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Large scale enantiomeric synthesis, purification, and characterization of ω-unsaturated amino acids via a Gly-Ni(II)-BPB-complex

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Abstract—The enantiomeric syntheses of ω-unsaturated amino acids and β-substituted ω-unsaturated amino acids were accomplished by using Gly-Ni-2[*N*-(*N*′-benzylprolyl)amino]benzophenone (BPB) as a chiral auxiliary. The synthesis provides excellent yields and high diastereoselectivities. The product crystallization followed by isomer epimerization strategy makes the reaction practical and useful for large-scale preparations. Dialkylation of the Ni(II)-complex, which was designed for mechanistic considerations, revealed that high diastereoselectivity is obtained due to the thermodynamic conformational stability of the Ni(II)-complex. The assignment of absolute configuration was accomplished by NMR, which is supported by corresponding X-ray structure and optical rotation data. Both enantiomerically pure amino acids can be synthesized in this alkylation–hydrolysis two-step strategy in multi gram scales.

1. Introduction

Proteinogenic amino acids have been extensively applied to the area of synthetic organic chemistry.[1] However, opportunities for the use of these naturally occurring amino acids for synthetic purposes are hampered by the limited number of functional groups on the side chains. In addition, replacing natural amino acids with nonproteinogenic counterparts often is applied to peptides and proteins in order to change their secondary structure and functionalities in order to enhance binding to specific receptors,[2] or to obtain more potent inhibition of target enzymes.[3] ω-Unsaturated amino acids are of value in terms of their biological importance and their utility as asymmetric synthetic building blocks.[4] The double bond is a masked functional group, and is stable to most acidic and basic reaction conditions. As a precursor, it can be easily transferred to ω-hydroxyl, ω-halogen, ω-epoxy, ω-amino, aldehyde, and carboxyl amino acids.[5] They also have been used in cyclization of peptides through ring closing metathesis.[6] They act as precursors of boron containing biomolecules,[7] which are interesting for application in boron neutron capture therapy.[8] The masked diol, obtained by osmylation of the double bond, is a useful equivalent of an α-amino acid aldehyde.[9]

In the course of our ongoing peptide and nonpeptidomimetic research, a practical large-scale synthesis of enantiomerically pure ω-unsaturated amino acids **1** and **2** (Fig. 1) has become required in several of our research projects. For example, both the enantiomerically pure forms of allylglycine were used as precursors in the synthesis of [3.3.0]-BTD[2,3] (bicyclic β-turn dipeptide) Leu-enkephalin analogues.[10] The two enantiomers of homoallylglycine have been used in the development of a novel strategy for [6,5]-bicyclic β-turn dipeptides.[11] Homoallylglycine and bishomoallylglycine, both in enantiomerically pure forms, currently are being used for the synthesis of [4.3.0]- and [5.3.0]-BTD[2,3]-Leu-enkephalin analogues. ω-Unsaturated

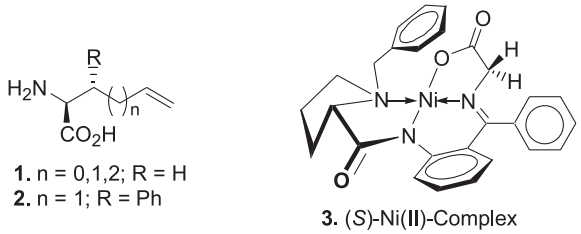

Figure 1. Structures of the ω-unsaturated amino acids and the (*S*)-Ni(II)-complex auxiliary.

Keywords: Ni(II)-complex chiral auxiliary; Alkylation; Diastereoselectivity; Epimerization; Amino acids.

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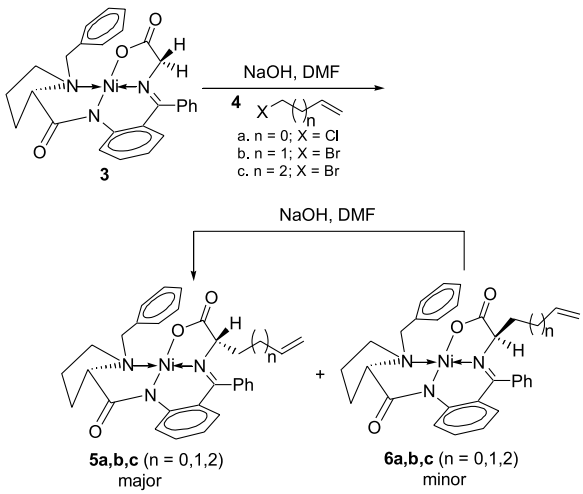
amino acids with β-substituents provide further constraints and functionality at β-positions.[12] β-Phenyl-δ, ϵ-unsaturated amino acid **2** was the first example we synthesized using a Ni(II)-complex, and it was used in the synthesis of functionalized thiazolizidinone [4.3.0]-bicyclic β-turn mimetics.[13] For all of these projects and other potential applications, enantiomerically pure ω-unsaturated amino acids are needed in multi-gram quantities.

Some ω-unsaturated amino acids have been isolated from mushrooms. For example, (*S*)-allylglycine was isolated from *Amanita*, while (*S*)-homoallylglycine was found in *Amanita gymnopus*.[14] *S*- and *R*-allylglycine are commercially available (Acros, Pittsburgh, PA, USA) and the enzymatic separation of *S*-allylglycine from its racemate is well described.[15] ω-Unsaturated amino acid analogue synthesis from Sharpless asymmetric epoxidation also has been reported.[16] However, it is more direct and less expensive to synthesize them by using a Ni(II)-complex in a two-step strategy, because the essential part of auxiliary, (*S*)-BPB {2-[*N*-(*N*′-benzylprolyl)amino]benzophenone}, can be reused in the synthesis of the Gly-Ni(II)-BPB-complex. This chiral auxiliary has been widely used in amino acid synthesis since it was developed by Belokon et al. in 1985.[17] Many different types of amino acids have been synthesized using different reactions, such as alkylation,[18] Michael addition,[19] and the aldol reactions.[20] Although these synthetic methodologies can introduce different side chain groups, the introduction of an ω-terminal double bond using a Ni(II)-complex was only reported by Collet et al. with low yields and limited preparative applications.[7,21] Application of Ni(II)-complexes for the synthesis of unsaturated amino acids as synthetic building blocks for constrained amino acids, and dipeptides is, however, limited by undeveloped methods especially for large-scale synthesis. We report herein a full account of the preparation of these amino acids on multi-gram scales. The mechanistic considerations involved in the alkylation, characterization of the stereochemical outcome, and the diastereoselectivities of the Ni(II)-complex products also were investigated and are discussed.

2. Results and discussion

2.1. Monoalkylation of Ni(II)-complex

The Ni(II)-complex was synthesized in three steps on a 50–100 g scale based on a reported method.[22] The alkylation of 4-bromo-1-butene **4b** on Ni(II)-complex has been reported in low yield,[7,21] which may be attributed to the limited solubility of Ni(II)-complex (<40 mg/mL) and sodium hydroxide in acetonitrile. The alkylation reaction was optimized by first modifying the solvent, and then temperature conditions were investigated. We found that although the Ni(II)-complex was soluble in methanol, the alkylation was slow and TLC showed only a 25% conversion in 16 h. The reaction can be accelerated by using excess NaOMe as base instead of sodium hydroxide. However, the reaction was not completed in 24 h and the Ni(II)-complex suffered significant decomposition during the prolonged reaction time under argon atmosphere. THF was not an efficient solvent either, but DMF gave much better results and also provided a homogenous reaction (Scheme 1). The enolate generation, which was indicated by formation of a green color occurred within 2 min, and the reaction was completed in 3 min at room temperature. No difference was observed when ground KOH was used instead of ground NaOH.



Scheme 1. The alkylation of the Ni(II)-complex.

The alkylation in DMF was optimized using different temperatures (Table 1). It was found that the reaction was prolonged at lower temperatures, and gave poorer diastereoselectivities, while elevated temperatures gave inconclusive results, and the Ni(II)-complex was partially decomposed. The best diastereoselectivity was obtained at ambient temperature with a reaction time of less than 5 min. Based on these reaction results and considering an exothermic reaction in a large scale synthesis, we scaled up the alkylation at ambient temperature in a water bath in 5 min, and the reaction was very efficient (Table 1).

5-Bromo-1-pentene **4c** was used in the Ni(II)-complex alkylation under the same reaction conditions with high diastereoselectivity (Table 1). When allyl bromide was used as an electrophile, an unidentified byproduct was generated, and lowing the reaction temperature to 0 °C did not result in any improvement. However, when the allylic chloride **4a** was used at room temperature, the reaction was very clean and gave a diastereoselectivity of 87:13. In order to avoid dialkylation, all the above electrophilic halides **4a**~**c** were

Table 1. The alkylation conditions and results in DMF

	Electrophile	Reaction temp. (°C)	Reaction time (min)	Isomer ratio[a]	Yield (%)[b]
1	**4b**	−30	35	92:8	95
2	**4b**	0	10	91:9	95
3	**4b**	20	5	95:5[c]	98
4	**4b**	20	10	95:5	96
5	**4b**	20	20	95:5	96
6	**4b**	50	5	Inconclusive	<80
7	**4a**	20	5	87:13[c]	96
8	**4c**	20	5	93:7[c]	98

[a] The diastereomeric ratio (2*S*/2*R*) was determined by ^{1}H NMR.
[b] Combined yield of two diastereomers.
[c] The diastereomeric ratios were obtained in the reactions on a 20 g scale. All the other results were obtained in <1 g scale.

used in slightly less than 1 equiv. For the 20 g scale reactions, no secondary alkylation was observed under these reaction conditions, and no elimination of halogen was detected.

The crude product mixture was dissolved in benzene and washed with brine four times to remove DMF. We also tried using toluene but the Ni(II)-alkylation product has limited solubility in it. While DCM and chloroform are good solvents, washing with brine was not efficient with these solvents. Fractional recrystallization was used to isolate the products, because the minor products often overlap on TLC (hexane/acetone=1:1), and thus it was not always easy to purify these diastereomers with flash liquid chromatograph. The enantiomeric purity of the major isomer **5a** and **5b** was improved by fractional recrystallization from a mixture of DCM and ether. A fast flash chromatograph was usually employed for the mother liquor after the first crystallization to separate the remaining diastereomeric mixture from impurities which came from the starting material of the Ni(II)-complex and from decomposition in the reaction. The reddish eluent was used for further recrystallization, and finally the minor enriched mixture was subjected to the same alkylation reaction conditions for 5 min. Epimerization transferred the minor product to the major one with the same diastereomeric ratio (Scheme 1). In this way, over 90–95% yield of alkylation products can be collected with >98% de. The *S*(2*R*) allyl alkylation product **6a** in mother liquor was further purified on an analytical silica gel HPLC column (IBM Silica 2872053, hexane/2-propanol=98:2, UV detector at 232 nm) for characterization. Attempts to characterize the minor product *S*(2*R*) of homoallyl alkylation **6b** using the same HPLC column failed due to poor resolution. In the case of 5-bromo-1-pentenyl bromide alkylation, both the major **5c** and minor **6c** products crystallize out in DCM/ether solution at the same time but as different crystals. The mother liquor, however, became a pure solution of major product **5c**. The crystal mixture was subjected to three fractional crystallizations until the mixture became enriched with the *S*(2*R*)-product.

The configuration of the major product generated from the *si*-face of the glycine enolate was assigned as *S*(2*S*).[18,19] The diastereomeric ratio was determined from the relative intensity of the peaks in the region of 8.0–8.5 ppm (Fig. 2) in the ^{1}H NMR of the crude product. The two most downfield proton peaks are doublets of the *ortho* protons H_a and H_b in a ratio of 1:2 in the Ni(II)-complex and its products, as indicated by the following results observed in DQF-COSY and 1D NOE experiments. The spin systems in aromatic ring B and C, identified in the DQF-COSY spectrum, were differentiated by the NOE correlation between the H_b protons and both α and δ protons in proline. The spin system in ring A is unique. The resonance from the H_a and H_d protons were unambiguously assigned using the NOE's between H_d and the protons in ring C, and between H_a and the protons in ring B. All the *S*(2*S*) products **5** have their H_a and H_b protons at about 8.0–8.2 ppm (Fig. 2, item ii). However, in the *S*(2*R*) products **6** proton spectra, the H_a proton resonance shifts downfield (~8.5 ppm), while an upfield shift occurs for the H_b (<8.0 ppm) (Fig. 2, item iii).

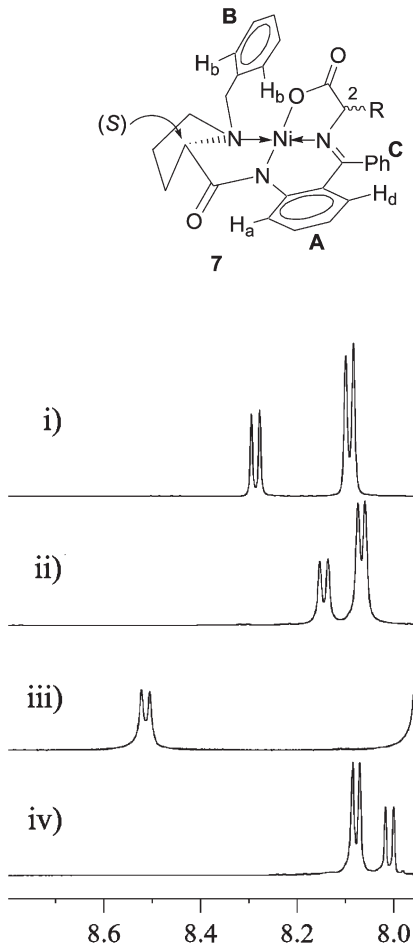
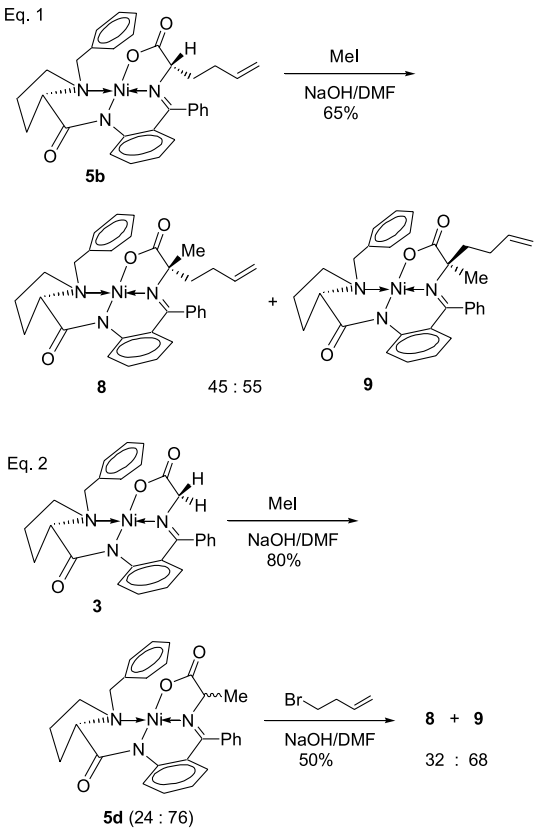


Figure 2. The proton NMR spectra of the downfield protons H_a and H_b of unalkylated and various alkylated complexes. (i) Ni(II)-complex **3**; (ii) *S*(2*S*)-monoalkylated product; (iii) *S*(2*R*)-monoalkylated product; (iv) dialkylated product.

2.2. Dialkylation and face selectivity

Previous studies have attempted to understand the origin of the high diastereoselectivity in alkylation reactions of the Gly-Ni(II)-BPB-complex.[18,19] Although the kinetic controlled reaction has been studied for dialkylation,[23] the difficulty in understanding the absolute configuration of the α, α-dimethyl product makes the results unclear. Since the exact model to mimic the kinetic vs thermodynamic selectivity in monoalkylation is not available due to fast epimerization, we designed the following dialkylation reactions (Scheme 2) by using different aliphatic electrophiles so that the kinetic ratio for reaction in dialkylation could be trapped. The reactions were accomplished in DMF and 10 equiv. of NaOH at ambient temperature. The dialkylation reaction times and their diastereoselectivities are listed in Table 2. For comparison, the monoalkylation of 4-bromo-1-butene **4b** and MeI also is listed.

In our first attempt at dialkylation, the purified homoallyl Gly-Ni-(*S*)-BPB **5b** was used in a reaction with MeI (Scheme 2). The reaction cannot be monitored because the product **9** shared the same R_f value as the starting material **5b** on TLC (acetone/hexane=1:1, R_f=0.45). The reaction was optimized for completion in 3 h by adding another



Scheme 2. Dialkylation of the Ni(II)-complex and their diastereoselectivity.

Table 2. Alkylation and their diastereoselectivities

Starting material	Electrophile	Reaction time	Diastereomeric ratio[a]		Yield
Ni(II)-**3**	**4b**	5 min	2*R*/2*S*	5:95	98
5b	MeI	3 h	**8/9**	45:55	65
Ni(II)-**3**	MeI	5 min	2*R*/2*S*	24:76	80
5d	**4b**	1.5 h	**8/9**	32:68	50

[a] The diastereomeric ratio was determined by ^{1}H NMR.

3 equiv. of MeI after the 1.5 h reaction. However, the diastereoselectivity was only 45:55; almost no *si*-face preference. We also synthesized the methyl Gly-Ni-(*S*)-BPB **5d** from the Ni(II)-complex as starting material (Scheme 2). This gave a 24:76 diastereomeric mixture. This mixture also can be obtained by using racemic alanine in generation of the Ni(II)-complex. However, an attempt to isolate the pure diastereomeric products by fractional crystallization failed. The mixture then was used for alkylation with 4-bromo-1-butene, and the reaction was completed in about 1.5 h. Although this reaction was faster than the first one, it was not as clean. The diastereomeric ratio was 32:68. Both of these kinetic control selectivities are much lower than the thermodynamic control monoalkylation results we observed in Table 1.

From the above results, we conclude that the kinetic *si*-face selectivity for monoalkylation is very limited. For the small electrophile, the *si*-face selectivity is not that obviously favored over the *re*-face reaction. We suggest that the high diastereoselectivity in alkylation actually may be generated by epimerization. The epimerization reaction proved to be very fast in transferring the minor enriched mixture to the major product. It explains why the room temperature reaction actually can provide better diastereoselectivity. We also found that the diastereoselectivity in asymmetric dialkylation increased if a large electrophile (1-bromo-4-butene compare to methyl iodide) was used in the second alkylation.

It should be pointed out that the newly generated chiral configuration in dialkylation products cannot be determined based on the most downfield proton peaks in NMR spectra. Both products gave H_a and H_b close to 8.2 ppm (see Fig. 2, item iv), Interestingly, we were able to determine the weak NOE interactions between the protons on the side chains and *N*^{P}-benzyl ring in both **8** and **9**. These unexpected results indicated that the *N*^{P}-benzyl ring stays on the Ni(II)-complex plane. This assumption was confirmed by the X-ray structure of **8** (Fig. 3), which is consistent with NMR NOE results. The α-configurations of **8** and **9** were assigned as in Scheme 2, relating them to the known absolute configuration of proline.

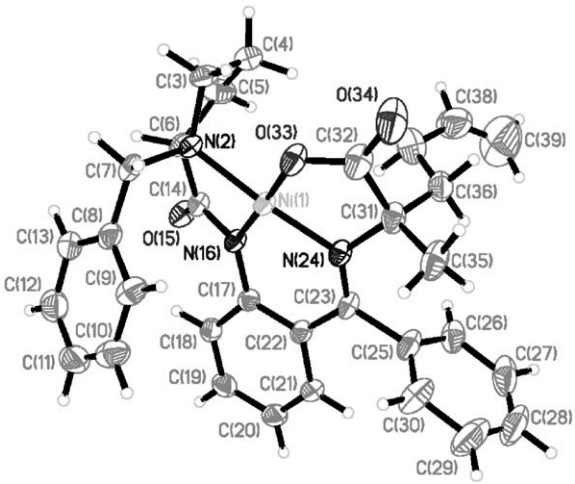


Figure 3. X-ray structure of the dialkylation product **8**.

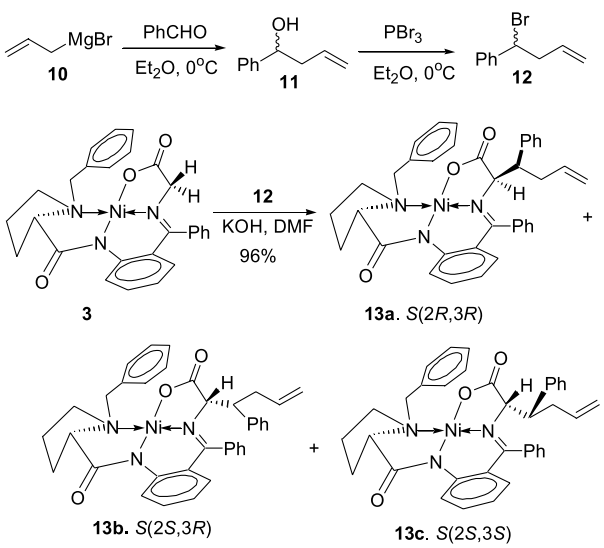
It is interesting to note that the chemical shifts of the most downfield protons H_a and H_b of the dialkylation products are similar by comparison to the starting material **3** and other *S*(2*S*) monoalkylation products **4a**–**c**. By examining all of the crystal structures,[19d,24] we found that the NMR results are consistent with the X-ray structure conformation. For the *S*(2*R*) products, the *N*^{P}-benzyl ring moves outside of Ni(II)-complex plane which results in no NOE interactions between the proton H_a and H_b in the Ni(II)-complex products. As a result, both the chemical shifts of H_a (8.5 ppm) and H_b (<8.0 ppm) became 'normal'. When the *N*^{P}-benzyl ring covers the top of Ni(II)-complex plane, the H_a was shielded and shifts upfield, while H_b was deshielded and shifts downfield. It is not completely clear why, in dialkylation products, the *N*^{P}-benzyl ring can stay on top of the Ni(II)-complex plane and both products **8** and **9** show H_a and H_b proton close to 8.1 ppm. However, it is noteworthy that all *S*(2*R*) products gave negative data for their optical rotations while the others are always positive. Presumably

these results also are related and consistent with different conformations of the Ni(II)-complex in these isomers.

From the above analysis, we assume that the face selectivity in Ni(II)-complex is not caused simply by the steric hindrance of the *N*[P]-benzyl ring[25] because it can move outside of the Ni(II)-complex plane. There is no evidence for the α-H existing in a pseudo-axial or pseudo-equatorial position[19a], because in the transition state, the Gly-Ni(II)-5-membered ring can be very close to planar. However, the difference in the thermodynamic stability of the two alkylated products, due to their different conformations, gives high diastereoselectivity. Efforts to increase the selectivity by increasing the steric hindrance of the *N*[P]-substituted benzyl ring[25] is not necessary in monoalkylation, because the minor product can be converted to the major one by epimerization. Asymmetric synthesis of α, α-dialkylated amino acids[26] using different nucleophiles also is not a practical method, due to the low diastereoselectivity and low isolated yield.

2.3. Alkylation with racemic secondary bromide

When a secondary bromide is used in the alkylation reaction, four possible isomers of the β-substituted alkylation products can be generated.[18b] The secondary bromide 1-bromo-3-butenyl-benzene **12** was synthesized in two steps from commercially available starting materials in moderate yield (Scheme 3).[27] Both the alcohol and bromide were purified by liquid chromatograph. Alkylation of the secondary bromide **12**, generated a mixture of three diastereomers (Scheme 3). This reaction was examined using different amounts of bromide at ambient temperature and the results are summarized in Table 3. The results showed that the diastereomeric ratio increased as the amount of bromide increased to 2.8 equiv. Although the diastereoselectivity was increased as the temperature decreased,[13] the selectivity dropped when the reaction was scaled up due to the exothermic nature of the reaction. In practice, 3.0 equiv. of racemic bromide was used so that the reaction gives high diastereoselectivity.



Scheme 3. The synthesis of a secondary bromide and its alkylation.

Table 3. The secondary bromide in alkylation

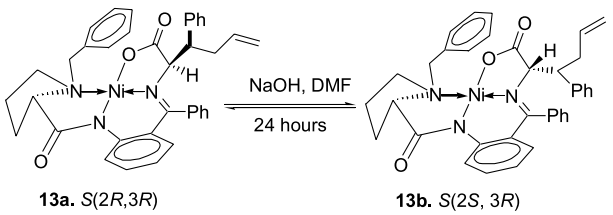
Entry	**12** (equiv.)	S.M.	**13a**[a]	**13b**[a]	**13c**[a]
1	1	7	21	10	62
2	2	0	15	6	76
3	2.5	0	15	4	81
4	2.8	0	10	4	86
5	3	0	11	3	86
6	4	0	9	6	85

[a] The diastereomeric ratios were determined by ^{1}H NMR.

High diastereoselectivity of *S*(2*S*,3*S*)/*S*(2*R*,3*R*) is generated from *si*-face selectivity. Again, it is lower than the results in Table 1, even though the electrophile is much bulkier due to the β-substitution. The major product *S*(2*S*,3*S*) is a kinetic product, while the *S*(2*S*,3*R*) minor product may have been produced from epimerization of the *S*(2*R*,3*R*) product. The high selectivity for *S*(2*S*,3*S*)/*S*(2*S*,3*R*) at position 3 is difficult to understand. A model in previous work[18a] suggested that one of the electrophilic enantiomers is matched in the reaction transition state. This explains why high diastereoselectivity was obtained when using 3 equiv. of bromide. As a matter of fact, we recovered the remaining bromide from the column, presumably an (*R*)-enriched form if the reaction is a typical S_N2 reaction. This enriched compound has an optical rotation of $[\alpha]_D^{24}=+8.9°$ (c=2.4, $CHCl_3$). However, when we used this enantiomerically enriched bromide (2 or 3 equiv.) in an alkylation with the (*R*)-Ni(II)-complex, presumably a matched case, the reaction did not provide any obvious diastereomeric improvement. It should be pointed out that although about 1.5 equiv. of bromide can be recovered and reused in the alkylation, its optical activity drops (racemized) dramatically during storage.

A fast flash column chromatograph was used to recover the bromide and to purify the product mixture before fractional crystallization. In the process, a 1:1 mixture of *S*(2*S*,3*S*) and *S*(2*R*,3*R*) crystals and an *S*(2*S*,3*S*) enriched mother liquor was obtained. A crystal carefully prepared for single X-ray crystallography, was found to be a diastereomeric co-crystal of *S*(2*S*, 3*S*) and *S*(2*R*, 3*R*).[24] Interaction between the racemic side chain groups could be the major packing force in initial crystalline formation, which can explain why a diastereomeric co-crystal forms. This 1:1 co-crystal mixture can be further isolated by flash liquid chromatograph. The *S*(2*S*,3*R*) **13b** minor product (~3%), which has a similar R_f value as the *S*(2*S*,3*S*) product, always coexisted in the mother liquor [R_f=0.62 for *S*(2*S*,3*S*) and 0.59 for *S*(2*R*,3*R*) in a 1:1 mixture of hexane and acetone]. The purity of the major product in the mother liquor was further improved by crystallization.

The unique NMR spectra of these monoalkylation products can be used to assign their configurations at position 2. Both the major *S*(2*S*,3*S*) and minor *S*(2*S*,3*R*) products have the typical H_a and H_b signal near 8.2 ppm (Fig. 2). The minor product *S*(2*R*,3*R*) has its H_a proton at 8.6 ppm, while the H_b is even further upfield, overlapping with the other aromatic protons. The 3*S* configuration in the major product *S*(2*S*,3*S*) was further confirmed by NOE studies of the [6,5]-bicyclic β-turn dipeptide[13] and by the X-ray structure of the co-crystal.[24] The minor product *S*(2*R*,3*R*) was crystallized



Scheme 4. Epimerization of the *S*(2*R*,3*R*) to the *S*(2*S*,3*R*) product.

and its single X-ray structure was obtained.[24] It was found that the crystalline form had two conformers that showed the *N*[P]-benzyl ring was outside of the Ni(II)-complex plane, which is consistent with the NMR result. The stereoisomer relationship of the *S*(2*R*,3*R*) and *S*(2*S*,3*R*) compounds can be confirmed by epimerization (Scheme 4). The assigned *S*(2*R*,3*R*) **13a** minor product was subjected to the same reaction conditions of alkylation, but at ambient temperature and at different reaction times, with the results shown in Table 4. The reaction gave a mixture of *S*(2*R*,3*R*):*S*(2*S*,3*R*)=16:84 at equilibrium after 20 h reaction. However, decomposition occurred frequently with more than half of the material destroyed in about 2 h, and over 70% of the starting material was decomposed in the 20 h reaction. The major product *S*(2*S*,3*R*) was isolated from the *S*(2*R*,3*R*) isomer by liquid chromatograph. This epimerization provides a unique way to obtain this pure minor product for characterization.

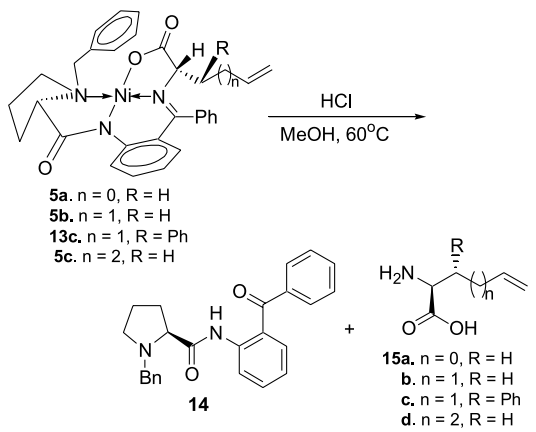
Table 4. The epimerization of Ni(II)-alkylation product

Entry	Reaction time (min)	Starting material[a]	Product[a] *S*(2*S*, 3*R*)
1	20	82	18
2	40	43	57
3	120	23	77
4	360	19	81
5	20 h	16	84

[a] The percentages were determined by ^{1}H NMR.

2.4. Hydrolysis of the Ni(II)-complex

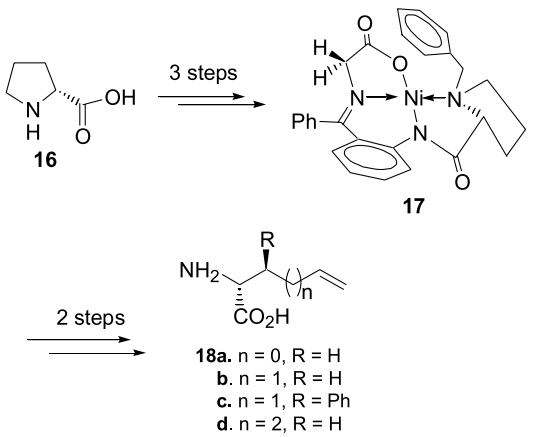
Amino acids **15a**–**d** were generated by decomposition of the Ni(II)-complex products with 3 N HCl in methanol (1:1) (Scheme 5). A mixture of methanol and DCM (approx. 2:1) was used to increase the solubility of the Ni(II)-alkylated product. Hydrolysis of β-phenyl-homoallylglycine **13c** was very slow and the disappearance of the reddish color



Scheme 5. Hydrolysis of the alkylated Ni(II)-complex.

indicated the completeness of hydrolysis. After evaporation, the above products mixture was diluted in aqueous solution, and (*S*)-BPB **14** was extracted with $CHCl_3$, recovering 96%. This byproduct can be used in the regeneration of Ni(II)-complex **3** without further purification. The mixture of amino acid and Ni^{2+} salt in aqueous phase was then concentrated and loaded on an H^+ form ion exchange resin column. It is very important to wash the column with deionized water to pH=7 before washing with the concentrated aqueous ammonia and water (4:1) mixture. For **15c** and **d**, a mixture of ammonia, water and ethanol (4:1:2) is needed for fast collection of the amino acid. The Ni^{2+} salt remained on the column which was regenerated with 1 N HCl solution. The amino acids were collected after evaporation of the ammonia aqueous solution and the residue was redissolved in small amounts of water and dried by lyophilization. All the amino acids can be collected in this way in over 95% yield.

(*R*)-Amino acids are important in peptidomimetics at position 2 of Leu-enkephalin analogues[28] and at position 7 in α-MSH analogues.[29] Thus *R*-allylglycine, *R*-homoallylglycine, and *R*-bishomoallylglycine derivatives have been synthesized in 3 g scales from the (*R*)-Ni(II)-complex, which was synthesized from (*R*)-proline in comparable yields (Scheme 6). (*R*)-2-Amino-hept-6-enyl carboxylic acid was synthesized on a 1 g scale by using bromide **12** as an electrophile.



Scheme 6. Synthesis of the (*R*)-Ni(II)-complex and the *R*-amino acids.

During purification of (*R*)-4-pentenyl-glycine-Ni(II)-BPB-complex, a purple minor product, *R*(2*S*), crystallized out before the red major product, *R*(2*R*). Both the *R*(2*R*) and *R*(2*S*) products were characterized using samples collected by hand picking individual crystals. It is interesting to note that visually the *R*(2*S*) minor product is a notably darker color, and apparently a different crystal form compared with its *S*(2*R*) enantiomer, which was synthesized from the (*S*)-Ni(II)-complex. However, in attempts to obtain better purity crystals in small scales for X-ray analysis, we found that the *R*(2*S*) and *S*(2*R*) compounds grew as identical red-orange plate-like crystals. Because of the visual differences, we were curious to see if a racemic crystal could be grown. When equal quantities of *R*(2*S*) and *S*(2*R*) were mixed in DCM and ether, red-orange plates were again obtained. X-ray diffraction determined that these crystals are identical to the pure individual enantiomers and thus indicates that

spontaneous self-resolution has occurred. The X-ray diffraction results of these molecules will be reported elsewhere.

3. Conclusions

The Ni(II)-complex derived from a glycine Schiff base with 2-[*N*-(*N*′-benzylprolyl)amino]benzophenone was found to be an ideal equivalent of nucleophilic glycine in reactions with various alkyl halides affording an efficient, generalized and practically useful method for the large scale preparation of enantiomerically pure ω-unsaturated amino acids. High diastereoselectivities and high yields were achieved by homogenous reaction and epimerization. The fractional crystallization employed in this method has been a reliable way to prepare diastereomerically pure Ni(II)-complex products on about a 20 g scale, which after hydrolysis affords multi-gram amounts of enantiomerically pure amino acids. This synthetic strategy and the crystallization purification methods are not limited to the synthesis of ω-unsaturated amino acids but to all the possible electrophiles that can be used in Ni(II)-complex alkylation. It should be indicated that the above simple but efficient method could not be used for the synthesis of vinylglycine analogues and β-substituted allylglycine analogues. A novel methodology to synthesize these ω-unsaturated amino acids by using the Ni(II)-complex as a chiral auxiliary are presently under investigation.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 MHz NMR spectrometer equipped with a Nalorac triple-resonance 3-axis gradient 5-mm probe. The chemical shifts were reported in δ, parts per million (ppm), relative to TMS (δ=0.00 ppm) as an internal standard. For amino acids in D_2O, ^{1}H chemical shifts were referenced to the HOD peak at 4.76 ppm, and ^{13}C chemical shifts were indirectly referenced to $CDCl_3$ at 7.26 ppm. In DMSO, the spectra were referenced to solvent peaks at 2.49 ppm for ^{1}H and 39.5 ppm for ^{13}C. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. The DQF-COSY[30a,b] and 1D transient selective NOE[30c,d] (350 ms mixing time) spectra were acquired. Mass spectrometric analyses were conducted by the Mass Spectrometry Facility at the Department of Chemistry of the University of Arizona on a Jeol HX-110A. Optical rotations were measured on a JASCO P1010 polarimeter. All the reagents and solvents, unless otherwise stated, are commercially available and were used as received. Flash column chromatograph was performed with 230–400 mesh size silica gel which was purchased from Aldrich Chemical Co. Thin-layer chromatograph (TLC) was performed with Merck silica gel 60 F_{254}. Melting points (Mp) are uncorrected and were obtained in open capillaries. The compounds were characterized by Mp, $[\alpha]_D$, ^{1}H, ^{13}C NMR and high resolution mass spectrometry (HRMS). All new compounds were determined to be >95% pure by ^{1}H NMR spectroscopy. Unless otherwise stated, all reactions were run under an atmosphere of argon.

4.1.1. 1-Bromo-3-butenyl-benzene (12). In a 500-mL flame-dried flask, 1 M allyl magnesium bromide in diethyl ether (100 mL, 100 mmol) was diluted with 140 mL of anhydrous ether. The solution was cooled down to 0 °C before benzaldehyde (10.1 mL, 100 mmol) was added slowly. It was kept at 0 °C for 1 h before being quenched by slowly adding 60 mL of 10% H_2SO_4. The organic phase was then separated and washed with $NaHCO_3$ and brine, and dried over anhydrous $MgSO_4$. The solution was concentrated in vacuo and the crude material was purified by flash liquid chromatograph. A colorless liquid product (**11**) was obtained (14.1 g, 95% yield).

The above alcohol **11** (14.1 g, 95 mmol) was dissolved in 250 mL anhydrous ether in a 500-mL flame-dried flask. The solution was cooled down to 0 °C and then PBr_3 (4.75 mL, 150 mmol) was added. The reaction was kept at 0 °C until completed in 45 min. It was quenched by saturated NH_4Cl aqueous solution (150 mL). The organic phase was then separated and washed with $NaHCO_3$ and brine, and dried over $MgSO_4$. The product solution was then concentrated in vacuo, and the residue was purified on a silica gel column using hexane. A slight yellowish liquid (12.8 g, 65% yield) was obtained. R_f=0.33 (hexane); ^{1}H (500 MHz, $CDCl_3$), δ 2.95–3.05 (2H, m), 4.96 (1H, t, *J*=7.5 Hz), 5.09–5.15 (2H, m), 5.70–5.77 (1H, m), 7.26–7.41 (5H, m); ^{13}C (125 MHz, $CDCl_3$), δ 44.2, 54.0, 118.1, 127.3, 128.4, 128.7, 134.7, 141.6; HRMS (FAB) calcd for $(C_{10}H_{11})^+$ 131.0861, found 131.0857.

4.2. General procedure for alkylation of Ni(II)-complex

Ni(II)-complex **3** (1 equiv.) and ground NaOH (10 equiv.) were added to a flask which was purged two times with argon. Anhydrous DMF (4 mL/mmol) was added by syringe and the mixture was allowed to react for 5 min at room temperature before bromide **4a**, **4b**, **4c** (0.98 equiv. each) or **12** (3.0 equiv.) was added in one portion, respectively. The reaction was then kept at room temperature for another 5 min (for bromide **12**, 1-bromo-but-3-enyl-benzene, 3 equiv., −30 °C, 45 min reaction). The solution was decanted into an aqueous solution (40 mL/mmol) containing 5% of HOAc. The suspension was dissolved in benzene (20 mL/mmol) and the emulsion was diminished by filtration through celite. The benzene solution was washed with brine (4×40 mL/mmol) and dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was first purified by fractional recrystallization in DCM/ether solution. The mother liquor was purified by flash liquid chromatograph before they were further purified by fractional recrystallization. The alkylation with electrophiles **4a**, **4b**, **4c** were performed in 20 g scales, while the alkylation with electrophile **12** was performed in 10 g scale.

4.2.1. (*S*)-Allylglycine-Ni-(*S*)-BPB (5a). Yield 83.5%, Mp: 203–205 °C; $[\alpha]_D^{24}$=+2440° (*c* 0.012, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 2.07–2.16 (2H, m), 2.41–2.57 (3H, m), 2.82 (1H, bs), 3.48 (1H, dd, *J*=6.0, 10.5 Hz), 3.49–3.64 (3H, m), 4.05 (1H, dd, *J*=4.0, 6.0 Hz), 4.46 (1H, d, *J*=12.5 Hz), 5.21 (1H, d, *J*=17.0 Hz), 5.42 (1H, d, *J*=10.0 Hz),

6.44–6.49 (1H, m), 6.65–6.70 (2H, m), 6.98 (1H, d, J=7.0 Hz), 7.17 (1H, t, J=7.0 Hz), 7.22 (1H, t, J=7.0 Hz), 7.29 (1H, bs), 7.37 (2H, t, J=7.5 Hz), 7.49–7.55 (3H, m), 8.07 (2H, d, J=7.0 Hz), 8.20 (1H, d, J=8.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.3, 30.7, 38.4, 56.8, 63.1, 70.3 (two carbons), 119.7, 120.6, 123.6, 126.4, 127.0, 127.7, 128.79, 128.83, 128.9, 129.7, 131.5, 132.1, 133.1, 133.2, 133.9, 142.4, 170.8, 178.8, 180.3; HRMS (FAB) MH^+ calcd for $C_{30}H_{30}N_3NiO_3$ 538.1641, found 538.1638.

4.2.2. (*R*)-Allylglycine-Ni-(*R*)-BPB. Yield 85%, ^{1}H and ^{13}C ($CDCl_3$) spectra are identical to (*S*)-allylglycine-Ni-(*S*)-BPB (**5a**).

4.2.3. (*R*)-Allylglycine-Ni-(*S*)-BPB (6a). Yield 12.5%, $[\alpha]_D^{24}=-1190°$ (*c* 0.049, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 1.87 (1H, bs), 2.06–2.10 (1H, m), 2.21–2.24 (1H, m), 2.50–2.64 (3H, m), 3.63 (1H, dd, J=4.0, 10.0 Hz), 3.73 (1H, d, J=13.0 Hz), 3.93 (1H, dd, J=3.5, 7.5 Hz), 4.10–4.14 (1H, m), 4.63 (1H, d, J=13.0 Hz), 5.03 (1H, d, J=17.0 Hz), 5.23 (1H, d, J=9.5 Hz), 6.04–6.10 (1H, m), 6.72 (1H, t, J=7.5 Hz), 6.79 (1H, d, J=7.5 Hz), 7.06 (1H, d, J=4.0 Hz), 7.20 (1H, bs), 7.28 (1H, m), 7.44–7.51 (6H, m), 7.93 (2H, d, J=7.0 Hz), 8.5 (1H, d, J=8.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.4, 30.7, 39.3, 58.0, 61.6, 68.9, 70.5, 119.0, 120.7, 123.7, 125.8, 126.9, 128.1, 128.6, 129.0, 129.1, 129.3, 129.7, 131.7, 132.3, 132.5, 133.1, 133.7, 134.2, 142.9, 171.4, 179.1, 182.3; HRMS (FAB) MH^+ calcd for $C_{30}H_{30}N_3NiO_3$ 538.1641, found 538.1644.

4.2.4. (*S*)-But-3-enyl-glycine-Ni-(*S*)-BPB (5b). Yield 93%, Mp: 207–209 °C (lit.,[21] 210 °C); $[\alpha]_D^{24}=+4471°$ (*c* 0.014, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 1.73 (1H, bs), 2.07–2.12 (1H, m), 2.17–2.21 (1H, m), 2.28–2.31 (1H, m), 2.53–2.58 (1H, m), 2.78 (1H, bs), 3.48–3.57 (2H, m), 3.61 (2H, d, J=12.5 Hz), 3.93 (1H, d, J=6.0 Hz), 4.47 (1H, d, J=12.5 Hz), 4.89 (1H, d, J=10.5 Hz), 4.99 (1H, d, J=17.0 Hz), 5.54–5.59 (1H, m), 6.65–6.71 (2H, m), 6.95 (1H, d, J=7.5 Hz), 7.16 (1H, t, J=7.0 Hz), 7.22 (1H, t, J=7.0 Hz), 7.29 (1H, bs), 7.38 (2H, t, J=7.5 Hz), 7.48–7.49 (1H, m), 7.51–7.54 (2H, m), 8.08 (2H, d, J=7.5 Hz), 8.15 (1H, d, J=8.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.7, 29.4, 30.7, 35.0, 57.0, 63.1, 69.9, 70.2, 115.7, 120.7, 123.7, 126.5, 127.3, 127.5, 128.8, 128.89, 128.91, 128.93, 129.7, 131.5, 132.1, 133.2, 136.6, 142.2, 170.4, 179.1, 180.4; HRMS (FAB) MH^+ calcd for $C_{31}H_{32}N_3NiO_3$ 552.1797, found 552.1807.

4.2.5. (*R*)-But-3-enyl-glycine-Ni-(*R*)-BPB. Yield 91%, ^{1}H and ^{13}C ($CDCl_3$) spectra are identical to (*S*)-allylglycine-Ni-(*S*)-BPB (**5b**).

4.2.6. (*S*)-Pent-4-enyl-glycine-Ni-(*S*)-BPB (5c). Yield 86%, Mp: 191–192 °C (lit.,[21] 192 °C); $[\alpha]_D^{24}=+2560°$ (*c* 0.033, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 1.65–1.67 (2H, m), 1.91–2.07 (4H, m), 2.14–2.23 (2H, m), 2.50–2.55 (1H, m), 2.76 (1H, bs), 3.47 (1H, dd, J=6.0, 10.0 Hz), 3.52–3.60 (3H, m), 3.91 (1H, d, J=5.0 Hz), 4.44 (1H, d, J=12.5 Hz), 4.95–5.00 (2H, m), 5.70–5.75 (1H, m), 6.62–6.67 (2H, m), 6.92 (1H, d, J=6.5 Hz), 7.14 (1H, t, J=7.0 Hz), 7.19 (1H, t, J=7.0 Hz), 7.27 (1H, bs), 7.34 (2H, t, J=7.0 Hz), 7.45–7.50 (3H, m), 8.05 (2H, d, J=7.0 Hz), 8.13 (1H, d, J=8.0 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.6, 24.6, 30.7, 33.2, 34.8, 56.9, 63.0, 70.2, 70.3, 115.2, 120.7, 123.6, 126.5, 127.1, 127.6, 128.82, 128.85, 128.87, 129.6, 131.5, 132.1, 133.15, 133.17, 136.8, 137.7, 142.2, 170.3, 179.3, 180.3; HRMS (FAB) MH^+ calcd for $C_{32}H_{34}N_3NiO_3$ 566.1954, found 566.1954.

4.2.7. (*S*)-Pent-4-enyl-glycine-Ni-(*S*)-BPB (5c). Yield 85%, ^{1}H and ^{13}C ($CDCl_3$) spectra are identical to (*S*)-pent-4-enyl-glycine-Ni-(*S*)-BPB (**5c**).

4.2.8. (*R*)-Pent-4-enyl-glycine-Ni-(*S*)-BPB (6c). Yield 9%, $[\alpha]_D^{24}=-1180°$ (*c* 0.040, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 1.50–1.52 (2H, m), 1.84–1.91 (4H, m), 1.98–1.20 (1H, m), 2.12–2.18 (1H, m), 2.22–2.24 (1H, m), 2.52–2.58 (1H, m), 2.64–2.69 (1H, m), 3.59 (1H, d, J=13.0 Hz), 3.67 (1H, d, J=6.0 Hz), 3.79 (1H, d, J=6.5 Hz), 4.21 (1H, t, J=5.0 Hz), 4.48 (1H, d, J=13.0 Hz), 4.93–4.97 (2H, m), 5.63–5.69 (1H, m), 6.72 (1H, t, J=7.5 Hz), 6.76 (1H, d, J=8.0 Hz), 7.00 (1H, d, J=6.5 Hz), 7.19 (1H, bs), 7.26 (1H, bs), 7.45–7.50 (6H, m), 7.99 (2H, d, J=7.0 Hz), 8.50 (1H, d, J=9.0 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.3, 24.6, 30.5, 33.2, 35.4, 58.6, 61.5, 69.1, 70.4, 115.1, 120.7, 123.7, 125.9, 126.9, 127.9, 128.6, 129.0, 129.1, 129.6, 131.6, 132.4, 133.5, 133.7, 134.1, 137.9, 142.8, 170.8, 179.7, 182.3; HRMS (FAB) MH^+ calcd for $C_{32}H_{34}N_3NiO_3$ 566.1954, found 566.1954.

4.2.9. (2*S*,3*S*)-(1-Phenyl)-3-butenyl-glycine-Ni(II)-(*S*)-BPB (13c). Yield 82%, Mp: 135–137 °C; $[\alpha]_D^{24}=+2183°$ (*c* 0.033, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 1.37–1.45 (1H, m), 1.68–1.76 (1H, m), 1.95 (1H, dt, J=7.0, 11.0 Hz), 2.12–2.23 (2H, m), 2.79 (1H, dt, J=6.0, 11.5 Hz), 3.24 (1H, t, J=8.5 Hz), 3.38 (1H, d, J=12.5 Hz), 4.21 (1H, d, J=12.5 Hz), 4.28 (1H, d, J=3.0 Hz), 4.63 (1H, dd, J=3.0, 9.0 Hz), 4.75–4.86 (1H, m), 4.82 (1H, d, J=3.0 Hz), 6.64–6.69 (2H, m), 7.08 (1H, t, J=7.5 Hz), 7.13 (2H, t, J=13.5 Hz), 7.27 (2H, t, J=7.5 Hz), 7.31 (1H, d, J=7.0 Hz), 7.38 (2H, d, J=7.0 Hz), 7.45–7.60 (6H, m), 8.00 (2H, d, J=7.5 Hz), 8.25 (1H, d, J=9.0 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.0, 30.7, 36.3, 50.2, 57.4, 63.6, 70.4, 73.2, 117.3, 120.4, 123.1, 126.1, 127.6, 127.7, 128.2, 128.65, 128.71, 128.91, 128.93, 129.3, 129.7, 129.9, 131.5, 132.3, 133.3, 133.5, 134.4, 135.0, 139.9, 143.0, 170.9, 177.4, 180.4; HRMS (FAB) MH^+ calcd for $C_{37}H_{35}N_3NiO_3$ 628.2110, found 628.2122.

4.2.10. (2*R*,3*R*)-(1-Phenyl)-3-butenyl-glycine-Ni(II)-(*R*)-BPB. Yield 83%, ^{1}H and ^{13}C ($CDCl_3$) spectra are identical to (2*S*,3*S*)-(1-phenyl)-3-butenyl-glycine-Ni(II)-(*S*)-BPB (**13c**).

4.2.11. (2*R*,3*R*)-(1-Phenyl)-3-butenyl-glycine-Ni(II)-(*S*)-BPB (13a). Yield 10%, Mp: 187–189 °C; $[\alpha]_D^{24}=-2030°$ (*c* 0.024, $CHCl_3$); ^{1}H (500 MHz, $CDCl_3$), δ 1.14–1.18 (1H, m), 1.31–1.35 (1H, m), 1.80–1.84 (1H, m), 2.04–2.10 (1H, m), 2.38–2.42 (1H, m), 2.48–2.56 (2H, m), 2.81 (1H, bs), 3.32–3.34 (1H, m), 3.37 (2H, AB, J=14.0, 35.5 Hz), 3.79 (1H, m), 4.29 (1H, d, J=2.5 Hz), 4.63–4.65 (1H, m), 4.85–4.95 (1H, m), 4.88 (1H, d, J=3.5 Hz), 6.76 (1H, t, J=7.5 Hz), 6.82 (1H, d, J=7.5 Hz), 7.13 (1H, d, J=6.0 Hz), 7.17 (1H, d, J=5.0 Hz), 7.28–7.34 (5H, m), 7.50 (1H, t, J=7.0 Hz), 7.53–7.60 (7H, m), 8.44 (1H, d, J=8.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.7, 31.4, 35.5, 50.9, 55.0, 59.2, 68.6, 73.5, 117.4, 120.7, 123.5, 126.4, 127.6, 127.9, 128.2, 128.66, 128.71, 128.90, 128.93, 129.3, 129.8, 130.5, 131.8,

131.9, 132.6, 133.8, 134.3, 134.9, 141.1, 143.2, 170.7, 176.9, 181.8; HRMS (FAB) MH^+ calcd for $C_{37}H_{35}N_3NiO_3$ 628.2110, found 628.2119.

4.2.12. (2*S*,3*R*)-(1-Phenyl)-3-butenyl-glycine-Ni(II)-(*S*)-BPB (13b). The above purified (2*R*, 3*R*)-product (170 mg, 0.271 mmol) and ground NaOH (120 mg, 3.0 mmol) were added to a 10-mL flask. The flask was purged with argon two times and anhydrous DMF (2 mL) was added by syringe. The mixture was kept at room temperature for 20 h before it was quenched by an aqueous acidic solution (20 mL, 5% HOAc). The product mixture was treated as in the general procedure for Ni(II)-complex alkylation, and the product was isolated by flash chromatograph. $[\alpha]_D^{24}$=+1565° (*c* 0.061, $CHCl_3$); ^1H (500 MHz, $CDCl_3$), δ 2.10–2.21 (1H, m), 2.61–2.67 (1H, m), 2.81–2.87 (1H, m), 2.90–2.95 (1H, m), 3.46–3.53 (3H, m), 3.57 (1H, d, *J*=12.5 Hz), 3.83–3.92 (1H, m), 4.10 (1H, d, *J*=6.0 Hz), 4.45 (1H, d, *J*=12.0 Hz), 4.94 (1H, dd, *J*=1.0, 10.0 Hz), 5.09 (1H, dd, *J*=1.0, 17.0 Hz), 5.54–5.61 (1H, m), 6.17 (1H, d, *J*=8.0 Hz), 6.53 (1H, dd, *J*=1.5, 8.5 Hz), 6.63 (1H, t, *J*=7.5 Hz), 6.72 (2H, d, *J*=7.0 Hz), 7.06–7.24 (7H, m), 7.30 (2H, t, *J*=7.5 Hz), 7.43–7.46 (2H, m), 8.05 (2H, d, *J*=7.0 Hz), 8.21 (1H, d, *J*=8.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.4, 30.9, 34.8, 52.1, 56.9, 63.0, 70.7, 75.7, 117.1, 120.6, 123.1, 126.5, 127.0, 127.5, 128.3, 128.6, 128.71, 128.79, 128.81, 128.84, 128.88, 129.5, 131.5, 132.4, 133.1, 133.6, 134.7, 135.7, 138.2, 142.6, 170.7, 177.0, 180.1; HRMS (FAB) MH^+ calcd for $C_{37}H_{35}N_3NiO_3$ 628.2110, found 628.2114.

4.3. Dialkylation of Ni(II)-complex

Eq. 1. Monoalkylated Ni(II)-product **5b** (277 mg, 0.5 mmol) and ground NaOH (40 mg, 5.0 mmol) were added to a flask which was purged two times with argon. Anhydrous DMF (2 mL) was added by syringe and the mixture was allowed to react for 5 min at room temperature before methyl iodide (94 μL, 1.5 mmol) was added. The reaction was then kept at room temperature for 90 min before a second addition of methyl iodide (94 μL, 1.5 mmol). After another 90 min reaction, the solution was decanted into an aqueous solution (40 mL) containing 5% of HOAc. The suspension was dissolved in benzene (40 mL) and the emulsion was diminished by filtration through celite. The benzene solution was washed with brine (4×40 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash liquid chromatograph, and product **8** (83 mg) and product **9** (100 mg) were obtained (65% total yield).

Eq. 2. Ni(II)-complex **3** (1.5 g, 3.0 mmol) and ground NaOH (1.2 g, 30 mmol) were added to a flask which was purged two times with argon. Anhydrous DMF (12 mL) was added by syringe and the mixture was allowed to react for 5 min before it was cooled to 0 °C. Methyl iodide (184 μL, 2.9 mmol) was added in one portion and the reaction was kept for another 5 min at 0 °C before quenching with an aqueous solution (120 mL) containing 5% of HOAc. The suspension was dissolved in benzene (120 mL) and the emulsion was diminished by filtration through celite. The benzene solution was washed with brine (4×80 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by recrystallization in DCM/ether solution and product **5d** (1.22 g, 80% yield) was obtained as a diastereomeric mixture.

The above methyl-Ni(II) product **5d** (256 mg, 0.5 mmol) and ground NaOH (40 mg, 5.0 mmol) were added to a flask which was purged two times with argon. Anhydrous DMF (2 mL) was added by syringe and the mixture was allowed to react for 5 min at room temperature before 1-bromo-4-butene (102 μL, 1.0 mmol) was added. The reaction was then kept at room temperature for 90 min before it was decanted into an aqueous solution (40 mL) containing 5% of HOAc. The suspension was dissolved in benzene (40 mL) and the emulsion was diminished by filtration through celite. The benzene solution was washed with brine (4×40 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash liquid chromatograph, and product **8** (45 mg) and product **9** (96 mg) were obtained (50% total yield).

4.3.1. (2*R*)-2-Buten-3′-yl-2-methyl-glycine-Ni(II)-(*S*)-BPB (8). $[\alpha]_D^{24}$=+1451° (*c* 0.032, $CHCl_3$); ^1H (500 MHz, $CDCl_3$), δ 1.26 (3H, s), 1.73 (1H, dt, *J*=4.0, 13.0 Hz), 1.83 (1H, dt, *J*=4.5, 13.0 Hz), 2.03–2.08 (2H, m), 2.46–2.51 (1H, m), 2.67–2.71 (2H, m), 2.98–3.03 (1H, m), 3.24–3.27 (1H, m), 3.44 (1H, dd, *J*=5.5, 10.5 Hz), 3.65 (1H, d, *J*=10.0 Hz), 3.69 (1H, d, *J*=13.0 Hz), 4.48 (1H, d, *J*=12.5 Hz), 5.03 (1H, d, *J*=10.0 Hz), 5.11 (1H, d, *J*=17.0 Hz), 5.78–5.84 (1H, m), 6.61–6.66 (2H, m), 6.99 (1H, d, *J*=7.5 Hz), 7.13 (1H, t, *J*=6.5 Hz), 7.29–7.32 (2H, m), 7.37–7.46 (3H, m), 7.46–7.47 (2H, m), 8.01 (1H, d, *J*=8.5 Hz), 8.08 (1H, d, *J*=7.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.2, 29.4, 29.8, 30.6, 39.2, 57.0, 63.3, 69.9, 77.6, 115.4, 120.7, 123.9, 126.9, 127.2, 127.9, 128.5, 128.8, 128.9, 129.3, 130.1, 131.5, 131.6, 133.3, 136.4, 136.8, 141.4, 172.5, 180.4, 182.1; HRMS (FAB) MH^+ calcd for $C_{32}H_{34}N_3NiO_3$ 566.1954, found 566.1968.

4.3.2. (2*S*)-2-Buten-3′-yl-2-methyl-glycine-Ni(II)-(*S*)-BPB (9). $[\alpha]_D^{24}$=+960° (*c* 0.031, $CHCl_3$); ^1H (500 MHz, $CDCl_3$), δ 1.46–1.50 (1H, m), 1.52 (3H, s), 1.75–1.79 (1H, m), 2.04–2.13 (4H, m), 2.46–2.51 (1H, m), 2.60–2.65 (1H, m), 3.33–3.39 (1H, m), 3.45 (1H, dd, *J*=5.5, 11.0 Hz), 3.64 (1H, d, *J*=12.5 Hz), 3.72 (1H, dd, *J*=6.0, 10.0 Hz), 4.39 (1H, d, *J*=12.5 Hz), 5.00 (1H, d, *J*=10.0 Hz), 5.04 (1H, dd, *J*=1.0, 17.0 Hz), 5.70–5.75 (1H, m), 6.61–6.67 (2H, m), 7.03 (1H, d, *J*=7.5 Hz), 7.12 (1H, dt, *J*=1.5, 7.5 Hz), 7.26–7.31 (2H, m), 7.36–7.49 (5H, m), 7.96 (1H, d, *J*=8.5 Hz), 8.14 (1H, d, *J*=7.5 Hz); ^{13}C (125 MHz, $CDCl_3$), δ 23.7, 27.8, 28.9, 30.6, 38.9, 57.6, 63.7, 70.4, 77.6, 115.1, 120.7, 124.1, 127.1, 127.7, 128.2, 128.3, 128.7, 128.9, 129.0, 129.4, 131.39, 131.43, 133.1, 133.9, 136.1, 136.8, 141.3, 172.4, 180.5, 182.6; HRMS (FAB) MH^+ calcd for $C_{32}H_{34}N_3NiO_3$ 566.1954, found 566.1958.

4.4. General procedure for hydrolysis of alkylation product of Ni(II)-complex

The Ni(II)-alkylated product (**5a**,**b**,**c** and **13c**) (1 equiv.) was dissolved in a methanol and DCM mixture (2:1, 3 mL/mmol) and added dropwise into a mixture of HCl (3 N, 2 mL/mmol) and methanol (2 mL/mmol) solution at 60 °C. The solution turned green (for the β-phenyl-substituted

product **13c**, 6 N HCl at 60 °C for 1 h). The methanol–water solution was evaporated and the residue was re-dissolved in water (3×5 mL/mmol) and evaporated to remove the HCl. NH_4OH (5 mL/mmol), and then water (5 mL/mmol) was added and the mixture was concentrated in vacuo to dryness. The residue was then dissolved in water (5 mL/mmol) and $CHCl_3$ (5 mL/mmol). The organic phase was separated and the water phase was washed with $CHCl_3$ (2×5 mL/mmol). The combined organic phase was washed with brine and dried over $MgSO_4$, and then concentrated in vacuo. (*S*)-BPB (about 96%) was recovered. The aqueous phase was evaporated to 10 mL and loaded on an ion-exchange column (DOWEX 50Wx2-100 resin) which was pre-washed with water to neutral pH. The column was eluted by water to pH=7 and then washed with ammonium hydroxide/water (4:1) until all the amino acid was washed out (for **5c** and **13c**, a mixture of ammonium hydroxide/water/ethanol (4:1:2) was used). The column can be regenerated by 1 N HCl. The aqueous solution collected from the column was concentrated and the colorless amino acid was collected after lyophilization.

4.4.1. (*S*)-2-Allylglycine (15a). Yield 96%, Mp: >275 °C (decomp.) (lit.,[7] 208 °C); $[\alpha]_D^{24}$=+21.1° (*c* 1.53, H_2O); ^1H (500 MHz, DMSO), δ 2.46–2.57 (2H, m), 3.69 (1H, t, *J*=5.5 Hz), 5.13–5.18 (2H, m), 5.62–5.70 (1H, m); ^{13}C (125 MHz, DMSO), δ 35.2, 54.3, 120.8, 131.7, 174.4; HRMS (FAB) MH^+ calcd for $C_5H_{10}NO_2$ 116.0712, found 116.0717.

4.4.2. (*R*)-2-Allylglycine (18a). Yield 90%, ^1H and ^{13}C (DMSO) spectra are identical to (*S*)-2-allylglycine (**15a**).

4.4.3. (*S*)-2-Amino-5-hexenoic acid (15b). Yield 96%, Mp: >270 °C; $[\alpha]_D^{24}$=+13.1° (*c* 1.30, H_2O) (lit.,[21] +13.6°); ^1H (500 MHz, DMSO), δ 1.83–1.87 (2H, m), 2.02–2.07 (1H, m), 2.14–2.19 (1H, m), 3.80 (1H, t, *J*=6.0 Hz), 4.96 (1H, d, *J*=10.5 Hz), 5.03 (1H, d, *J*=17.5 Hz), 5.71–5.77 (1H, m); ^{13}C (125 MHz, DMSO), δ 28.7, 29.2, 51.5, 116.3, 137.1, 170.8; HRMS (FAB) MH^+ calcd for $C_6H_{11}NO_2$ 130.0868, found 130.0870.

4.4.4. (*R*)-2-Amino-5-hexenoic acid (18b). Yield 92%, ^1H and ^{13}C (DMSO) spectra are identical to (*S*)-2-amino-5-hexenoic acid (**15b**).

4.4.5. (*S*)-2-Amino-6-heptenoic acid (15d). Yield 96%, Mp: 225 °C (decomp); $[\alpha]_D^{24}$=+10.0° (*c* 1.02, H_2O) (lit.,[21] +8.4°); ^1H (500 MHz, D_2O), δ 1.37–1.42 (2H, m), 1.73–1.80 (2H, m), 2.00–2.04 (2H, q, *J*=7.0 Hz), 3.64 (1H, t, *J*=5.5 Hz), 4.93 (1H, d, *J*=10.0 Hz), 4.98 (1H, d, *J*=17.0 Hz), 5.76–5.80 (1H, m); ^{13}C (125 MHz, D_2O), δ 23.9, 30.2, 32.9, 55.1, 115.4, 139.0, 175.3; HRMS (FAB) MH^+ calcd for $C_7H_{14}NO_2$ 144.1025, found 144.1021.

4.4.6. (*R*)-2-Amino-6-heptenoic acid (18d). Yield 90%, ^1H and ^{13}C (D_2O) spectra are identical to (*S*)-2-amino-6-eptenoic acid (**15d**).

4.4.7. (2*S*, 3*S*)-2-Amino-3-phenyl-hexenoic acid (15c). Yield 98%, Mp: 132–135 °C; $[\alpha]_D^{24}$=+2.98° (*c* 4.3, H_2O); ^1H (500 MHz, D_2O), δ 2.61–2.74 (2H, m), 3.34 (1H, dt, *J*=5.0, 10.0 Hz), 4.17 (1H, d, *J*=5.0 Hz), 4.95 (1H, d, *J*=10.0 Hz), 5.06 (1H, d, *J*=17.0 Hz), 5.61–5.68 (1H, m), 7.26 (2H, d, *J*=7.0 Hz), 7.32 (1H, t, *J*=7.0 Hz), 7.37 (2H, t, *J*=7.0 Hz); ^{13}C (125 MHz, D_2O), δ 34.2, 45.7, 57.8, 117.6, 128.2, 128.6, 129.1, 135.3, 136.8, 171.1; HRMS (FAB) MH^+ calcd for $C_{12}H_{15}NO_2$ 206.1181, found 206.1184.

4.4.8. (2*R*, 3*R*)-2-Amino-3-phenyl-hexenoic acid (18c). Yield 95%, ^1H and ^{13}C (D_2O) spectra are identical to (2*S*,3*S*)-2-amino-3-phenyl-hexenoic acid (**15c**).

Crystallographic data (excluding structure factors) for the structure **8** in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 231756. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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