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Efficient Synthesis of Sterically Constrained Symmetrically α,α-Disubstituted α-Amino Acids under Operationally Convenient Conditions

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Homologation of the nucleophilic glycine equivalent Ni-Gly-PABP [Ni(II) complex of glycine Schiff base with 2-[*N*-(α-picolyl)amino]benzophenone (PABP)] **2** via alkyl halide alkylations and Michael addition reactions was systematically studied as a general method for preparing symmetrically α,α-disubstituted α-amino acids (*sym*-α,α-AA). The dialkylation reactions are conducted under operationally convenient conditions without recourse to inert atmosphere, dried solvents, and low temperatures, thus enjoying key advantages of the experimental simplicity and attractive cost structure. The method has been shown to be particularly successful for the dialkylation of complex **2** with activated and nonactivated alkyl halides, including propargyl derivatives, affording a generalized and practical access to the corresponding *sym*-α,α-AA. This study has also shown some limitation of the method, as it cannot be extended to α- or *β*-branched alkyl halides or Michael acceptors to be used for the dialkylation of glycine equivalent **2**. High chemical yields of the dialkylated products, combined with the simplicity of the experimental procedure, render this method worth immediate use for multigram scale preparation of the *sym*-α,α-AA.

Introduction

With completion of the first draft of the human genome and the completion or near completion of the genomes of several other animals, plants, and bacteria,[1] the de novo design of peptides and peptidomimetics with a presupposed three-dimensional structure rapidly becomes a subject of major interest and importance in the multidisciplinary area of organic, bioorganic, peptide chemistry as well as biology and medicine.[2] The availability of synthetic methods allowing design and synthesis of novel sterically constrained amino acids and related compounds will be a critical component of any effort to understand the proteome and its relation to life, health, and disease.[3] In particular, identification of α,α-dimethylglycine (DMeG) [α-methylalanine, α-aminoisobuturic acid (Aib)] and its higher homologues in natural peptides[4] and discovery of its propensity to predictably influence three-dimensional structure of peptides[5,6] generated a great deal of interest in the development of new synthetic methods for preparation of various symmetrically α,α-disubstituted α-amino acids (*sym*-α,α-AA) to satisfy the increasing demand in these sterically constrained tailor-made amino acids[7,8] for biological studies.[9]

However, amino acids other than DMeG are not readily available; therefore, their biological properties and applications, as sterically constrained scaffolds for the rational design of peptides and proteins, are still awaiting systematic studies. Analysis of the relevant literature has revealed that, despite substantial interest in *sym*-α,α-

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(5) DMeG and its higher homologues were shown to impart well-defined conformational constraints to a peptide backbone, strongly preferring folded conformations and inducing helical secondary structures of either the 3_{10-} or α-helical type. (a) Karle, I. L.; Kaul, R.; Rao, R. B.; Raghothama, S.; Balaram, P. *J. Am. Chem. Soc.* **1997**, *119*, 12048. (b) Marshall, B. R.; Hodgkin, E. E.; Langs, D. A.; Smith, G. D.; Zabrocki, J.; Leplawy, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *31*, 129. (c) Toniolo, C.; Crisma, M.; Bonora, G. M.; Benedetti, E.; Di Blasio, B.; Pavone, V.; Pedone, C.; Santini, A. *Biopolymers* **1991**, *31*, 129. (d) Huston, S. E.; Marshall, G. R. *Biopolymers* **1994**, *34*, 75. (e) Aleman, C. *Biopolymers* **1994**, *34*, 841. (f) Toniolo, C.; Bianco, A.; Formaggio, F.; Crisma, M.; Bonora, B. M.; Benedetti, E.; Del Duca, V.; Saviano, M.; Di Blasio, B.; Pedone, C. *Bioorg. Med. Chem.* **1995**, *3*, 1211. (g) Okuyama, K.; Ohuchi, S. *Biopolymers* **1996**, *40*, 85. (h) Karle, I. L. *Biopolymers* **1996**, *40*, 157.

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(7) 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 (see ref 8). 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 more appropriate use as a common name for such amino acids.

(8) *Fluorine-Containing Amino Acids. Synthesis and Properties*; Kukhar′, V. P., Soloshonok, V. A., Eds.; John Wiley and Sons Ltd.: Chichester, 1994.

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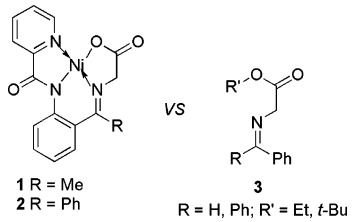

FIGURE 1.

AA, there has been no single generalized and practical method[10] for their preparation developed to date.

As some of our current projects required ready access to multigram quantities of various *sym*-α,α-AA, we set for ourselves a goal of developing a simple and practical method for preparing these compounds on a relatively large scale. Herein, we report a full account[11] of a systematic study on the dialkylation of nucleophilic glycine equivalents **1** and **2** (Figure 1) which led to the development of a simple and generalized method for synthesis of *sym*-α,α-AA. The practicality of the method and its scope and limitations for preparing different types of the target amino acids are critically compared with the literature approaches.

Results and Discussion

One of the traditional and widely used approaches to *sym*-α,α-AA is the Bucherer−Bergs and Strecker reactions of *sym*-dialkyl ketones with cyano derivatives as a source of an amino function.[12] This explains the high availability of DMeG as a consequence of the abundance of acetone. However, as was shown by Mclaughlin and Hammer,[13,14] these methods, besides application of lethally toxic KCN, are not suitable for preparation of some sterically bulky *sym*-α,α-AA, as, for instance, dibenzylglycine. These synthetic limitations and overall impracticality of the classical methods for generalized and efficient[10] synthesis of *sym*-α,α-AA led to the development of various alternative approaches. Most recently, Mclaughlin and Hammer reported a methodologically interesting approach to *sym*-α,α-AA using the dialkylation of ethyl α-nitroacetate as a masked nucleophilic glycine equivalent.[13] This method was shown to be successful for preparing various functionalized *sym*-α,α-AA via Michael addition reactions. Unfortunately, application of alkyl halides for dialkylation of the α-nitroacetate was found to be limited to activated reagents such as benzyl bromides, *tert*-butyl 2-bromoacetate, and allyl iodide.[13] Another methodologically different approach to *sym*-α,α-AA, reported by Charette,[15] is based on the double-nucleophilic addition of Grignard reagents to alkoxy-(methoxy, benzyloxy)acetonitriles followed by the deprotection and oxidation of the primary alcohol moiety. From a synthetic standpoint, this approach has many drawbacks, including the multistep procedure, resulting in low overall yield of the target products, protection−deprotection manipulations, operationally inconvenient conditions (−40 °C), and sensitivity of the reaction outcome to some additives and promoters.[15] Another example of synthetic organic chemists' ingenuity is provided by Rassu−Casiraghi's group, who studied the *N*-BOC-2-(*tert*-butyldimethylsiloxy)pyrrole as a deeply masked α-amino acid enolate equivalent and showed its potential application for synthesis of *sym*-α,α-AA, including dibenzylglycine.[16] Unfortunately, this method suffers methodological deficiency of a multistep (at least eight transformations) procedure, inconvenient reaction conditions, and low overall yields of the target products. Of particular interest for us was the report by Ezquerra−Moreno-Mañas's group who studied the dialkylation of the glycine Schiff base **3** (R = Ph, R′ = Et) (Figure 1) under the convenient phase-transfer conditions.[17] The authors demonstrated that the methylene moiety in derivative **3** can be dialkylated under the mild conditions (0 °C) using benzyl and allyl bromides. Unfortunately, low yields of the target products cannot render this method synthetically useful. More recently, Denmark et al. reported one example of dialkylation of Schiff base **3** with quantitative chemical yield.[18] In this case, diethylation of **3** with ethyl iodide was conducted as a stepwise procedure using KHMDS to generate the corresponding enolate at −73 °C. Though successful, this procedure does not enjoy

(9) The following references illustrate application of *sym*-α,α-AA other than DMeG in peptide design. For examples involving α,α-dibenzylglycine see refs a−c; α,α-diethylglycine, d−h; α,α-dipropylgylcine, d−u; α,α-dibutylglicine, h, p−r; α,α-dipentylglicine, u. (a) Crisma, M.; Valle, G.; Bonora, G. M.; Toniolo, C.; Lelj, F.; Barone, V.; Fraternali, F.; Hardy, P. M.; Maia, H. L. S. *Biopolymers* **1991**, *31*, 637. (b) Valle, G.; Crisma, M.; Bonora, G. M.; Toniolo, C.; Lelj, F.; Barone, V.; Fraternali, F.; Hardy, P. M.; Langran-Goldsmith, A.; Maia, H. L. S. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1481. (c) Cotton, R.; Hardy, P. M.; Langran-Goldsmith, A. E. *Int. J. Pept. Protein Res.* **1986**, *28*, 245. (d) Cirilli, M.; Coiro, V. M.; Di Nola, A.; Mazza, F. *Biopolymers* **1998**, *46* (4), 239. (e) Balaram, P. *Pure Appl. Chem*. **1992**, *64* (8), 1061. (f) Izdebski, J.; Kunce, D.; Leplawy, M. T.; Pachulska, M.; Redlinski, A. *Pol. J. Chem*. **1991**, *65* (7−8), 1427. (g) Toniolo, C.; Benedetti, E. *Macromolecules* **1991**, *24* (14), 4004. (h) Prasad, S.; Rao, R. B.; Balaram, P. *Biopolymers* **1995**, *35* (1), 11. (i) Prasad, S.; Mitra, S.; Subramanian, E.; Velmurugan, D.; Rao, R. B.; Balaram, P. *Biochem. Biophys. Res. Commun*. **1994**, *198* (2), 424. (j) Di Blasio, B.; Pavone, V.; Isernia, C.; Pedone, C.; Benedetti, E.; Toniolo, C.; Hardy, P. M.; Lingham, I. N. *J. Chem. Soc., Perkin Trans. 2* **1992**, (4), 523. (k) Hardy, P. M.; Lingham, I. N. *Int. J. Pept. Protein Res.* **1983**, *21* (4), 406. (l) Kaul, R.; Banumathi, S.; Velmurugan, D.; Rao, R. B.; Balaram, P. *Biopolymers* **2000**, *54* (3), 159. (m) Karle, I. L.; Rao, R. B.; Kaul, R.; Prasad, S.; Balaram P *Biopolymers* **1996**, *39* (1), 75. (n) Prasad, S.; Mitra, S.; Subramanian, E.; Velmurugan, D.; Rao, R. B.; Balaram, P. *Biochem. Biophys. Res. Commun*. **1994**, *198* (2), 424. (o) Hardy, P. M.; Lingham, I. N. *Int. J. Pept. Protein Res.* **1983**, *21* (4), 392. (p) Crisma, M.; Valle, G.; Toniolo, C.; Prasad, S.; Rao, R. B.; Balaram, P. *Biopolymers* **1995**, *35* (1), 1. (q) Prasad, S.; Rao, R. B.; Balaram, P. *Biopolymers* **1995**, *35* (1), 11. (u) Abshire, C. J.; Planet, G. *J. Med. Chem*. **1972**, *15* (3), 226. (r) Karle, I. L.; Gurunath, R.; Prasad, S.; Rao, R. B.; Balaram, P. *Int. J. Pept. Protein Res*. **1996**, *47* (5), 376.

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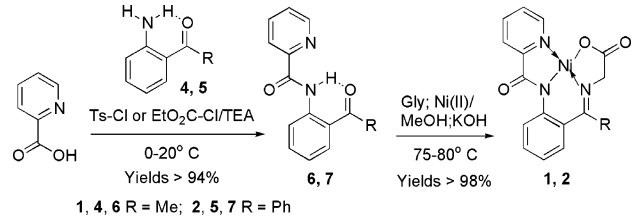
SCHEME 1

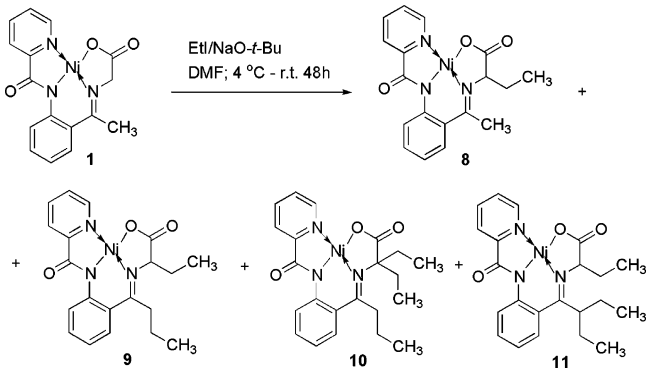


advantages of the operationally convenient conditions and thus is unattractive to scale-up. On the other hand, from the methodological standpoint, dialkylation of a properly protected glycine derivative might be the most straightforward and generalized approach to the synthesis of *sym*-α,α-AA.

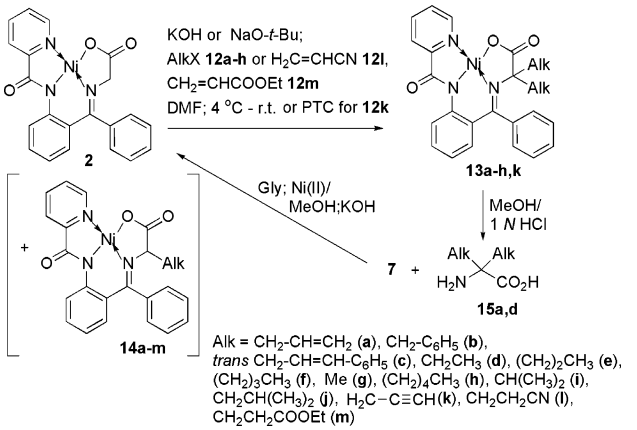
Taking advantage of our extensive experience in chemistry of Ni(II) complexes of amino acids,[19] we envisioned that the Ni(II) complexes **1**, introduced by us,[20] and **2**, designed by Belokon's group[21] (Figure 1 and Scheme 1), might be ideal starting glycine equivalents for preparation of *sym*-α,α-AA via the dialkylation. Compounds **1** and **2** are inexpensive and readily available in a multigram (>100 g) quantity according to the protocol recently developed by us.[22] Complexes **1** and **2** are stable yet highly reactive nucleophilic glycine equivalents, and their homologation can be carried out at ambient temperature and without recourse to inert atmosphere or rigorously dried and degassed solvent. Moreover, the generation of the corresponding enolates from **1** and **2** can be effectively achieved by using regular inorganic bases (KOH, NaOH) or alkoxides. All these advantageous features of **1** and **2** render them synthetically superior over the traditionally used Schiff base **3** (Figure 1) for a particular purpose of preparing *sym*-α,α-AA via the dialkylation.

Taking into account the highly sterically constrained nature of the expected α,α-dialkylation products, we decided first to study dialkylation of the Ni(II) complex **1** derived from less sterically bulky 2-[*N*-(α-picolyl)amino]-acetophenone (PAAP) **6** (Scheme 1). We conducted a series of experiments on dialkylation of **1** using commercial-grade DMF as a solvent, sodium hydroxide or sodium *tert*-butoxide as a base, and several activated and inactivated alkyl halides as alkylating reagents. The results obtained, though interesting, did not render the dialkylation of the acetophenone-derived complex **1** as synthetically useful for preparing the target *sym*-α,α-AA. The most representative example is given in Scheme 2. Thus, depending on the reaction conditions used (reaction time and amount of the alkylating reagent), up to four products **8**−**11** can be isolated from the reaction mixture.

SCHEME 2



SCHEME 3



Monoalkylated product **8** was observed as a major product on the initial stage (15 min). Completion of the second alkylation required about 1 h and was exclusively directed on the acetimino group to yield complex **9**. Interestingly, the third alkylation, observed after 12−24 h, occurred on the aminobuturic acid moiety and in the α-position to the ketimine group with comparable rates. Compounds **8** and **9** were isolated in analytically pure form by column chromatography and fully characterized, while products **10** and **11** were obtained as an inseparable mixture.

By contrast, the first attempt to dialkylate complex **2**, derived from a glycine Schiff base with 2-[*N*-(α-picolyl)-amino]benzophenone (PABP) **7** (Scheme 1), gave synthetically promising results. Thus, treatment of **2** in commercial-grade DMF with allyl bromide (**12a**) (2.5 equiv) in the presence of KOH (10 equiv) at ambient temperature resulted in an exothermic reaction, giving rise to the target dialkylated product **13a** in high chemical yield (Scheme 3; Table 1, entry 1). Under the same conditions, reaction of complex **2** with benzyl bromide (**12b**) occurred at lower rate but resulted in complete dibenzylation of the glycine moiety in **2** affording product **13b** as an individual product (entry 2). Attempts to reduce the amount of the base resulted in incomplete dialkylation reactions giving rise to a mixture of the major products **13a**,**b** and monoalkylated derivatives **14a**,**b** (5−10%). We also noticed that an increase in the reaction time lowered the yields of the target products due to the formation of some unidentified dark-colored byproducts, perhaps oxidized Ni(III) derivatives. Therefore, we decided to use commercially available and

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TABLE 1. Dialkylations of Ni(II) Complex 2 with Alkyl Halides 12a−m[a]

						products **13** and **14**	
entry	**12a−m**	X	base	ratio base/ **12a−m**	time	yield,[b] %	ratio **13**/**14**[c]
1	**a**	Br	KOH	10/2.5	30 min	83	>99/1
2	**b**	Br	KOH	10/2.5	1 h	90	>99/1
3	**a**	Br	NaO-*t*-Bu	3.0/3.0	15 min	94	>99/1[d]
4	**b**	Br	NaO-*t*-Bu	3.0/3.0	15 min	89	>99/1
5	**c**	Br	NaO-*t*-Bu	3.0/3.0	15 min	94	>99/1
6	**d**	Br	NaO-*t*-Bu	3.5/3.5	20 min	94	76/24
7	**d**	Br	NaO-*t*-Bu	4.0/4.0	2 h	92	90/10
8	**d**	Br	NaO-*t*-Bu	4.5/4.5	2 h	91	98/2
9	**e**	Br	NaO-*t*-Bu	4.0/4.0	2 h	90	91/9
10	**f**	Br	NaO-*t*-Bu	4.0/4.0	2 h	91	94/6
11	**g**	I	NaO-*t*-Bu	3.5/3.5	15 min	91	>99/1
12	**d**	I	NaO-*t*-Bu	3.5/3.5	15 min	92	>99/1
13	**e**	I	NaO-*t*-Bu	3.5/3.5	15 min	91	>99/1[d]
14	**f**	I	NaO-*t*-Bu	3.5/3.5	15 min	91	>99/1
15	**h**	I	NaO-*t*-Bu	3.5/3.5	15 min	93	>99/1
16	**i**	I	NaO-*t*-Bu	3.5/3.5	20 min	97	<1/99
17	**j**	I	NaO-*t*-Bu	3.5/3.5	15 min	98	<1/99
18	**k**	Br	NaOH	PTC	45 min	97	5/95
19	**k**	Br	NaOH	PTC	24 h	>98	>99/1
20	**l**	−	NaOH	PTC	15 min	93	<1/99
21	**m**	−	NaOH	PTC	15 min	95	<1/99

[a] All reactions were run in commercial-grade DMF at ambient temperature in the presence of the base indicated. [b] Isolated yield of crude product. [c] Determined by NMR (300 MHz) analysis of the crude reaction mixtures. [d] The reaction was conducted on >10 g scale.

inexpensive sodium *tert*-butoxide as a base allowing us to conduct the reactions under homogeneous conditions. To our satisfaction, the reaction of allyl bromide (**12a**) with **2** in the presence of only 3 equiv of the base occurred at substantially higher rate and afforded diallylated complex **13a** as an individual product with improved chemical yield (entry 3). This reaction was conducted on >10 g scale to prepare free amino acid **15a** (vide infra). Under the same conditions, reactions of **2** with benzyl (**12b**) and cinnamyl bromide (**12c**) occurred at the same rates and virtually complete dialkylation, giving rise to the target compounds **13b**,**c** in high isolated yields (entries 4 and 5).

We next decided to explore the generality of this method for dialkylation of complex **2** using nonactivated alkyl halides. Under the same conditions, except for an increase in the amounts of the alkylating reagent and base (3.5 equiv of each), the reaction between **2** and ethyl bromide (**12d**) yielded a mixture of di- (**13d**) and monoalkylated (**14d**) products in a ratio of 76/24 (entry 6). Continuation of this reaction for up to 2 h did not result in a noticeable increase of **13d**. However, a further increase in the amounts of the alkylating reagent and the base allowed us to improve the ratio of products **13d** and **14d** to a satisfactory level of 98/2 (entries 7 and 8). Similar results were obtained in the reactions of **2** with propyl (**12e**) and butyl bromides (**12f**) (entries 9 and 10).

Critical analysis of the results obtained suggested that application of the activated alkyl bromides **12a−c** for dialkylation of the glycine equivalent **2** might be rendered as an efficient and synthetically useful approach for preparing products **13a−c** and thus the target amino acids **15a−c**. On the other hand the dialkylation of **2** with nonactivated bromides **12d−f**, though successful, still needed improvement to achieve the complete dialkylation. Therefore, we decided to use nonactivated alkyl iodides as alkylating reagents. We found that only 3.5 equiv of methyl iodide (**12g**) and the base is enough for complete, fast, and clean dimethylation of **2** to afford compound **13g** in high isolated yield (entry 11). Inspired by these results, we conducted the reaction of complex **2** with ethyl (**12d**), propyl (**12e**), butyl (**12f**), and pentyl (**12h**) iodides, all of which gave similarly excellent chemical outcomes affording their respective dialkylated **13d−f**,**h** as individual products in yields of 91−93% (entries 12−15). As the prices of alkyl bromides and alkyl iodides are very close, the application of the iodides verses bromides becomes practically useful considering lower amounts of the reagents needed and the enhanced chemical outcome obtained. On the other hand, attempts to use α- or *β*-branched alkyl halides exposed some limitations of this method. For instance, alkylation of complex **2** with isopropyl **12i** and isobutyl **12j** bromides or iodides, even under the forced conditions (temperature), resulted in quantitative formation of only monoalkylated products **14i**,**j** (entries 16 and 17).

Taking into account the synthetic versatility of terminal alkyne groups, dialkylation of complex **2** with propargyl bromide (**12k**) was of particular interest. Unfortunately, all attempts to alkylate glycine equivalent **2** with bromide **12k** in DMF solution using NaO-*t*-Bu or NaOH as bases resulted in a substantial amount of unidentified byproducts rather than affording the target alkylation products. Perhaps the strongly basic reaction conditions used were incompatible with the reactivity of the propargyl group. Therefore, we decided to try the dialkylation under much milder phase-transfer conditions (PTC). The reaction of complex **2** with bromide **12k** was conveniently carried out at room temperature in dichloromethane using tetrapropylammonium iodide as the catalyst and 30% aqueous NaOH as the base. To our satisfaction, quantitative conversion of complex **2** to the monosubstituted intermediate product **14k** took place within 45 min, with further clean conversion of **14k** to the target disubstituted complex **13k** occurring in >98% yield after running the reaction overnight.

Finally, we studied the dialkylation of glycine equivalent **2** via Michael addition reactions using acrylonitrile (**12l**) and ethyl acrylate (**12m**) as Michael acceptors. We found that application of the strongly basic homogeneous conditions (DMF/NaOH or NaO-*t*-Bu) were incompatible with high reactivity of Michael acceptors **12l** and **12m**, leading to a substantial amounts of unidentified byproducts along with the monoalkylated complexes **14l** and **14m**. We then conducted the reactions using milder PTC hoping to obtain the target disubstituted products. However, despite the quick and clean monoalkylation (entries 20 and 21), the reactions did not proceed further affording only the monosubstituted derivatives **14l** and **14m** in high chemical yields.

Products **13a−h** were isolated simply by pouring the reaction mixture into ice−water followed by filtration of the precipitate. To demonstrate the isolation of the target *sym*-α,α-AA **15** from their Ni(II) complexes **13**, dialkylated **13a** and **13d** were decomposed without any purification under the standard conditions[19c,d,20] to yield free amino acids **15a** (91%) and **15d** (93%) along with virtually complete recovery of ligand **7**, which was converted

back to the glycine equivalent **2** (Schemes 1 and 3). The products **13k** and **14m,n** obtained under PTC were isolated by the addition of water to the reaction mixture and then extracting the aqueous phase with methylene chloride. The organic phase was dried with magnesium sulfate, filtered, and evaporated to yield a crystalline compound, which was washed with water and hexane to yield the final products **13k** and **14m**,**n**.

Conclusion

In summary, we have demonstrated that the readily available and inexpensive Ni(II) complex **2** is a synthetically superior glycine equivalent for preparing sterically constrained symmetrically α,α-disubstituted amino acids. The dialkylation reactions are conducted under operationally convenient conditions without recourse to inert atmosphere, dried solvents and low temperatures, thus enjoying key advantages of the experimental simplicity and attractive cost structure. The method has been shown to be particularly successful for the dialkylation of complex **2** with activated and nonactivated alkyl halides, including propargyl derivatives, affording a generalized and practical access to the corresponding *sym*-α,α-AA. This study has also shown some limitation of the method, as it cannot be extended to α- or *β*-branched alkyl halides or Michael acceptors to be used for the dialkylation of glycine equivalent **2**. High chemical yields of the dialkylated products, combined with simplicity of the experimental procedure render this method worth immediate use for multigram scale preparation of the *sym*-α,α-AA.

Experimental Section

General Methods. Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. All the reactions were carried out under atmosphere without any special caution to exclude air. Unless indicated, ^{1}H and ^{13}C NMR spectra, were taken in $CDCl_3$ solutions at 299.95 and 75.42 MHz, respectively, on an instrument in the University of Oklahoma NMR Spectroscopy Laboratory. Chemical shifts refer to TMS as the internal standard. Unless otherwise noted, the R_f values (TLC) were obtained using chloroform/acetone mixture in a volume ratio of 7/1.

Yields refer to isolated yields of products of greater than 95% purity as estimated by ^{1}H and ^{13}C NMR spectrometry. All new compounds were characterized by ^{1}H, ^{13}C NMR, and high-resolution mass spectrometry (HRMS-ESI).

Alkylation of Complex 1 with Ethyl Iodide. To a solution of 0.950 g (9.887 mmol) of sodium *tert*-butoxide in DMF (10 mL/0.95 g), cooled in an ice bath to 4 °C, were added1.005 g (2.834 mmol) of complex **1** and 1.542 g (9.887 mmol) of ethyl iodide (**12d**), and the reaction was stirred at 4 °C for 5 min, after which time the ice bath was removed and the reaction mixture was allowed to warm to room temperature. The reaction was quenched by pouring the reaction mixture over ice−water. The resulting crystalline precipitate was filtered off and washed with water and *n*-hexane to yield the products **8**−**11**, which were separated by column chromatography.

Ni(II) Complex of 2-Aminobuturic Acid Schiff Base with PAAP (8). Obtained by quenching the reaction after 15 min (monitored by TLC): R_f = 0.17. mp >200 °C; ^{1}H NMR δ 1.50 (3H, t, J = 7.5 Hz), 2.10 (1H, dq, J = 7.5, 3.9 Hz), 2.21 (1H, dq, J = 13.8, 7.5 Hz), 2.51 (3H, s), 4.29 (1H, q, J = 7.5, 3.9 Hz), 7.02 (1H, m), 7.26−7.45 (2H, m), 7.69 (1H, dd, J = 8.4, 1.5 Hz), 7.87 (1H, dm, J = 5.4 Hz), 7.97 (1H, td, J = 7.5, 1.5 Hz), 8.22 (1H, dm, J = 3.6 Hz), 8.79 (1H, dd, J = 8.7, 1.2 Hz); ^{13}C NMR δ 9.81, 18.68, 28.23, 71.73, 121.75, 123.77, 123.95, 126.60, 126.75, 129.91, 132.54, 140.25, 141.67, 146.80, 153.07, 169.21, 169.46, 179.42; HRMS [M + Na^+] calcd for $C_{18}H_{17}N_3NaNiO_3$ 405.0292, found 405.0101.

Ni(II) Complex of 2-Aminobuturic Acid Schiff Base with 1-[2′-[*N*-(α-Picolyl)amino]phenyl]butan-1-one (9). Obtained by quenching the reaction after 1 h (monitored by TLC): R_f = 0.28; mp >200 °C; ^{1}H NMR δ 1.13 (3H, t, J = 7.2 Hz), 1.58 (3H, t, J = 7.4 Hz), 1.70 (2H, hex, J = 7.7 Hz), 2.13 (1H, m), 2.31 (1H, m), 2.69−2.88 (2H, m), 4.23 (1H, dd, J = 3.8, 7.4 Hz), 7.02 (1H, m), 7.36 (1H, m), 7.41 (1H, m), 7.61 (1H, d, J = 8.1 Hz), 7.87 (1H, m), 7.97 (1H, m), 8.19 (1H, d, J = 5.1 Hz), 8.76 (1H, d, J = 8.4 Hz); ^{13}C NMR δ 10.1, 14.3, 22.8, 29.2, 33.0, 71.5, 121.7, 123.7, 124.0, 125.4, 126.6, 129.9, 132.4, 140.2, 142.3, 146.8, 153.1, 169.3, 172.7, 178.9; HRMS [M + H^+] calcd for $C_{20}H_{22}N_3NiO_3$ 411.1006, found 411.1209.

Ni(II) Complex of 2-Amino-2-ethylbuturic Acid Schiff Base with 1-[2′-[*N*-(α-Picolyl)amino]phenyl]butan-1-one (10) and Ni(II) Complex of 2-Aminobuturic acid Schiff Base with 2-Ethyl-1-[2′-[*N*-(α-picolyl)amino]phenyl]butan-1-one (11). Obtained as an inseparable mixture by column chromatography by quenching the reaction after 24 h (monitored by TLC): R_f = 0.41. Compound **10**: ^{1}H NMR δ 0.98 (3H, t, J = 7.5 Hz), 1.28 (6H, t, J = 7.5 Hz), 1.44 (2H, m), 2.18 (4H, m), 3.13 (2H, m), 7.0 (1H, m), 7.34−7.42 (2H, m), 7.41 (1H, m), 7.88 (1H, m), 7.97 (1H, m), 8.29 (1H, m), 8.52 (1H, m). Compound **11**: ^{1}H NMR δ 0.83 (3H, t, J = 7.5 Hz), 1.10 (3H, t, J = 7.5 Hz), 1.46 (2H, m), 1.70 (3H, t, J = 7.5), 1.75−2.10 (3H, m), 2.67 (1H, hept, J = 13.8, 6.3 Hz), 2.95 (1H, m), 4.16 (1H, dd, J = 8.1, 3.3 Hz), 6.94 (1H, m), 7.34 (1H, m), 7.42 (1H, m), 7.68 (1H, m), 7.87 (1H, m), 7.97 (1H, m), 8.13 (1H, m), 8.61 (1H, m); HRMS [M + H] calcd for $C_{22}H_{25}N_3NaNiO_3$ 461.1147, found 461.0996.

Dialkylation of Ni(II) Complex 2 with Activated Bromides 12a−c Yielding Complexes 13a−c. General Procedure. To a solution of sodium *tert*-butoxide (3 equiv) in DMF (10 mL/1 g of complex **2**) were added complex **2** (1 equiv) and the corresponding alkylating reagent **12a−c** (3 equiv). The reaction was stirred at ambient temperature (room temperature water bath) for 15 min, and upon completion (monitored by TLC), the reaction mixture was poured into ice−water and the resulting solid was filtered, washed with water, and *n*-hexane to afford the products **13a−c** in yields ranging from 89 to 94% and of greater than 99% purity. For the chemical yields, see Table 1, entries 3−5.

The corresponding monoalkylated products **14a−c** were prepared under the same conditions except that the base and the alkylating reagent were used in a ratio of 1.5/1.1, respectively.

Ni(II) Complex of α,α-Diallylglycine Schiff Base with PABP (13a): R_f = 0.60; mp 247.3−248.9 °C; ^{1}H NMR δ 2.31 (2H, ddt, J = 15.5, 6.8, 1.5 Hz), 2.50 (2H, ddt, J = 15.5, 6.8, 1.5 Hz), 5.24−5.35 (4H, m),6.19−6.33 (2H, m), 6.67 (1H, m), 6.71 (1H, m), 7.26−7.35 (3H, m), 7.41−7.57 (4H, m), 7.89 (1H, m), 7.99 (1H, m), 8.36 (1H, m), 8.70 (1H, m); ^{13}C NMR δ 43.16, 82.43, 119.14, 121.04, 123.45, 123.47, 124.85, 126.55, 127.34, 127.74, 128.59, 129.60, 131.89, 132.53, 133.39, 134.25, 136.38, 140.10, 140.45, 142.12, 144.43, 147.02, 152.81, 169.64, 173.49, 180.34; HRMS [M + H^+] calcd for $C_{27}H_{23}N_3NiO_3$ 497.1810, found 497.1416.

Ni(II) Complex of 2-Amino-pent-4-enoic Acid Schiff Base with PABP (14a): R_f = 0.47; mp 232.5−233.2 °C; ^{1}H NMR δ 2.48−2.53 (2H, m), 4.11 (1H, dd, J = 5.4, 4.5 Hz), 5.15 (1H, m), 5.32 (1H, m), 6.44 (1H, m), 6.75−6.82 (2H, m), 7.10 (1H, m), 7.32 (1H, m), 7.43−7.56 (5H, m), 7.90 (1H, m), 8.01 (1H, m), 8.22 (1H, d, J = 4.8 Hz), 8.92 (1H, d, J = 8.4 Hz); ^{13}C NMR δ 38.9, 71.1, 119.6, 121.3, 123.3, 123.9, 126.6, 126.8, 127.0, 127.8, 128.7, 129.1, 129.8, 131.9, 133.3, 133.8, 134.4, 140.4, 143.0, 146.8, 153.1, 169.7, 171.8, 178.6; HRMS [M + Na^+] calcd for $C_{24}H_{19}N_3NaNiO_3$ 479.1093, found 479.0992.

Ni(II) Complex of α,α-Dibenzylglycine Schiff Base with PABP (13b): $R_f = 0.62$; mp 295.2−296.6 °C; ^{1}H NMR δ 2.78 (2H, d, J = 15.9 Hz), 3.37 (2H, d, J = 15.9 Hz), 6.65−6.67 (2H, m), 6.82−6.85 (2H, m), 6.96−7.02(2H, m), 7.20−7.34 (12H, m) 7.50 (1H, m), 7.75 (1H, m), 7.82−7.92 (2H, m), 8.52 (1H, m); ^{13}C NMR δ 30.88, 82.70, 120.95, 122.94, 123.46, 125.86, 126.26, 127.22, 127.40, 127.70, 128.01, 128.28, 128.67, 129.35, 129.59, 132.37, 134.17, 135.70, 136.40, 139.42, 142.13, 146.59, 152.75, 168.70, 171.53, 178.48; HRMS [M + H$^+$] calcd $C_{36}H_{30}N_3NiO_3$ 597.3014, found 597.1463.

Ni(II) Complex of 2-Amino-3-phenylpropionic Acid Schiff Base with PABP (14b): $R_f = 0.65$; mp 262.7−264.0 °C; ^{1}H NMR δ 2.86, 3.13 (2H, ABX, J = 13.5, 5.9, 3.2 Hz), 4.36 (1H, dd, J = 5.9, 3.2 Hz), 6.76−6.88 (3H, m), 7.13−7.26 (3H, m), 7.28−7.42 (5H, m), 7.52−7.61 (3H, m), 7.68 (1H, m), 7.77 (1H, m), 7.90 (1H, m), 8.71 (1H, d, J = 8.7 Hz); ^{13}C NMR δ 40.1, 72.9, 121.3, 123.4, 123.5, 126.2, 127.0, 127.1, 127.3, 127.5, 128.0, 129.0, 129.2, 130.0, 131.0, 133.2, 133.5, 134.2, 135.6, 139.7, 143.0, 146.5, 153.0, 169.0, 171.0, 177.8; HRMS [M + H$^+$] calcd for $C_{28}H_{21}N_3NaNiO_3$ 529.1680, found 529.0767.

Ni(II) Complex of α,α-Di-(*trans*)-cinnamylglycine Schiff Base with PABP (13c): $R_f = 0.79$; mp 247.5−249.3 °C; ^{1}H NMR δ 2.46 (2H, dd, J = 15.2, 6.0 Hz), 2.73 (2H, dd, J = 15.2, 6.0 Hz), 6.63−6.76 (7H, m), 7.12−7.41 (13H, m), 7.49−7.58 (4H, m), 7.76 (1H, m), 8.13 (1H, m) 8.61 (1H, m); ^{13}C NMR δ 42.13, 83.56, 121.11, 123.22, 123.52, 123.74, 125.91, 126.15, 127.00, 127.52, 127.60, 128.15, 128.94, 129.68, 132.52, 134.04, 134.10, 136.13, 136.72, 139.58, 142.22, 146.55, 152.42, 169.14, 172.76, 179.46; HRMS [M + H$^+$] calcd for $C_{39}H_{34}N_3NiO_3$ 649.3753, found 649.1760.

Ni(II) Complex of 2-Amino-5-phenylpent-4-enoic Acid Schiff Base with PABP (14c): $R_f = 0.43$; mp 182.1−183.7 °C; ^{1}H NMR δ 2.56−2.71 (2H, bm), 4.22 (1H, m), 6.69−6.81 (3H, m), 7.04−7.06 (3H, m), 7.12 (1H, m), 7.24−7.39, (5H, m), 7.53−7.56 (4H, m), 7.77 (1H, t, J = 7.5 Hz), 7.97 (1H, bm), 8.79 (1H, d, J = 8.7 Hz); ^{13}C NMR δ 30.10, 71.07, 121.68, 123.79, 124.07, 126.35, 126.72, 127.08, 127.44, 127.58, 127.75, 127.98, 128.67, 128.78, 129.28, 129.58, 130.29, 133.63, 133.82, 134.66, 135.86, 136.97, 140.25, 143.44, 146.92, 153.00, 169.65; HRMS [M + Na$^+$] calcd for $C_{30}H_{23}N_3NaNiO_3$ 555.2052, found 555.0589.

Dialkylation of Ni(II) Complex 2 with Nonactivated Iodides 12d−h Yielding Complexes 13d−h. General Procedure. To a solution of sodium *tert*-butoxide (3.5 equiv) in DMF (10 mL per 1 g of complex **2**), cooled in an ice bath to 4 °C, were added complex **2** (1 equiv) and the corresponding alkylating reagent **12d−h** (3.5 equiv). The reaction was stirred at 4 °C for 5 min, after which time the ice bath was removed and the reaction mixture was allowed to warm to room temperature. After an additional 10 min (monitored by TLC), the reaction was poured into ice−water, and the resulting solid was filtered and washed with water and *n*-hexane to afford the products **13d−h** of greater than 99% purity. For the chemical yields, see Table 1, entries 11−15.

The corresponding monoalkylated products **14d−h** were prepared under the same conditions except that the base and the alkylating reagent (bromides) were used in a ratio of 1.5/1.1, respectively.

Ni(II) Complex of α,α-Diethylglycine Schiff Base with PABP (13d): $R_f = 0.52$; mp 322.1−323.0 °C; ^{1}H NMR δ 1.27 (6H, t, J = 7.2 Hz), 1.52 (2H, dq, J = 14.7, 7.2 Hz), 1.71 (2H, dq, J = 14.7,7.2 Hz), 6.68 (1H, m), 6.72 (1H, m), δ 7.24−7.34 (3H, m), 7.42−7.55 (4H, m), 7.90 (1H, m), 7.99 (1H, m), 8.40 (1H, m), 8.71 (1H, m); ^{13}C NMR δ 9.54, 32.79, 84.53, 121.04, 123.46, 123.48, 126.55, 127.31, 127.33, 128.71, 129.40, 132.40, 134.19, 136.49, 140.10, 142.01, 147.00, 152.88, 169.65, 173.17, 181.72; HRMS [M + H$^+$] calcd for $C_{25}H_{24}N_3NiO_3$ 473.1626, found 473.1322.

Ni(II) Complex of 2-Aminobutyric Acid Schiff Base with PABP (14d): $R_f = 0.45$; mp 265.4−266.5 °C; ^{1}H NMR δ 1.39 (3H, t, J = 7.5 Hz), 1.73 (1H, m), 1.97 (1H, m), 3.99 (1H, dd, J = 7.5; 3.3 Hz), 6.74−6.81 (2H, m), 7.06 (1H, m), 7.32 (1H, m), 7.43−7.52 (5H, m), 7.91 (1H, m), 8.01 (1H, m), 8.24 (1H, d, J = 4.8 Hz), 8.93 (1H, d, J = 8.1 Hz); ^{13}C NMR δ 9.7, 28.4, 72.0, 121.1, 123.2, 123.8, 126.5, 126.7, 126.7, 127.5, 128.5, 128.9, 129.5, 133.1, 133.6, 134.2, 140.2, 142.7, 146.6, 153.0, 169.6, 171.5, 179.0; HRMS [M + Na$^+$] calcd for $C_{23}H_{19}N_3NaNiO_3$ 467.0986, found 467.2276.

Ni(II) Complex of α,α-Di-*n*-propylglycine Schiff Base with PABP (13e): $R_f = 0.63$; mp 282.5−283.3 °C; ^{1}H NMR δ 0.91 (6H, t, J = 7.5 Hz), 1.35−1.45 (2H, m), 1.57−1.95 (6H, m), 6.69−6.74 (2H, m), 7.19−7.23 (2H, m), 7.30 (1H, m), 7.41−7.56 (4H, m), 7.89 (1H, m), 7.98 (1H, m), 8.38 (1H, m), 8.70 (1H, m); ^{13}C NMR δ 14.27, 18.62, 42.32, 83.78, 121.51, 123.93, 123.97, 127.02, 127.79, 127.84, 129.13, 129.93, 132.87, 134.67, 136.98, 140.57, 142.46, 147.44, 153.36, 170.12, 173.43; HRMS [M + H$^+$] calcd for $C_{27}H_{28}N_3NiO_3$ 501.2158, found 501.1381.

Ni(II) Complex of 2-Aminopentanoic Acid Schiff Base with PABP (14e): $R_f = 0.63$; mp 252.1−252.8 °C; ^{1}H NMR δ 0.80 (3H, t, J = 7.2 Hz), 1.57−1.69 (2H, m), 2.02 (1H, m), 2.17 (1H, m), 4.02 (1H, dd, J = 8.4; 3.0 Hz), 6.75−6.81 (2H, m), 7.07 (1H, m), 7.32 (1H, m), 7.42−7.52 (5H, m), 7.91 (1H, m), 8.01 (1H, m), 8.23 (1H, d, J = 5.4 Hz), 8.92 (1H, d, J = 8.1 Hz); ^{13}C NMR δ 13.7, 18.4, 37.3, 70.9, 121.1, 123.2, 123.8, 126.5, 126.7, 126.8, 127.5, 128.5, 128.8, 129.5, 133.0, 133.6, 134.2, 140.2, 142.7, 146.6, 153.0, 169.6, 171.2, 179.1; HRMS [M + H$^+$] calcd for $C_{24}H_{22}N_3NiO_3$ 459.1361, found 459.0934.

Ni(II) Complex of α,α-Di-*n*-butylglycine Schiff Base with PABP (13f): $R_f = 0.67$; mp 221.7−222.5 °C; ^{1}H NMR δ 0.93 (6H, t, J = 7.4 Hz), 1.21−1.34 (4H, m), 1.39−1.49 (2H, m), 1.59−1.87 (6H, m), 6.65−6.74 (2H, m), 7.19−7.23 (2H, m), 7.31 (1H, m), δ 7.42−7.55 (4H, m), 7.90 (1H, m), 7.99 (1H, m), 8.39 (1H, m), 8.72 (1H, m); ^{13}C NMR δ 14.46, 23.10, 27.33, 40.20, 83.75, 121.49, 123.93, 123.96, 127.02, 127.79, 127.87, 129.12, 129.92, 132.87, 134.71, 136.96, 140.58, 142.51, 147.47, 153.36, 170.19, 173.41, 182.60; HRMS [M + H$^+$] calcd for $C_{29}H_{32}N_3NaNiO_3$ 529.2680, found 529.1837.

Ni(II) Complex of 2-Aminohexanoic Acid Schiff Base with PABP (14f): $R_f = 0.62$; mp 249.7−250.6 °C; ^{1}H NMR δ 0.82 (3H, t, J = 7.2 Hz), 1.11−1.32 (2H, m), 1.49−1.70 (2H, m), 1.96−2.09 (2H, m), 4.00 (1H, q, J = 3.7 Hz), 6.74−6.80 (2H, m), 7.06 (1H, m), 7.27−7.37 (2H, m), 7.41−7.54 (4H, m), 7.90 (1H, m), 8.00 (1H, m), 8.23 (1H, d, J = 5.4 Hz), 8.92 (1H, d, J = 8.4 Hz); ^{13}C NMR δ 14.16, 22.73, 27.41, 35.46, 71.53, 121.62, 123.65, 124.26, 127.01, 127.16, 127.32, 128.00, 128.96, 129.35, 130.00, 133.53, 134.10, 134.69, 140.70, 143.19, 147.14, 153.50, 170.13, 171.76, 179.66; HRMS [M + Na$^+$] calcd for $C_{25}H_{23}N_3NaNiO_3$ 495.1517, found 495.1092.

Ni(II) Complex of α,α-Dimethylglycine Schiff Base with PABP (13g): $R_f = 0.36$; mp 328.2−328.9 °C; ^{1}H NMR δ 1.25 (3H, s), 1.44 (3H, s), 6.72−6.74 (2H, m), 7.21−7.25 (2H, m), 7.31 (1H, m), 7.43−7.52 (4H, m), 7.91 (1H, m), 8.00 (1H, m), 8.38 (1H, m), 8.72 (1H, m); ^{13}C NMR δ 29.07, 75.21, 121.06, 123.38, 123.51, 126.58, 127.34, 128.35, 128.94, 129.15, 132.50, 134.29, 136.27, 140.15, 141.83, 146.75, 152.94, 169.53, 173.08, 182.63; HRMS [M + H$^+$] calcd for $C_{23}H_{20}N_3NiO_3$ 445.1095, found 445.0939.

Ni(II) Complex of 2-Aminopropionic Acid Schiff Base with PABP (14g): $R_f = 0.44$; mp 258.2−259.1 °C; ^{1}H NMR δ 1.58 (3H, d, J = 7.1 Hz), 4.03 (1H, q, J = 7.1 Hz), 6.74−6.78 (2H, m), 7.08 (1H, m), 7.27−7.36 (2H, m), 7.42−7.55 (4H, m), 7.90 (1H, m), 8.00 (1H, m), 8.23 (1H, d, J = 5.1 Hz), 8.92 (1H, d, J = 8.4 Hz); ^{13}C NMR δ 21.56, 67.18, 121.20, 123.31, 123.84, 126.42, 126.76, 126.83, 127.67, 128.54, 128.96, 129.58, 133.16, 133.46, 134.25, 140.32, 142.71, 146.64, 153.04, 169.70, 171.65, 180.36; HRMS [M + Na$^+$] calcd for $C_{22}H_{17}N_3NaNiO_3$ 454.0720, found 454.0523.

Ni(II) Complex of α,α-Di-*n*-pentylglycine Schiff Base with PABP (13h): $R_f = 0.81$; mp 221.8−223.4 °C; ^{1}H NMR δ 0.89 (6H, t, J = 7.1 Hz), 1.19−1.47 (10H, m), 1.58−1.88 (6H, m), 6.66−6.74 (2H, m), 7.19−7.22 (2H, m), 7.31 (1H, m), 7.42−7.53 (4H, m), 7.89 (1H, m), 7.99 (1H, m), 8.39 (1H, m), 8.72 (1H, m); ^{13}C NMR δ 14.67, 23.00, 24.99, 32.20, 40.43, 83.80, 121.51, 123.93, 123.96, 127.03, 127.81, 127.85, 129.14, 129.91,

132.86, 134.70, 136.98, 140.58, 142.50, 147.49, 153.36, 170.18, 173.40, 182.55; HRMS [M + H^+] calcd for $C_{32}H_{39}N_3NaNiO_3$ 571.2345, found 571.2650.

Ni(II) Complex of 2-Aminoheptanoic Acid Schiff Base with PABP (14h): R_f = 0.63; mp 246.1−248.3 °C; ^{1}H NMR δ 0.80 (3H, t, J = 6.9 Hz), 1.13−1.32 (4H, m), 1.53−1.66 (2H, m), 1.68−2.11 (2H, m), 3.99 (1H, m), 6.74−6.78 (2H, m), 7.06 (1H, m), 7.26−7.37 (2H, m), 7.42−7.52 (4H, m), 7.90 (1H, m), 8.00 (1H, m), 8.23 (1H, d, J = 5.4 Hz), 8.91 (1H, d, J = 8.7 Hz); ^{13}C NMR δ 14.31, 22.59, 25.02, 31.70, 35.70, 71.44, 121.54, 123.57, 124.18, 126.93, 127.08, 127.26, 127.92, 128.90, 129.26, 129.91, 133.44, 134.00, 134.60, 140.62, 143.10, 147.06, 153.42, 170.04, 171.65, 179.58; HRMS [M + Na^+] calcd for $C_{26}H_{25}N_3NaNiO_3$ 509.1783, found 509.0991.

Dialkylation of Ni(II) Complex 2 with Propargyl Bromide 12k under PTC. Synthesis of 14k and 13k. To a solution of 1.013 g (2.435 mmol) of complex **2** in 10 mL of CH_2Cl_2 (10 mL /1.013 g) at room temperature was added tetrapropylammonium iodide 0.188 g (0.600 mmol), 10 mL of 30% aqueous sodium hydroxide solution (1 mL /1 mL of CH_2Cl_2), and 1.250 g (10.508 mmol) of propargyl bromide (80%). The resultant mixture was rigorously stirred for 18 h at room temperature. To the resultant slurry were added additional amounts of water and CH_2Cl_2, and the aqueous phase was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and then evaporated in a vacuum to yield a crystalline compound. This compound was washed with water and hexane and then dried to yield the final product **13k**. The monoalkylated complex **14k** was the major product if the reaction was worked up after 20 min.

Ni(II) Complex of α,α-Dipropargylglycine Schiff Base with PABP (13k): R_f = 0.56; mp 255.2−258.2 °C; ^{1}H NMR δ 2.19, 2.86 (4H, ABX, J = 17.1, 2.7, 2.7 Hz), 2.43 (2H, t, J = 2.6 Hz), 6.74 (2H, d, J = 3.9 Hz), 7.34 (1H, m), 7.46 (1H, m), 7.50−7.56 (5H, m), 7.88−7.91 (1H, dm, J = 1.5 Hz), 7.99 (1H, m), 8.38 (1H, d, J = 5.1 Hz), 8.74 (1H, d, J = 8.4 Hz); ^{13}C NMR δ 30.1, 30.1, 73.8, 73.8, 77.1, 78.2, 78.6, 121.1, 123.5, 123.6, 126.7, 127.8, 127.8, 128.4, 128.6, 129.9, 130.7, 132.9, 134.5, 133.9, 140.2, 142.5, 147.2, 152.9, 167.7, 174.6, 179.4; HRMS [M + Na^+] calcd for $C_{27}H_{19}N_3NaNiO_3$ 515.1414, found 515.0762.

Ni(II) Complex of 2-Aminopent-4-ynoic Acid Schiff Base with PABP (14k): R_f = 0.37; mp 242.3−244.5 °C; ^{1}H NMR δ 2.28−2.55 (2H, m), 4.02 (1H, m), 6.74−6.79 (2H, m), 7.31 (1H, m), 7.43 (1H, m), 7.49−7.54 (5H, m), 7.88 (1H, m), 7.99 (1H, dm, J = 1.4 Hz), 8.20 (1H, d, J = 5.4 Hz), 8.92 (1H, d, J = 8.7 Hz); ^{13}C NMR δ 24.3, 68.9, 121.2, 123.4, 123.8, 126.5, 126.6, 126.8, 128.9, 129.1, 129.9, 133.4, 133.5, 134.4, 140.2, 143.3, 146.9, 153.0, 169.7, 172.5, 177.8; HRMS [M + Na^+] calcd for $C_{24}H_{17}N_3NaNiO_3$ 477.0934, found 477.0460.

Michael Addition Reactions of Ni(II) Complex 2 with Acrylonitrile (12l) and Ethyl Acrylate (12m). To a solution of complex **2** (1 equiv) in CH_2Cl_2 (10 mL/1 g) at room temperature were added tetrapropylammonium iodide (0.25 equiv), 30% aqueous sodium hydroxide (1 mL/1 mL CH_2Cl_2), and Michael acceptor **12l**,**m** (3.5 equiv). The resultant mixture was rigorously stirred for 15 min (monitored by TLC) at room temperature. To the resultant slurry were added additional amounts of water and CH_2Cl_2, and the aqueous phase was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and then evaporated in a vacuum to yield a crystalline compound. The compound was washed with water and hexane then dried to yield the final product **14l**,**m**.

Ni(II) Complex of 2-Amino-4-cyanobutyric Acid Schiff Base with PABP (14l): R_f = 0.33; mp 229.0−229.4 °C; ^{1}H NMR δ 2.37−2.60 (2H, m), 2.82−2.91 (2H, m), 4.01 (1H, m), 6.74−6.83 (2H, m), 7.10 (1H, m), 7.45 (1H, m), 7.51−7.58 (4H, m), 7.92 (1H, m), 8.02 (1H, m), 8.02 (1H, m), 8.19 (1H, d, J = 4.8 Hz), 8.20 (1H, d, J = 6.0), 8.92 (1H, d, J = 8.7 Hz); ^{13}C NMR δ 13.6, 30.9, 69.0, 77.1, 121.4, 123.4, 124.1, 126.1, 126.7, 126.9, 127.0, 127.3, 129.0, 129.4, 130.1, 133.1, 133.8, 134.5,-140.5, 143.0, 146.6, 152.9, 169.7, 173.1, 177.7, 206.6; HRMS [M + Na^+] calcd for $C_{24}H_{18}N_4NaNiO_3$ 492.1081, found 492.0830.

Ni(II) Complex of 2-Aminopentanedioic Acid 5-Ethyl Ester Schiff Base with PABP (14m): R_f = 0.36; mp 239.6−239.8 °C; ^{1}H NMR δ 1.16 (3H, t, J = 7.2 Hz), 1.88−1.99 (2H, m), 3.22−3.32 (2H, m), 2.32−2.57 (2H, m), 3.98−4.08 (3H, m), 6.74−6.81 (2H, m), 7.26 (1H, m), 7.34 (1H, m), 7.48 (1H, m), 7.52−7.54 (4H, m), 7.91 (1H, m), 8.01 (1H, m), 8.22 (1H, d, J = 4.5 Hz), 8.95 (1H, d, J = 8.4 Hz); ^{13}C NMR δ 14.1, 29.4, 29.9, 61.0, 70.2, 121.3, 123.2, 123.9, 126.4, 126.6, 126.8, 127.8, 128.7, 128.9, 129.7, 133.4, 133.6, 134.5, 140.4, 142.8, 146.7, 153.0, 169.7, 172.3, 172.7, 178.6; HRMS [M + Na^+] calcd for $C_{26}H_{23}N_3NaNiO_5$ 539.1612, found 539.0834.

Decomposition of Compounds 13a and 13d and Isolation of Free Amino Acids 15a,d. General Procedure.[19c,d, 2] A solution of complex **13a**,**d** (22.5 mmol) in MeOH (90 mL) was slowly added to a mixture of aqueous 3 N HCl and MeOH (180 mL, ratio 1/1) at 70 °C with stirring. The reaction mixture was evaporated in a vacuum to dryness after it was determined that the decomposition was complete by TLC ($CHCl_3$/acetone 5/1). Water (120 mL) was added, and the resultant mixture was treated with an excess of NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated in a vacuum to afford free PABP (5.92−6.33 g, 87−93%). The aqueous phase evaporated under vacuum, redissolved in the minimum amount of water, and loaded on a Dowex 50X2 100 ion-exchange column, which was washed with water until neutral. The column was then washed with 8% aqueous NH_4OH. This fraction (350 mL) was collected and evaporated under vacuum to afford the corresponding amino acids **15a** (3.18 g, 91%) and **15d** (2.74 g, 93%).

α,α-Diallylglycine (15a): mp 217.8 °C dec; ^{1}H NMR (CD_3OD) δ 2.46 (2H, dd, J = 7.2, 14.3 Hz), 6.67 (2H, dd, J = 7.2, 14.3 Hz), 5.20−5.28 (4H, m), 5.75−5.89 (2H, m); ^{13}C NMR (CD_3OD) δ 40.66, 63.51, 119.95, 131.27, 173.48; HRMS [M + H^+] calcd for $C_8H_{14}NO_2$ 156.1024, found 156.1021.

α,α-Diethylglycine (15d): mp 252.6 °C dec; ^{1}H NMR (CD_3OD) δ 0.98 (6H, t, J = 7.5 Hz), 1.76 (2H, dq, J = 14.7, 7.5 Hz), 1.91 (2H, dq, J = 14.7, 7.5 Hz); ^{13}C NMR (CD_3OD) δ 7.62, 29.42, 66.04, 174.64; HRMS [M + H^+] calcd for $C_6H_{14}NO_2$ 132.1024, found 132.0945.

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Supporting Information Available: Copies of NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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