
3	*n*-Butyl	(*S*)-**c**	30	98	>96[c]
4	*i*-Propyl	(*S*)-**d**	120	No reaction	
5	Me	(*R*)-**a**	25	95	>96[c]
6	Ph	(*S*)-**e**	30	96	>90
7	4-OMe–C_6H_4	(*S*)-**f**	60	91	>88
8	4-CF3–C_6H_4	(*S*)-**g**	5	95	>94
9	C_6F_5	(*S*)-**h**	2	92	>96[c]

[a] All reactions were run in dry DMF in the presence of 15 mol% of DBU at room temperature. Molar ratio (*S*)- or (*R*)-**2**/**9a**–**h**: 1.0/1.1.
[b] Isolated yield of pure product.
[c] Only one product was observed in the reaction mixture.
[d] Determined by ^{1}H NMR of the crude reaction mixture.

and complex **2**. The reaction occurred at high rate, comparable with that of the aliphatic series (entry 6). On the other hand, the stereochemical outcome was found to be a bit less perfect, as in the crude ^{1}H NMR of the reaction mixture one could find some signals (<5%) possibly belonging to other than (*S*)-**10e** diastereomer. Michael acceptor (*S*)-**9f**, containing electron-releasing *p*-methoxy group, reacted with complex **2** at noticeably slower reaction rate and with slightly lower diastereoselectivity (entry 7). By contrast, the addition between the trifluoromethyl containing (*S*)-**9g** and complex **2** occurred at very fast rate and with improved stereochemical outcome (entry 8). Of particular interest was the reaction of pentafluorophenyl derivative (*S*)-**9h**. Due to high electrophilicity of the C, C double bond in compound (*S*)-**9h** its reaction with Ni(II)-complex **2** occurred almost instantly giving rise to the product **10h** in high chemical yield (entry 9). Notably, the stereochemical outcome of this reaction was the highest in the aromatic series as sole product **10h** was detected in the crude reaction mixture by ^{1}H NMR.

Methyl and phenyl containing products **10a**,**e** were hydrolyzed under the standard conditions[7h,13] to furnish the corresponding β-substituted pyroglutamic acids **11a**,**e** as well as ligand, which was reused for preparation of starting complex **2**.[8] On the basis of spectroscopic data and optical rotations of compounds **11a**,**e** their absolute configuration was assigned as (2*R*,3*R*) for **11a** and (2*R*,3*S*) for **11b**.[14] These stereochemical results are in full agreement with the data obtained in the previous works using *N*-(*E*-enoyl)-oxazolidinones **1** as chiral Michael acceptors.[7]

In summary, we have demonstrated that inexpensive and readily available in both enantiomeric forms methyl pyroglutamate **7b** can be used as a chiral auxiliary in the place of expensive Evans-type 4-phenyloxazolidin-2-one **5**. Taking into account almost 100-fold difference in the price between these chiral auxiliaries, successful application of methyl pyroglutamate derived Michael acceptors render our organic base-catalyzed, room-temperature Michael addition reactions even more practical and appealing for large-scale preparations of enantiomerically pure β-substituted glutamic/pyroglutamic acids and related compounds.

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References and notes

1. For recent collection of leading papers, see: 'Asymmetric Synthesis of Novel Sterically Constrained Amino Acids', Tetrahedron Symposia-in-Print; #88; Guest Editors: Hruby, V. J.; Soloshonok, V. A. *Tetrahedron* **2001**, *57*, 30.
2. (a) Hruby, V. J. *Life Sci.* **1982**, *31*, 189; (b) Hruby, V. J.; Al-Obeidi, F.; Kazmierski, W. M. *Biochem. J.* **1990**, *268*, 249; (c) Hruby, V. J. *Biopolymers* **1993**, *33*, 1073; (d) Hruby, V. J.; Li, G.; Haskell-Luevano, C.; Shenderovich, M. D. *Biopolymers* **1997**, *43*, 219; (e) Cai, M.; Cai, C.; Mayorov, A. V.; Xiong, C.; Cabello, C. M.; Soloshonok, V. A.; Swift, J. R.; Trivedi, D.; Hruby, V. J. J. *Pept. Res.* **2004**, *63*, 116.
3. For a review on asymmetric synthesis of β-substituted glutamic/pyroglutamic acids, see: Soloshonok, V. A. *Curr. Org. Chem.* **2002**, *6*, 341–364.
4. For recent reviews on χ-constrained amino acids, see: Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585.
5. For recent review on various synthetic transformations of pyroglutamic acid and its derivatives, see: Najera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245.
6. For Michael addition reactions between chiral nucleophilic glycine equivalents and α,β-unsaturated carboxylic acid esters, 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.
7. For Michael addition reactions between chiral/achiral nucleophilic glycine equivalents and chiral/achiral *N*-(*E*-enoyl)-1,3-oxazolidin-2-ones, see: (a) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron: Asymmetry* **1999**, *10*, 4265; (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41*, 135–139; (c) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Org. Lett.* **2000**, *2*, 747; (d) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Angew. Chem.,*

In. Ed. **2000**, *39*, 2172; (e) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Meervelt, L. V.; Yamazaki, T. J. *Org. Chem.* **2000**, *65*, 6688; (f) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **2000**, *41*, 9645; (g) Cai, C.; Soloshonok, V. A.; Hruby, V. J. J. *Org. Chem.* **2001**, *66*, 1339; (h) Soloshonok, V. A.; Ueki, H.; Tiwari, R.; Cai, C.; Hruby, V. J. J. *Org. Chem.* **2004**, *69*, 98.

8. For recent, improved procedure for Ni(II)-complex **2** preparation, see: Ueki, H.; Ellis, T. K.; Martin, C. H.; Soloshonok, V. A. *Eur. J. Org. Chem.* **2003**, 1954.
9. For a convenient, room-temperature organic base-catalyzed protocol for preparing chiral *N*-(enoyl)-1,3-oxazolidine-2-ones, see: Soloshonok, V. A.; Ueki, H.; Jiang, C.; Cai, C.; Hruby, V. J. *Helv. Chim. Acta* **2002**, *85*, 3616.
10. According to the Aldrich catalog: 5 g of (*S*)-4-phenyl-1,3-oxazolidin-2-one **7** costs $ 179.30; (*S*)-pyroglutamic acid is more than 100 times cheaper, priced at $ 148.80 for 500 g.
11. For some recent applications of chiral auxiliaries derived from pyroglutamic acid, see: Itoh, T.; Miyazaki, M.; Ikeda, S.; Nagata, K.; Yokoya, M.; Matsuya, Y.; Enomoto, Y.; Ohsawa, A. *Tetrahedron* **2003**, *59*, 3527; Kawanami, Y.; Murao, S.; Ohga, T.; Kobayashi, N. *Tetrahedron* **2003**, *59*, 8411; Mantecon, S.; Vaquero, J. J.; Alvarez-Builla, J.; Luz de la Puente, M.; Espinosa, J. F.; Ezquerra, J. *Org. Lett.* **2003**, *5*, 3791; Adam, W.; Zhang, A. *Eur. J. Org. Chem.* **2004**, *1*, 147.
12. (a) Menezes, R. F.; Zecca, C. A.; Sheu, J.; Smith, M. B. *Tetrahedron Lett.* **1989**, *30*, 3295; (b) Defoin, A.; Pires, J.; Streith, J. *Synlett* **1991**, 417; (c) Defoin, A.; Pires, J.; Streith, J. *Synlett* **1990**, 111.
13. General procedure for the reactions of glycine complexes with (5*S*)-*N*-(*E*-enoyl)-5-methoxycarbonyl-2-pyrrolidinones. To a suspension of Ni(II)-complex (1.0 mmol) in DMF (3.0 mL), (5*S*)-*N*-(*E*-enoyl)-5-methoxycarbonyl-2-pyrrolidinones (1.1 mmol) was added with stirring. The mixture was stirred at rt for 10–15 min to get a homogeneous solution, and then DBU (22 mg, 0.15 mmol) was added. The course of reaction was monitored by TLC (SiO_2). Upon disappearance of the starting compounds, the reaction mixture was poured into icy 5% aqueous acetic acid (100 mL) and stirred with a glass bar to initiate crystallization of the product. The crystalline product was filtered off, thoroughly washed with water, and dried in vacuo to give addition products. For standard procedure for hydrolysis of Ni(ii)-complexes and isolation of target amino acids, see Refs. 6 and 7. (2*R*,3*S*)-3-Phenylpyroglutamic acid: yield: 82%; mp 138.0–139.0 °C; $[\alpha]_D^{25}$ −81.0 (*c* 1.3, CH_3OH); ^1H NMR ($CDCl_3$) δ 2.31 (1H, dd, J = 6.0, 17.1 Hz), 2.73 (1H, dd, J = 9.3, 17.1 Hz), 3.45–3.61 (1H, m), 4.21 (1H, d, J = 5.1 Hz), 7.12–7.26 (5H, m); ^{13}C NMR ($CDCl_3$) δ 39.3, 45.6, 64.6, 127.9, 128.4, 129.9, 143.9, 174.9, 179.6; HRMS(FAB) $[M+H]^+$ calcd for $C_{11}H_{12}NO_3$ 206.0817, found 206.0813.
14. The (2*R*,3*S*) relative stereochemistry for the aromatic (R = Ph) derivatives is a consequence of the Cahn–Ingold–Prelog priority (see Ref. 15) and is stereochemically equivalent to the (2*R*,3*R*) configuration in the aliphatic (R = Me) series of compounds.
15. Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385.