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Design, Synthesis, and Evaluation of a New Generation of Modular Nucleophilic Glycine Equivalents for the Efficient Synthesis of Sterically Constrained α-Amino Acids

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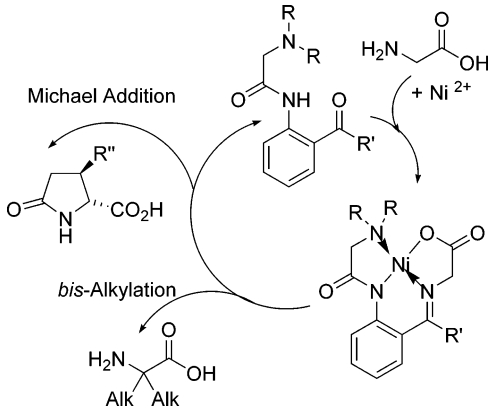
Received August 3, 2006



A new generation of modular achiral glycine equivalents have been evaluated with respect to their synthetic utility for the production of tailor-made, sterically constrained α-amino acids, which proved to be the most efficient approach developed to date for the synthesis of symmetrical α,α-disubstituted-α-amino acids. Among the new series of achiral glycine equivalents, one 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, the application of these complexes allowed for the preparation of several *β*-substituted pyroglutamic acids which include electron-releasing and sterically demanding substituents in the structure thus increasing the synthetic efficiency and expanding the generality of these Michael addition reactions.

Introduction

The synthesis of tailor-made[1] amino acids has been at the forefront of synthetic organic chemistry research for some time.[2] This is due, in most part, to the breadth of their application, which ranges from food additives to sophisticated pharmaceuticals.[3] This is especially true for sterically constrained or polyfunctional unnatural amino acids due to the profound influence their physical and chemical properties may impart on vital biologically active systems.[4] Their ability to influence the three-dimensional shape,[5] biological activity,[4] and degradative resistance in proteins[6] has also proven to be essential in the modern era of de novo designed peptides.[7]

It has been these pharmacological and medicinally relevant applications that have provided the motivation to devise a sound synthetic methodology that is general, environmentally benign, and industrially attractive for the synthesis of these profoundly influential compounds. To date, there are numerous approaches to the symmetric and asymmetric synthesis of sterically constrained amino acids,[8] although each seems to be plagued by limitations. Therefore, after evaluating the previously published methodologies, the most straightforward, practical, and general approach seems to be the homologation of nucleophilic glycine equivalents. Although there are many deficiencies

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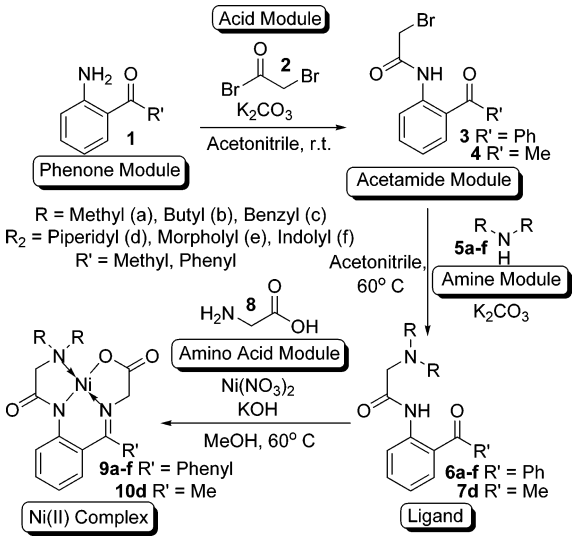
10.1021/jo0616198 CCC: $33.50
Published on Web 10/04/2006

that need to be addressed with respect to this synthetic approach, it seems that most involve the insufficient design of the glycine equivalents themselves. The majority of the commercially available glycine equivalents may be characterized as having unacceptable properties such as chemical instability, poor industrial scalability, or poor economic feasibility.

Results and Discussion

Therefore, to overcome these shortcomings, our laboratory has recently developed a new series of modified glycine equivalents based on a modular skeleton[9] that has provided superior chemical reactivity, stability, solubility, and cost efficiency, even compared to their Ni(II)-containing counterparts previously introduced by our laboratory[10] and others.[11] The modular design concept of the glycine equivalents has opened various avenues of opportunity for a whole host of reaction conditions, given the advantage of virtually complete substrate adaptability.

SCHEME 1



There are several modules that must be combined to assemble the desired Ni(II) complexes; however, a simple, general, and reliable synthetic route has been devised for this purpose (Scheme 1). The first step is the coupling to the proper "phenone" module with the corresponding "acid" module to form the intermediate "acetamide" module. This is accomplished by the slow addition of a 2-aminophenone **1**/acetonitrile solution to slurry of bromoacetyl bromide **2**, potassium carbonate, and acetonitrile. This procedure is usually accomplished with yields greater than 90% and nearly ideal chemical purity. Next, the ligand **6a**−**f** or **7a**−**f** will be produced from the substitution of the bromine atom from the acetamide module intermediate **3** or **4** with virtually any secondary amine **5a**−**f**. This reaction is also accomplished in an acetonitrile solution with potassium carbonate, to liberate the hydrobromic salt of the amine produced; however, the application of heat is generally utilized to accelerate the reaction rate. It should also be noted that the previous two reactions may be conducted via a one-pot reaction; however, we have found it more convenient to store large amounts of the acetamide intermediates **3** or **4** for their eventual conversion to their corresponding ligands **6a**−**f** or **7a**−**f** as needed. The final reaction of the glycine equivalent synthesis is the Schiff base formation, between the ligand **6a**−**f** or **7a**−**f** and glycine **8**, coupled with the simultaneous Ni(II) complexation accomplished in methanol with heat to accelerate the reaction. Potassium hydroxide is utilized to catalyze the imine formation as well as to neutralize the corresponding acid formed from the reaction.

Now that the ease and cost efficiency for the synthesis of the new generation of glycine equivalents has been established, the versatility, chemical stability, and chemical reactivity need to be evaluated. Therefore, it was determined that these glycine equivalents **9a**−**f** or **10a**−**f** should first be subjected to extreme conditions to confirm the stability of the complex as well as to ensure that the methylene moiety, introduced into the ligand **6a**−**f** or **7a**−**f** via the addition of bromoacetyl bromide **2**, is nonenolizable and therefore would not interfere with the overall atom economy of the process or the recyclable nature of the ligand **6a**−**f** or **7a**−**f**. Therefore, to evaluate these possibilities

(1) The rapidly growing list of amino acids isolated from various natural sources makes the terms *unnatural*, *unusual*, *noncoded*, or *nonproteinogenic amino acids*, which are most frequently used in the literature, dependent on the success of specific scientific achievements. For instance, amino acids containing the most xenobiotic element fluorine have been shown to be synthesized by microorganisms. Moreover, recent spectacular developments in the generation of bacteria with an expanded genetic code make all above-mentioned definitions rather obsolete. Therefore, the time-independent term *tailor-made*, meaning rationally designed/synthesized amino acids with presupposed physical, chemical, 3D-structural, and biological features, in the absence of a better definition, seems to be a more appropriate use as a common name for such amino acids. (a) Kukhar', V. P.; Soloshonok, V. A., Eds.; *Fluorine-Containing Amino Acids*. *Synthesis and Properties*; John Wiley and Sons Ltd.: Chichester, 1994. (b) Mehl, R. A.; Anderson, J. C.; Santoro, S. W.; Wang, L.; Martin, A. B.; King, D. S.; Horn, D. M.; Schultz, P. G. *J. Am. Chem. Soc*. **2003**, *125*, 935.

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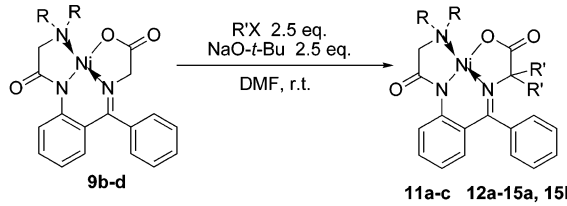
SCHEME 2



Entry	R	R'	X	Time	Product	Conversion[a] Bis/Mono	Yield[b]
1	Bu (**9b**)	Bn	Br	15 min	**11a**	>99/1	93
2	Bn (**9c**)	Bn	Br	15 min	**11b**	>99/1	90
3	Piperidyl (**9d**)	Bn	Br	15 min	**11c**	>99/1	91
4	Bu (**9b**)	Allyl	Br	15 min	**12a**	>99/1	92
5	Bu (**9b**)	Cinnamyl	Br	15 min	**13a**	>99/1	88
6	Bu (**9b**)	Me	I	25 min	**14a**	>99/1	87
7	Bu (**9b**)	Propargyl[c]	Br	24 h	**15a/15b**	33/67	30

as well as any unforeseen complications, homologation reactions of the complexes **9b**−**d** were attempted in the presence of sodium *tert*-butoxide and benzyl bromide (Scheme 2). The initial experiment conducted, with the dibutylated complex **9b** as the glycine equivalent, was found to be successful with 3.5 equiv of the base and the electrophile because the corresponding α,α-dibenzylated glycine-containing complex was found in greater than 90% yield with no other observable products. It was later discovered that the excess of the base and benzyl bromide could be decreased to 2.5 equiv each with similar results, contrary to the results obtained with the application of their picolinic acid-containing predecessors (Scheme 2 (table); entry 1).[12] These reactions were then repeated using various alkyl groups on the amino function of the Ni(II) complexes **9** to ensure some generality. It was found that the complexes incorporating either a piperidine **9d** or dibenzylamine **9c** moiety yielded similar results as both reactions resulted in greater than 90% yield and greater than 99% conversion to the desired products **11b** or **11c** (entries 2 and 3). These experiments were complimented by two more reactions that were conducted to demonstrate that these results were reproducible with various other alkyl halides. Therefore, it was found that the dibutylated Ni(II) complex **9b** would also react with allyl or cinnamyl bromide in the presence of the sodium *tert*-butoxide with success similar to the earlier example generating the corresponding products **12a** or **13a** in high chemical yield of 92 or 88%, respectively (entries 4 or 5). It was also found that the introduction of two unactivated alkyl groups could be accomplished; however, the application of the more reactive alkyl iodide was necessary for the reaction to reach completion, such as the synthesis of **14a** via homologation with methyl iodide (entry 6). Although the direct alkylation of the complex **9b** with propargyl bromide was unsuccessful due to the production of various byproducts, seemingly from the reactivity of the alkyl halide, slightly milder phase-transfer conditions were more appropriate for this process; however, longer reaction times or more concentrated aqueous bases are necessary to complete the reaction which only proceeded to 33% conversion to the bisalkylated product **15a** in 24 h while 67% of the monoalkylated product **15b** remained (entry 7).

Although these alkylation experiments were useful for examining the stability of this new series of methylene-activated glycine derivatives as well as for demonstrating an efficient route to the production of α,α-disubstituted-α-amino acids, the flexibility of the modular design did not seem to have a major impact on the outcome of the reactions. However, as our focus was diverted toward the synthesis of another structurally and chemically unique group of amino acids, *β*-substituted pyroglutamic acids, the adaptability of these complexes proved to be extremely advantageous. The reaction conditions for the Michael addition reactions, employed for the synthesis of the *β*-substituted pyroglutamic acids, are undoubtedly milder; however, the level of intricacy is multiplied as two stereogenic centers will be established by the formation of one bond. Therefore, the homogeneity of the enolate formed on the glycine structure, provided by the Ni(II)-complexed glycine equivalent, as well as the steric constraints surrounding the site of addition becomes of paramount importance to aid in the organization of the transition state thereby providing the potential for increased yields as well as diastereoselectivities. Given the complex nature of these reactions compounded by the necessity of milder bases, these reactions provide an excellent platform to compare the reactivity of various derivatives within the series of the new glycine equivalents. This is especially true given the simple workup procedures utilized, as established from previous efforts as the crude reaction mixtures were merely poured over a solution of icy 5% acetic acid to quench the reactions followed by simple filtration.

The initial reactivity comparison studies were conducted to determine the effect of the alkyl group of the amino moiety of the complexes with respect to their differences in lipophilicity, as well as their electronic and steric properties.[13] The two (*S*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **16a**,**b**[14] chosen for these experiments included a *para*-methoxyphenyl or an *iso*-propyl substituent in the *β* position to limit the rate, by virtue of their corresponding electronic and steric contributions, of the corresponding reactions to increase the accuracy while determining the relative reactivity of each of the complexes. Each of the following reactions discussed in this section was conducted under a set of standard conditions at ambient temperature, which included the use of commercial-grade DMF as the solvent and 15 mol % of DBU as the catalyst (Scheme 3). The initial experiments conducted, involving the application of the piperidine-derived Ni(II) complex **9d**, were impressive, as in both examples explored, the corresponding products **17d** and **18d** were obtained in high chemical yield (>95 and >99%, respectively) and high diastereoselectivity (>98% de)[15] following the complete conversion from the starting material **9d** in 20−25 min (entries 1 and 2). Although the reaction rate was decreased from the previous example, the complete conversion of the dibenzylamine-containing complex **9c** to the product **17c** was realized for the application of the aromatic-substituted Michael acceptor **16a**, in 2.5 h (entry 3). However, after 26 h, the reaction of the Michael acceptor bearing the *iso*-propyl group **16b** was limited to 88% conversion to the appropriate product **18c** (entry 4). The decrease in the reaction rates of the dibenzylated Ni(II) complex **9c** could be accounted for by the

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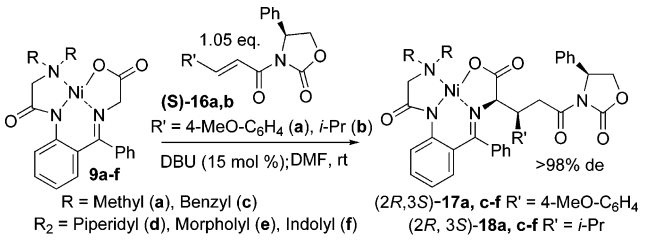
(15) The diastereoselectivity described for the products of the described reactions was assigned by ^{1}H NMR analysis of the crude reaction mixtures as well as by the optical rotations of the purified products on the basis of our laboratory's previous investigations of similar systems (see ref 16 and 17).

SCHEME 3

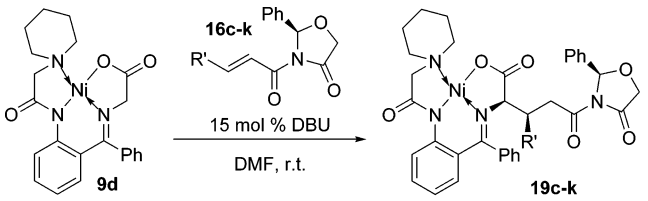


Entry	Substrate	Acceptor	Products	Time	Conversion[a]	% Yield
1	**9d**	**16a**	**17d**	20 min	>99	>95
2	**9d**	**16b**	**18d**	25 min	>99	>99
3	**9c**	**16a**	**17c**	2.5 h	>99	>99
4	**9c**	**16b**	**18c**	26 h	88	>86
5	**9a**	**16a**	**17a**	2.0 h	>99	>99
6	**9a**	**16b**	**18a**	26 h	62	>60
7	**9e**	**16a**	**17e**	2.25 h	>99	>95
8	**9e**	**16b**	**18e**	18.0 h	>99	>79
9	**9f**	**16a**	**17f**	2.5 h	83	>78
10	**9f**	**16b**	**18f**	26 h	60	>58

increase in the free rotation of the benzyl groups coupled with the enhanced size of the substituents.

With these preliminary results in mind, the remaining reactions were conducted utilizing complexes that contained amino groups which were expected to also demonstrate optimal reactivity; therefore, the results of the following experiment were initially unexpected. The incorporation of a dimethylamino group into the Ni(II) complex framework **9a** was expected to increase the reactivity by eliminating the steric considerations while not seeming to effect the overall electronic nature of the complex. Although the reaction with the aromatic-containing Michael acceptor **16a** proceeded, it took 2 h for the reaction to progress to completion providing the corresponding product **17a** in excellent chemical yield (99%, entry 5), whereas the reaction with the sterically challenged iso-propylated acceptor **16b** did not achieve complete conversion (62%) even after 2 h (entry 6). However, the unexpected outcomes from the reactions could be easily explained by observing the reaction as it progressed because it was evident that the Ni(II) complex **9a** was not completely soluble at the standard concentration utilized for these experiments, 0.1 g in 2 mL, intrinsically decreasing the reaction rate. Although the application of the morpholyl-derived Ni(II) complex **9e** proved synthetically useful as reactions with both of the Michael acceptors **16a**,**b** proceeded to completion and provided acceptable chemical yields of the products **17e** and **18e**, >95 and >79%, respectively, the rates of the reactions were drastically slower, taking 2.25 h for the *para*-methoxyphenyl-derived acceptor **16a** and 18 h for the *iso*-propyl-containing acceptor **16b** (entries 7 and 9), when compared with their cyclic counterpart, the piperidyl-derived complex **9d** (entries 1 and 2). There seems to be little to no rationale that the effect could arise from steric effects; however, the introduction of the oxygen atom into the ring could introduce a number of electronic differences. In the last example investigated within this series, the indolyl group incorporated into the structure of the glycine equivalent **9f** is cyclic; however, it may be the overall size of this group that could account for the dismal reactivity, as neither reaction proceeded to completion given the time allotted for the reaction. The reaction which included the Michael acceptor bearing the aromatic substituent **16a** obtained 83% conversion to **17f** in 2.5 h (entry 9), and the reaction with

SCHEME 4



Entry	R'	Products	Time	Conversion[a]	% Yield
1	Me	**19c**	3 min	>99	86[b]
2	Ph	**19d**	3 min	>99	>99
3	2-MeO-Ph	**19e**	1.75 h	>98	>98
4	2-CF_3-Ph	**19f**	1 h	>98	>98
5	2,6-F_2-Ph	**19g**	4 min	>99	>99
6	*N*-Bn-Indolyl	**19h**	20 h	16	14
7	*N*-Ts-Indolyl[c]	**19i**	30 min	>99	81[b]
8	*N*-Tr-Imidazolyl[c]	**19j**	24 h	0	0
9	*t*-butyl	**19k**	24 h	0	0

the *iso*-propyl-derived acceptor **16b** achieved a dismal 60% conversion to **18f** within 26 h (entry 10).

After analyzing the information obtained by these relative reactivity experiments, it was not difficult to identify the most likely candidate for further investigation. The piperidine moiety proved to be the most compatible group to incorporate into the Ni(II) complex for enhanced reactivity under the conditions for these Michael addition reactions. Their reactivity far surpasses that of the previously published glycine equivalents including the picolinic acid-derived Ni(II) complexes explored within our laboratory.[16] Therefore, the generality and limitations for the application of this new glycine equivalent, with respect to this type of chiral Michael addition reactions, were of great interest. The first two experiments that were investigated were fairly straightforward as both of the Michael acceptors were not as electron-rich or bulky as the previous two that were employed for the reactivity study. As expected, the crotonyl- and cinnamic acid-derived Michael acceptors **16c** and **16d** were successfully incorporated into the glycine equivalent to produce the corresponding β-substituted pyroglutamic acid precursors **19c** and **19d** in high chemical yield, 86% and >99%, respectively, with a diastereomeric purity greater than 98% in both cases (Scheme 4 (table), entries 1 and 2). The Michael acceptor with the 2-methoxyphenyl moiety incorporated into the structure **16e** was explored as an interesting example which includes two key features that would decrease the reactivity of the acceptor due to the electron-donating nature of the substituent as well as to its location on the phenyl ring which would also serve to increase the steric constraint around the active site. Although the electronic and steric factors contributed by the Michael acceptor **16e** did slow the reaction rate, the reaction did proceed to completion, providing the appropriate product **19e** in high chemical yield without compromising the stereochemical outcome (entry 3). As evidenced from the outcome from the previous reactions, the rate of these 1,4 addition reactions is effected by both the electronic and steric bulk contributed by the Michael acceptor; however, it was rather difficult to

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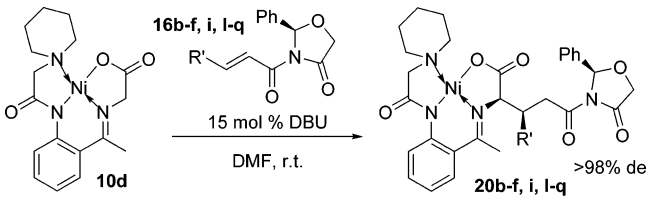
determine the effect of each factor independently. From the following experiment, conducted with a Michael acceptor-containing a *o*-trifluoromethylphenyl group, introduced to retain the steric effects from the previous example while reversing the electronic contribution of the acceptor, **16f**, it was evident that the steric factor seemed to play a large role in determining the rate of the reaction. Although the reaction proceeded to completion providing the appropriate product **19f** in excellent yield (>98%) and diastereomeric purity (>98% de), 1 h was necessary to complete the reaction (entry 4). The following experiment involved the application of an electron-poor Michael acceptor which included a 2,6-difluorophenyl group incorporated into the structure **16g**. Again, the reaction proceeded to completion providing the corresponding product **19g** in a diastereomeric form (>98% de) and very high chemical yield (>99%); however, only 4 min was required for this experiment to be completed (entry 5). Although the electronic donation of the 2-methoxyphenyl-containing Michael acceptor **16e** did not prevent the progression of the earlier reported reaction, it was found that the electronic contributions of a *N*-benzyl-indolyl moiety into the skeleton of the reactive site of the Michael acceptor proved too much as the reaction between the complex **9d** and the Michael acceptor **16h** progressed sluggishly only providing 16% conversion to the corresponding product **19h** in 20 h (entry 6). However, by employing the electron-withdrawing capabilities of a tosyl group, the electron-donating character of the indolyl moiety could be sufficiently reduced to allow the Michael addition reaction to proceed as evidenced by the completion (>99% conversion) of the reaction between the piperidine-containing Ni(II) complex **9d** and the corresponding Michael acceptor **16i** in 30 min (entry 7). Although the piperidine-derived complex **9d** has proven to be quite useful to this point, it does seem that limitations do exist, as no products could be obtained from the reaction conducted with the *N*-trityl-imidazolyl-substituted Michael acceptor **16j** even after 24 h. This, however, is not so unexpected given the shear bulk of the *N*-trityl-imidazolyl group coupled with the electron-releasing nature of the substituent. Presumably, because of the massive steric demands of the group, similar results could be obtained with the incorporation of a *tert*-butyl group into the Michael acceptor **16k** as no products were observed within the 24 h reaction time.

Although the superior reactivity demonstrated by the piperidine-derived Ni(II) complex **9d** has far surpassed expectations, it seems that there remains some room for improvement. As discussed earlier, the transition state of these Michael addition reactions is extremely crowded, therefore one may assume that relieving some of the possible steric interactions could lead to favorable increases in reactivity. So far in this study, only the substituents of the amino function of the complexes have been evaluated for this purpose; however, previous investigations within our laboratory[17,18] have demonstrated that utilizing an *o*-aminoacetophenone module rather than the 2-aminobenzophenone one in the construction of the Ni(II) complexes can lead to increased reactivity without risking any adverse effects on the stereochemical outcome. Therefore, the following reactions will involve the study of the acetophenone-derived, piperidine-containing complex **10d** (Scheme 5). As expected from previous experiences, the Michael addition reactions involving this new complex **10d**, crotonyl, and cinnamic acid-derived chiral Michael acceptors **16c**,**d** were limited only by the time necessary to conduct the first TLC analysis (Scheme 5 (table); entries 1 and 2). The reactions both proceeded to completion, in >99% conversion, in under 2 min providing the corresponding products **20c**,**d** in greater than 98% yield. However, the first bit of promising information came with the conclusion of the following reaction, as the Michael acceptor bearing the *iso*-propyl group **16b** reacted with the acetophenone-derived complex **10d** (entry 3) at a faster rate than the benzophenone complex utilized earlier (Scheme 3 (table); entry 4) providing complete consumption of the starting material **10d** in 15 min. The reaction of the Michael acceptor which included the *o*-methoxyphenyl substituent **16e** for this reaction also provided exciting results as the reaction rate was cut from 1.75 to 0.5 h merely by the application of the acetophenone complex **10d**, whereas the complete chemical conversion (>99%) and yield of the products **20e** (94%) were not effected by the modification of the Ni(II) complex (Scheme 5 (table); entry 4). The presence of an electron-withdrawing *p*-trifluoromethylphenyl in the Michael acceptor **16f** did not break with the trend for this set of reactions, as the reaction proceeded approximately six times faster with the acetophenone-derived complex **10d** (20 min) compared to the more bulky benzophenone-containing complex **9d** (entry 5). Revisiting the application of the *N*-Ts-indolyl-containing Michael acceptor **16i** with the new improved glycine equivalent **10d** also proved useful as the complete conversion of the starting material **10d** to products **20i** was observed in approximately 10 min, whereas in the previous case, nearly 30 min (entry 6) was necessary to obtain similar results.

With the accomplishment of enhanced reactivity, compared to previously published examples, added to the list of advantages which already includes enhanced solubility, chemical stability, and cost efficiency, it is easy to foresee the general utility and synthetic applicability of this series of glycine equivalents for the methodology based on their homologation. However, there are more items that must be addressed such as the disassembly

SCHEME 5



R' = *i*-propyl (**b**), Me (**c**), Ph (**d**), 2-MeO-Ph (**e**), 2-CF_3-Ph (**f**), *N*-Ts-Indolyl (**i**), 4-Cl-Ph (**l**), 3,4-Cl_2-Ph (**m**), 3,5-F_2-Ph (**n**), 3-CF_3-Ph (**o**), Et (**p**), 2,6-Me_2-4-MeO-Ph (**q**)

Entry	R'	Products	Time	Conversion[a]	% Yield
1	Me	**20c**	2 min	>99	98
2	Ph	**20d**	2 min	>99	98
3	4-Cl-Ph	**20l**	3 min	>99	92
4	3,4-Cl_2-Ph	**20m**	3 min	>99	96
5	3,5-F_2-Ph	**20n**	3 min	>99	91
6	2-CF_3-Ph	**20f**	20 min	>99	89
7	3-CF_3-Ph	**20o**	2 min	>99	92
8	Et[b]	**20p**	7 min	>99	95
9	*i*-Propyl	**20b**	15 min	>99	70
10	2-MeO-Ph	**20e**	30 min	>99	94
11	*N*-Ts-Indolyl[b]	**20i**	10 min	>99	98
12	2,6-Me_2,4-MeO-Ph[b,c]	**20q**	24 h	38	35

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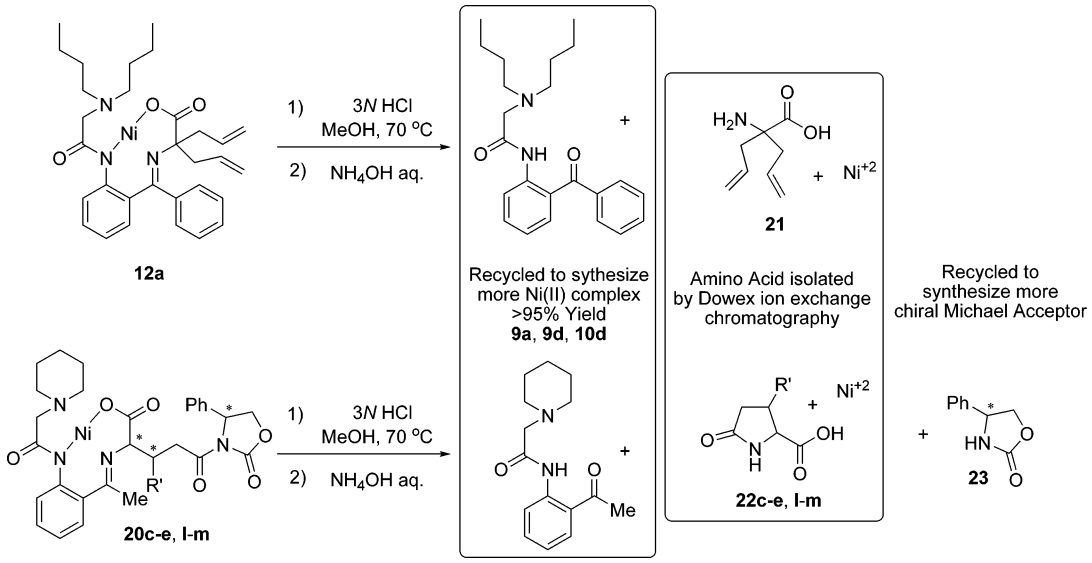
SCHEME 6



of the complexes as well as the recovery of the target amino acids. Although the chemical stability that has been referred to throughout this manuscript might lead one to believe that the disassembly of the Ni(II) complexes might be difficult, it turns out to be rather simple and straightforward assuming the appropriate conditions are employed, as the Ni(II) complex will disassemble under sufficiently concentrated aqueous acids. Therefore, 3 N hydrochloric acid will suffice to disassemble the complexes which are typically in a solution of warm methanol for purposes of solubility. Once the complex has been broken down into its pieces (the target amino acid, metal ions, and the ligand), the solution is treated with ammonium hydroxide to quench the hydrochloric salt of the organic soluble ligand which can be recovered by extraction into methylene chloride and reused to form a new lot of Ni(II) complexes of glycine in nearly quantitative yield, extinguishing any concern about the poor atom economy of this methodology. The addition of the ammonium hydroxide solution plays an additional role in the case of the disassembled Michael adducts as it catalyzes the ring closure and release of the chiral auxiliary **23** which can be reused to form a new portion of chiral Michael acceptors. The resulting aqueous solution of the amino acids and Ni(II) ions may be subjected to ion-exchange chromatography for purposes of isolation of the free amino acid in 82−94% yield (Scheme 6).

In summary, a new series of achiral glycine equivalents have been evaluated with respect to their synthetic utility for the production of tailor-made, sterically demanding, and functionalized amino acids. Among the new series of achiral glycine equivalents, the piperidine-derived, acetophenone-containing complex **10d** 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 **16a**−**l** representing a general and practical synthesis of sterically constrained *β*-substituted pyroglutamic acids. In particular, the application of these complexes allowed for the preparation of several *β*-substituted pyroglutamic acids which include electron-releasing and sterically demanding substituents in the structure thus increasing the synthetic efficiency and expanding the generality of these Michael addition reactions.

Experimental Section

Condensation of 2-Aminobenzophenone 1 and Bromoacetyl bromide 2 Yielding *N*-(2-Benzoyl-phenyl)-2-bromo-acetamide 3 and 4. A solution of bromoacetyl bromide **2** (46.46 g, 230.28 mmol) in acetonitrile (2 mL/1 g of bromoacetyl bromide) was slowly added to a slurry of 2-aminobenzophenone **1** (20.18 g, 102.32 mmol) and potassium carbonate (70.71 g, 511.61 mmol) in 240 mL of acetonitrile. The reaction was stirred at ambient temperature (room-temperature water bath) for 1 h, and upon completion (monitored by TLC), the acetonitrile was evaporated under vacuum. Water (200 mL) was then added to the crude mixture and extracted with dichloromethane (200 mL) three times. The organic portions were combined, dried, and concentrated under vacuum to afford the corresponding α-bromoamide product in 98% yield and greater than 99% chemical purity.

Alkylation of Secondary Amines with *N*-(2-Benzyoly/acetyl-phenyl)-2-bromo-acetamide, Yielding the Corresponding *N*-(2-Benzoyl/acetyl-phenyl)-2-dialkylamino-acetamide 6a−f or 7d. General Procedure. To a slurry of *N*-(2-benzoyl/acetyl-phenyl)-2-bromo-acetamide **3** and **4** (1 equiv) and potassium carbonate (1.2 equiv) in acetonitrile (10 mL/1 g of *N*-(2-benzoyl-phenyl)-2-bromo-acetamide) was added the corresponding secondary amine **5a**−**f** (1.1 equiv). The reaction was allowed to proceed for 2 h at 60−70 °C (monitored by TLC) before the reaction mixture was concentrated under vacuum. Water was added to the viscous liquid, followed by extraction with dichloromethane. The organic portions were combined, dried with magnesium sulfate, and concentrated in a vacuum to afford the corresponding *N*-(2-benzoyl/acetyl-phenyl)-2-dialkylamino-acetamide **6a**−**f** or **7d** in nearly quantitative yield and high chemical purity >99%.

Synthesis of the Ni(II) Complexes of Glycine Schiff Bases with *N*-(2-Benzyoly/acetyl-phenyl)-2-dialkylamino-acetamides 9a−f and 10d. General Procedure. A solution of potassium hydroxide (9 equiv) in methanol (7 mL/1 g of KOH) was added to a suspension of *N*-(2-benzyoly/acetyl-phenyl)-2-dialkylamino-acetamides **6a**−**f** and **7d** (1 equiv), glycine (5 equiv), and nickel nitrate hexahydrate (2 equiv) in methanol (10 mL/1 g of **6a**−**f** and **7d**) at 60−70 °C. Upon complete consumption of the *N*-(2-benzyoly/acetyl-phenyl)-2-dialkylamino-acetamides **6a**−**f** and **7d**, monitored by TLC, the reaction mixture was poured over a slurry of ice and 5% acetic acid. After the complete precipitation, products **9a**−**f** and **10d** were filtered and dried, in an low-temperature oven (50 °C) overnight. The product was obtained in high chemical yield (99%) and high chemical purity without further purification.

Dialkylation of Ni(II) Complexes 9b−d with Activated Alkyl Bromides Yielding Complexes 11a−c and 12a−14a. General Procedure. To a solution of sodium *tert*-butoxide (2.5 equiv) in DMF (10 mL/1 g of complex **9b−d**) were added complex **9b−d** (1 equiv) and the corresponding alkylating reagent (2.5 equiv). The reaction was stirred at ambient temperature (room-temperature water bath) for 15 min. Upon completion (monitored by TLC), the reaction mixture was poured into ice water, and the resulting precipitate was filtered and washed with water to afford the products **11a−c** and **12a−14a** in yields ranging from 92 to 96% and in greater than 99% purity.

Phase-Transfer Homologation of a Ni(II) Complex of the Glycine Schiff Base with *N*-(2-Benzoyl-phenyl)-2-dibutylamino-acetamide 9b with Propargyl Bromide. General Procedure. To a solution of **9b** in CH_2Cl_2 (1 mL/g) at room temperature were added tetrapropylammonium bromide (0.25 equiv), 30% sodium hydroxide solution (1 mL/mL of CH_2Cl_2), and propargyl bromide (3.5 equiv). The resultant mixture was rigorously stirred overnight at room temperature. To the resultant slurry mixture were added additional water and CH_2Cl_2, and the water was extracted several times with CH_2Cl_2. The organic layer was dryed with $MgSO_4$, filtered, and then evaporated in a vacuum to yield a crystalline compound. This compound was washed first with water and then with hexane and then dried completely to yield the final products.

Michael Addition of the Oxazolidinone-Derived Amides of Unsaturated Acids 16a,b and Nucleophilic Glycine Equivalents 9a,c−f. General Procedure. To a flask containing **9a,c−f** (0.10 g) were added 3-((*E*)-3-phenylacryloyl)oxazolidin-2-one (1.05 equiv) and 1.5 mL of DMF and DBU (15 mol %). The reaction mixture was stirred at room temperature and monitored by TLC. After the disappearance of the starting glycine equivalent by TLC, the reaction mixture was poured into a beaker containing 100 mL of ice water. After the ice had melted, the corresponding product **17a**,**c−f** or **18a**,**c−f** was filtered from the aqueous solution and dried in an oven to afford the appropriate product in high chemical yields.

Michael Addition of the Oxazolidinone-Derived Amides of Unsaturated Acids 16c−k and Nucleophilic Glycine Equivalent 9d. General Procedure. To a flask containing **9d** (0.10 g) were added 3-((*E*)-3-phenylacryloyl)oxazolidin-2-one **16c−k** (1.05 equiv) and 1.5 mL of DMF and DBU (15 mol %). The reaction mixture was stirred at room temperature and monitored by TLC. After the disappearance of the starting glycine equivalent by TLC, the reaction mixture was poured into a beaker containing 100 mL of ice water. After the ice had melted, the corresponding product **19c−k** was filtered from the aqueous solution and dried in an oven to afford the appropriate product in high chemical yields.

Michael Addition of the Oxazolidinone-Derived Amides of Unsaturated Acids 16b−f,i,l−q and the Nucleophilic Glycine Equivalent 10d. General Procedure. To a flask containing **10d** (0.10 g) were added 3-((*E*)-3-phenylacryloyl)oxazolidin-2-one **16b−f,i,l−q** (1.05 equiv) and 1.5 mL of DMF and DBU (15 mol %). The reaction mixture was stirred at room temperature and monitored by TLC. After the disappearance of the starting glycine equivalent by TLC, the reaction mixture was poured into a beaker containing 100 mL of ice water. After the ice had melted, the corresponding product **20b−f,i,l−q** was filtered from the aqueous solution and dried in an oven to afford the appropriate product in high chemical yields.

Decomposition of the Ni(II) Complex of the α,α-Diallylglycine Schiff Base with *N*-(2-Benzoyl-phenyl)-2-dibutylamino-acetamide 12a Yielding α,α-Diallylglycine 21 and *N*-(2-Benzoyl-phenyl)-2-dibutylamino-acetamide 6b. To a solution of 22 mL (14.5 mL/1 g of complex **12a**) of MeOH and 11 mL (7.25 mL/1 g of complex **12a**) of 3 N HCl at 70 °C was added 1.471 g (2.527 mmol) of complex **12a**. The solution was stirred for 30 min and then evaporated. The acid **21** and Ni(II) were extracted in 50 mL of DI water from ligand **6b** and CH_2Cl_2 and then evaporated. Following the evaporation, the crystalline compounds were dissolved in the minimum amount of DI water and placed on an ion-exchange column using Dowex 50 × 2−100 resin. The column was first washed with DI water until neutral, followed by 8% aqueous ammonium hydroxide (500 mL) to elute acid **21**. This solution was evaporated to afford 0.3843 g (2.476 mmol, 98% yield) of acid **21**. The Ni(II) was eluted with concentrated HCl after the column was returned to neutral with DI water. Ligand **6b** was recovered by the evaporation of the organic layer from the aforementioned separation.

Decomposition of Complexes 20c−e,l−m; Isolation of (2*S*,3*S*)-3-Alkyl- and (2*S*,3*R*)-3-Arylpyroglutamic Acids 22c−e,l−m; Recovery of Ligand 10d; and Starting Chiral Auxiliary (*S*)-23. General Procedure. A solution of pure complex **22c−e,l−m** (25 mmol) in MeOH (50 mL) was slowly added to a stirring solution of aqueous 3 N HCl in MeOH (90 mL, ratio 1:1, acid/MeOH) at 70 °C. Upon the disappearance of the red color, the reaction mixture was evaporated in a vacuum until dryness. Water (85 mL) was added, and the resultant mixture was treated with an excess of concentrated ammonium hydroxide and extracted with methylene chloride. The methylene chloride extracts were dried over magnesium sulfate and evaporated in a vacuum to afford 10.59 g of a 1:1 mixture (99%) of ligand **10d** and chiral auxiliary (*S*)-**23**. The aqueous solution was evaporated in a vacuum, dissolved in a minimum amount of water, and loaded on a cation-exchange resin Dowex 50 × 2 100 column. The column was washed with water, and the acidic fraction was collected to give the pyroglutamic acid **22c−e**,**l−m**. An analytically pure sample of the product was obtained by crystallization of the compound from THF/*n*-hexane.

Acknowledgment. This work was supported by the Department of Chemistry and Biochemistry, University of Oklahoma, as well as by the U.S. Department of Education (GAANN Fellowship for T.K.E.). The authors gratefully acknowledge generous financial support from Central Glass Company (Tokyo, Japan) and Ajinomoto Company (Tokyo, Japan).

Supporting Information Available: Full characterization and ^1H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0616198