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Application of modular nucleophilic glycine equivalents for truly practical asymmetric synthesis of β-substituted pyroglutamic acids

Vadim A. Soloshonok,[a,*] Hisanori Ueki,[a] Trevor K. Ellis,[a] Takeshi Yamada[a] and Yasufumi Ohfune[b]

[a]*Department of Chemistry and Biochemistry, University of Oklahoma, Norman, OK 73019, USA*
[b]*Graduate School of Science, Department of Material Science, Osaka City University, Sugimoto, Sumiyoshi, Osaka 558-8585, Japan*

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Abstract—A new series of achiral glycine equivalents have been evaluated with respect to their synthetic utility for the production of β-substituted pyroglutamic acid derivatives. Among them, the piperidine-derived complex was found to be a superior glycine derivative for the Michael additions with various (*R*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones representing a general and practical synthesis of sterically constrained β-substituted pyroglutamic acids. In particular, application of complex allowed for the first time preparation of the corresponding isopropyl derivatives thus increasing the synthetic efficiency and expanding generality these Michael addition reactions.

α-Amino acids, indispensable building blocks of all living things, are arguably the most publicly recognized and scientifically studied class of organic compounds.[1] Therefore, it is not surprising that the development of synthetic methods for their preparation has been and still remains one of the most active and important areas of research in the broad fields of life sciences.[2] Taking into account the biological importance, diversity, and numerous potential applications for these unique compounds, one may agree that progress in the development of synthetic methodologies for the practical preparation of amino acids would have a profound impact on many fields of research related to human health, ranging from the food industry to top-notch research in genomics.[3,4] In the recent decade, non-proteinogenic, in particular sterically constrained amino acids, have attracted a great deal of interest primarily due to their indispensable application in de novo design of peptides and peptidomimetics.[5,6]

Recently we[7] and others[8] have reported an operationally convenient, practical synthesis of highly sterically constrained *sym*-α,α-dialkylamino acids **2** as well as cyclic indolyl-type derivatives **3** via alkyl halide alkylation of the newly introduced Ni-complexes **1a**,**b**.[9] We also demonstrated the application of glycine Schiff base complexes **1a**,**b** for highly diastereoselective synthesis of β-substituted pyroglutamic acids **4** via Michael addition reactions with chiral (*R*)- or (*S*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **5** (Scheme 1).[10] However, systematic studies conducted by our group on the homologation of complexes **1a**,**b** have revealed that though these derivatives are generally more superior than traditional glycine equivalents,[11] they have some synthetic limitations such as low solubility in most of organic solvents and low reactivity in the reactions with sterically bulky alkylating reagents and Michael acceptors. For instance, complexes **1a**,**b** extremely sluggishly react with isopropyl containing acceptor **5** (R = *i*-Pr) and cannot be bis-alkylated with isobutyl halides altogether.

Taking into account the highly important role of β-substituted pyroglutamic acids **4** as starting compounds for the preparation of χ-constrained glutamic acids, glutamines, prolines, ornithines, and arginines[12]

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* Corresponding author. Tel.: +1 4053258279; fax: +1 4053256111; e-mail: vadim@ou.edu

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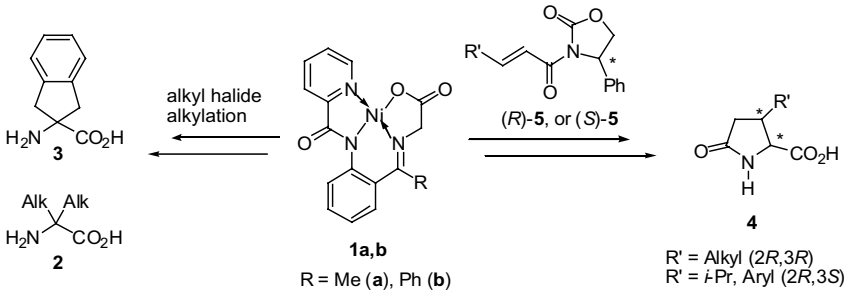


Scheme 1.

as well as their numerous potential synthetic and medicinal applications as sterically constrained analogs of natural pyroglutamic acid,[13] the development of a more general and synthetically efficient approach to compound **4** was highly desirable.

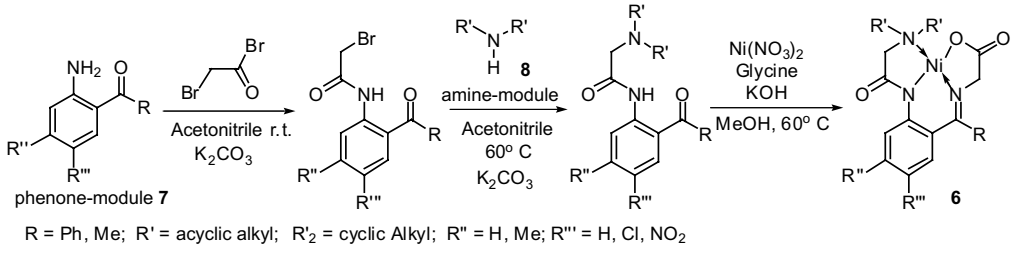
To overcome the limitations of derivatives **1a**,**b**, as well as inherent limitations of a single compound in general, we have recently developed the modular design of a new generation of nucleophilic glycine equivalent (NGE) **6** (Scheme 2).[14] The vast number of points of flexibility incorporated into this design allows virtually complete control of chemical (reactivity, CH-acidity of the Schiff base glycine moiety) and physical properties (solubility, crystallinity) of glycine derivatives **6**. Thus, simply by choosing the appropriate substituents on 'phenone-module' **7** and 'amine-module' **8**, we can tailor the desired reactivity and solubility of the derivatives **6**. Furthermore, as one can see from Scheme 2, the synthesis of glycine derivatives **6** involves inexpensive and readily available starting compounds and can be easily conducted on a kilogram scale.[15] We have demonstrated the synthetically superior characteristics of various derivatives **6** for the general synthesis of α-amino acids via their homologation under a variety of reaction conditions.

Herein we disclose the preliminary results on the highly diastereoselective Michael addition reactions between various new glycine derivatives **6** and chiral (*S*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **5** allowing for the general, and practical synthesis of β-substituted pyroglutamic acids **4** under operationally convenient reaction conditions.

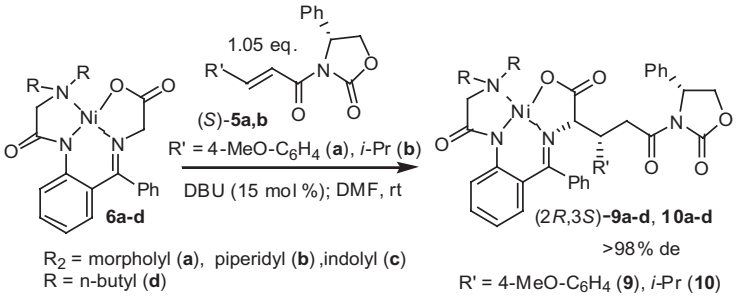
For the preliminary study we chose a series of glycine Schiff bases **6a**–**d**, derived from unsubstituted benzophenone-module **7** (R = Ph, R″ and R‴ = H) and various secondary amines (amine-module **8**) differing in lipophilicity, electronic and steric properties. As a test reaction, to study the synthetic efficiency of **6a**–**d**, we conducted their addition reactions with *p*-methoxyphenyl- and *i*-propyl-derived Michael acceptors **5a**,**b**, proved to be the most difficult substrates to react with the complexes **1a**,**b**.

All reactions between **6a**–**d** and **5a**,**b** were conducted under standard conditions at ambient temperature, using commercial grade DMF and 15 mol % of DBU as a catalyst (Scheme 3). As one can see from Table 1, the reaction between the morpholyl-derived complex **6a** and the *p*-methoxyphenyl containing Michael acceptor (*S*)-**5a** provided synthetically useful results as complete conversion of the starting material to the corresponding product **9a** was realized within 2.5 h in high chemical yield (entry 1). On the other hand, when the *i*-propyl containing Michael acceptor (*S*)-**5b** was used substantially increased reaction time, 18 h, was necessary in order to obtain complete conversion of **6a** to the product **10a**, which was isolated in a slightly lower chemical yield (entry 2). Although these results were encouraging, the outcome obtained with the application of the piperidine-derived complex **6b** was somewhat surprising. The reactions of **6b** with either of the two Michael acceptors (*S*)-**5a**,**b** occurred at very high rates providing the corresponding products **9b**, or **10b** in nearly complete chemical yields (entries 3 and 4).

Conversely, the indolyl-derived complex **6c** provided the most disappointing results of the series. The starting complex **6c** failed to proceed to completion with either of the two Michael acceptors (*S*)-**5a**,**b**, even with prolonged reaction times (entries 5 and 6). The reactivity of dibutyl-derivative **6d** with sterically bulky acceptor (*S*)-**5b** (entry 7) resembled that of **6c**, while the addition of **6d** with (*S*)-**5a** proceeded to completion in 2 h (entry



Scheme 2.



Scheme 3.

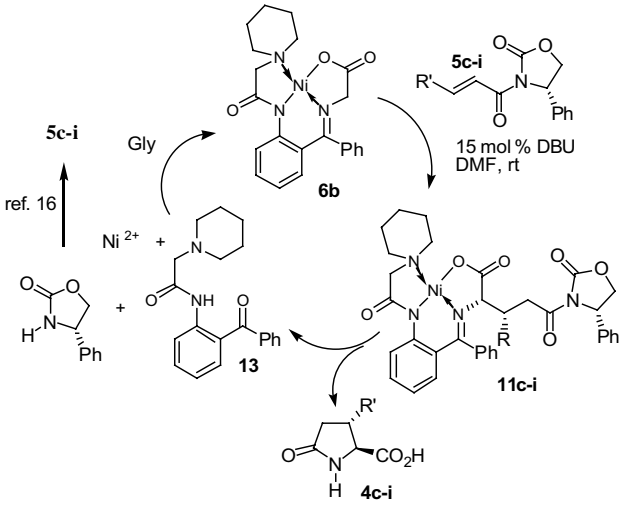
Table 1.

Entry	Substrate	Acceptor	Time	Conversion[a]	% Yield
1	**6a**	**5a**	2.25 h	>99	>95
2	**6a**	**5b**	18 h	>99	>79
3	**6b**	**5a**	20 min	>99	>95
4	**6b**	**5b**	25 min	>99	>99
5	**6c**	**5a**	2.5 h	83	>78
6	**6c**	**5b**	26 h	60	>55
7	**6d**	**5a**	2.0 h	>99	>95
8	**6d**	**5b**	26 h	90	85

[a] Determined by NMR on crude reaction mixtures.

8). Although it is difficult, at this stage, to explain the dramatic difference in reactivity of derivatives **6a**–**d**, this trend may be attributed to differences in solubility as the piperidine derivative **6b** provides a homogeneous reaction mixture from the onset of the reaction, while this is not the case for the other examples.

With the identification of the most reactive complex **6b**, a study concerning the generality of this methodology was conducted by investigating the effects of various substituents in the β-position of the Michael acceptors (*R*)-**5a**–**i** (Scheme 4). As expected the piperidine-derived complex **6b** reacted with the crotonyl, and cinnamic acid derived chiral Michael acceptors (*R*)-**5c**,**d** almost instantaneously, 3 min or less as the reaction seemed to be complete by the time the first TLC was analyzed, providing the corresponding products **11c**,**d** in high chemical yields (Table 2; entries 1 and 2). On the other hand, due to the electron donating nature and increased steric bulk introduced by the incorporation of the *o*-methoxyphenyl moiety in the beta position of the Michael acceptor (*R*)-**5e**, a slightly longer reaction time, 1.75 h, was required in order to provide complete conversion to the target product **11e**, which was also isolated in an excellent chemical yield (entry 3). In contrast, the use of the *o*-trifluoromethylphenyl substituted Michael acceptor (*R*)-**5f** eliminated the unfavorable electronic character demonstrated in the previous example while retaining the steric bulk. As expected the reaction rates were increased, 1 h, providing the complete conversion to the anticipated product **11f** in quantitative chemical yield (entry 4).



Scheme 4.

Table 2.

Entry	R	Time	Conversion[a]	% Yield
1	Me	3 min	>99	86[b]
2	Ph	3 min	>99	>99
3	2-MeO–Ph	1.75 h	>98	>98
4	2-CF_3–Ph	1 h	>98	>98
5	2,6-F_2–Ph	4 min	>99	>99
6	*N*-Bn-Indolyl	20 h	xxx	14
7	*N*-Ts-Indolyl	30 min	>99	81[c]

[a] Determined by crude NMR.
[b] The yield was low because of incomplete filtration due to the particle size.

Alternatively, the application of the 2,6-difluorophenyl containing Michael acceptor (*R*)-**5g** in the reaction with **6b**, provided a synthetic outcome similar to the cinnamic acid derivative (*R*)-**5d** (entry 5). The corresponding product **11g** was isolated in excellent chemical yield following the complete conversion of the starting complex **6b** in less than 4 min (entry 5). Therefore, given the highly reactive nature of glycine equivalent **6b**, an investigation was performed with the very bulky, and electron rich indolyl containing Michael acceptors (*R*)-**5h**,**i**. Although the reaction did progress sluggishly, only 14% of the expected product **11h** was obtained after a reaction time of 20 h with the *N*-benzylated indolyl substituted Michael acceptor (*R*)-**5h** (entry 6). However,

the electron withdrawing capability of the tosyl moiety in the *N*-Ts-indolyl derivative (*R*)-**5i** provided enhanced results as the target product **11i** was obtained in high yield in 30 min, without any residual starting material (entry 7).

Several powerful aspects of this methodology have gone without mention thus far, the first being that all of the products obtained are diasteriomerically pure, >98% de, and are isolated by simply pouring the reaction mixtures over icy 5% aqueous acetic acid followed by filtration of the corresponding precipitate. To further emphasize the operational convenience of this method it should be mentioned that these reactions were conducted at room temperature, without recourse to inert atmospheres, or pre-dried solvents. Thus obtained products **11**, without the need for further purification, were cleanly disassembled in methanol solution in the presence of 3 N HCl. Following the evaporation of methanol, the addition of 8% aqueous ammonium hydroxide lead to the formation of the corresponding pyroglutamic acids **4a**–**i**, which were isolated in high chemical yield. Along with the target amino acids **4a**–**i**, ligand **13** and the chiral auxiliary (*R*)-12 were quantitatively recovered and separated by chromatography in high chemical yield, 97% and 82%, respectively, and used to regenerate the starting glycine complex **6b** and Michael acceptors **5a**–**i**.[14,16]

In summary a new series of achiral glycine equivalents have been evaluated with respect to their synthetic utility for the production of β-substituted pyroglutamic acid derivatives. Among them, the piperidine-derived complex was found to be a superior glycine derivative for the Michael additions with various (*R*)- or (*S*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones representing a general and practical synthesis of sterically constrained β-substituted pyroglutamic acids. In particular, application of complex allowed for the first time preparation of the corresponding isopropyl derivatives thus increasing the synthetic efficiency and expanding generality these Michael addition reactions.

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