HETEROCYCLES, Vol. 64, 2004, pp. 505 - 514
Received, 15th September, 2004, Accepted, 10th November, 2004, Published online, 12th November, 2004

ASYMMETRIC SYNTHESIS OF ALL SIX REGIOISOMERS OF *N*-BOC-DIMETHYLPHENYLALANINES

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Abstract – All possible regioisomers of dimethyl-substituted (*S*)-phenylalanine were efficiently synthesized by reacting the Ni(II)-complex of the chiral Schiff base of glycine with (*S*)-2-*N*-(*N*-benzylprolyl)-aminobenzophenone.

Considerable interest has developed in amino acids that are not typically found in proteins,[1] due to their importance in the medicinal and biotechnological fields.[2] Amino acids, which are sometimes found as constituents in certain peptides and proteins, have been shown to have exceptional utility as chiral building blocks.[3] Peptides and proteins are among the most important chemical messengers along with their receptor targets, because they can have an influence on many vital processes in human and animal biology. Recent structure-activity relationship studies have shown that the introduction of 2',6'-dimethylphenylalanine (**1a**) in place of the aromatic amino acids of the opioide peptide residue leads to a significant enhancement in receptor affinity and functional potency.[4] Large amounts of a variety of enantiomerically pure dimethyl-subtituted phenylalanines were required for our structure-activity relationship studies of opioide peptide. However, to our knowledge, a method for asymmetric synthesis of all possible regioisomers of dimethylphenylalanine, except for

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This paper is dedicated to Professor Pierre Potier on his 70 th birthday.

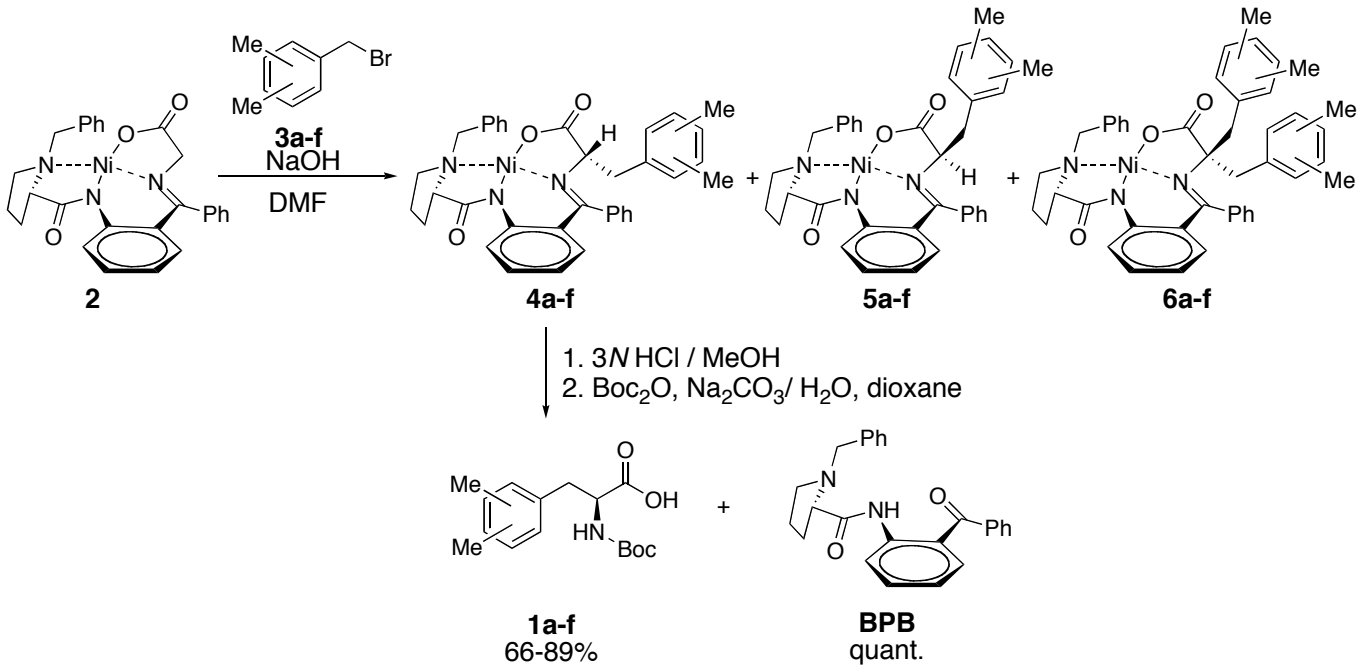
2',6'-dimethylphenylalanine (**1a**) and 2',4'-dimethylphenylalanine (**1c**), has not been reported to date. The preparation of enantiomerically pure dimethylphenylalanines (**1a**) and (**1c**) by the following routes has been reported: The asymmetric hydrogenation of acetamidoacrylate,[5] the asymmetric alkylation of a Schiff base derived from a sultam-derived glycinate,[4g] the phase-transfer catalytic asymmetric alkylation of a glycine ester benzophenone Schiff base,[6] and the asymmetric alkylation of the Ni(II)-complex (**2**) of a Schiff base of glycine with (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone (BPB).[7] Among these methods, the asymmetric alkylation of **2** has several major advantages, including the simplicity of both the experimental procedures involved, ease of product isolation, low cost, and readily available starting materials, compared with other chiral equivalents of a nucleophilic glycine.[8] In addition, a large scale asymmetric synthesis can be performed and the chiral ligand BPB can be recycled. Herein, we describe the asymmetric synthesis of all six regioisomers of dimethyl-substituted *N*-Boc-(*S*)-phenylalanine (**1a**-**f**) by alkylation of the Ni(II)-complex (**2**).

The starting Schiff base, chiral glycine Ni(II)-complex (**2**) was prepared using a procedure reported by Belokon *et al.*[8] 2,6- (**3a**), 2,5- (**3b**) 2,4- (**3c**), 2,3- (**3d**), 3,5- (**3e**), and 3,4-Dimethylbenzyl bromides (**3f**) were prepared by reduction of the commercially available dimethylbenzoic acids followed by bromination.

The crucial step in the synthesis of dimethyl-substituted (*S*)-phenylalanines (**1a**-**f**), alkylation of the Ni(II)-complex (**2**) with dimethylbenzyl bromides (**3a**-**f**), was carried out using powdered NaOH (10 equiv.) as a base in DMF at room temperature for 5 min to afford the alkyl compounds (**4a**-**f**, **5a**,**d**, **6b**-**f**) after a simple work-up (see EXPERIMENTAL). These results are summarized in the Table. The reaction of **2** with **3a** yielded only monoalkylated products (**4a** and **5a**) in high diastereoselectivity (Entry 1). On the other hand, the alkylation of **2** with other dimethylbenzyl bromides (**3b**-**f**) afforded monoalkylated products (**4b**-**f**) in 57–87% yields, along with dialkylated products (**6b**-**f**) in 10–18% yield (Entries 2–6). Dialkylation presumably occurs because **3b**-**f** are less bulkier than **3a**.

Finally, decomposition of monoalkylated Ni(II)-complex (**4a**-**f**) with 3*N* HCl in MeOH followed by protection of the amino group provided the desired *N*-Boc-(*S*)-dimethylphenylalanines (**1a**-**f**) in 66–89% yields together with the recovery of BPB.

In summary, we report on the large scale synthesis of all six regioisomers of dimethyl-substituted *N*-Boc-(*S*)-phenylalanines (**1a**-**f**) by alkylation of the Ni(II)-complex (**2**) in high yields.



Scheme

Table. Reaction of Ni(II)-complex (**2**) with **3a-f**[a]

Entry	Position of Methyl Group	Yield (%)[a]		
		4	**5**	**6**
1	2,6-dimethyl (**a**)	93	6	–
2	2,5-dimethyl (**b**)	87	–	11
3	2,4-dimethyl (**c**)	82	–	13
4	2,3-dimethyl (**d**)	72	6	10
5	3,5-dimethyl (**e**)	68	–	12
6	3,4-dimethyl (**f**)	57	–	18

[a] Isolated yields.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrophotometer. MS spectra were recorded on a JEOL JMN-DX 303/JMA-DA 5000 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-EX 270 spectrometer (^{1}H: 270 MHz, ^{13}C: 67.8 MHz), using tetramethylsilane as an internal standard. Elemental analyses were performed on a Perkin-Elmer 2400 CHN Elemental Analyzer. Optical rotations were measured on a JASCO P-1020 polarimeter. Column chromatography was carried out on Merck Silica Gel 60 (230-400 mesh for flash chromatography).

General procedure for the reaction of (*S*)-Gly-Ni(II)-BPB (2) with dimethylbenzyl bromide derivative (3a–f)

(*S*)-Gly-Ni(II)-BPB (**2**, 2.5 g, 5 mmol) was added to a stirred suspension of pulverized NaOH (2.0 g, 50 mmol) in dry DMF (10 mL), with stirring under an argon stream for 1.5 h at rt. A solution of dimethylbenzyl bromide derivative (**3a**–**f**, 1.1 g, 5.5 mmol) in dry DMF (10 mL) was added dropwise to the mixture, with stirring for 5 min at rt. The reaction mixture was poured into ice water (350 mL). The precipitated crystalline product was separated from the mixture by filtration. The crystalline product was dissolved in $CHCl_3$, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by silica gel flash column chromatography (hexane:acetone = 1:1) to give alkylated products (**4a**–**f**, **5a**,**d**,**6b**–**f**) in yields depicted in Table.

Reaction of (*S*)-Gly-Ni(II)-BPB (2) with 2',6'-dimethylbenzyl bromide (3a)

4a: Yield 93%, mp 123 °C (EtOH) [lit.,[7] 122–124 °C]. $[\alpha]_D^{20}$ +2803° (*c* = 1.0 in $CHCl_3$). IR (KBr) cm^{-1}: 3477, 2968, 1669, 1635, 1164, 1070, 752. ^{1}H-NMR ($CDCl_3$) δ: 2.07–2.13 (1H, m), 2.14 (6H, s), 2.24–2.36 (1H, m), 2.57–2.61 (1H, m), 2.64–2.74 (1H, m), 3.50–3.58 (2H, m), 3.52 (1H, d, *J* = 13.7 Hz), 3.82–4.00 (1H, m), 4.08 (1H, dd, *J* = 10.4, 14.0 Hz), 4.29 (1H, dd, *J* = 4.2, 10.1 Hz), 4.41 (1H, d, *J* = 12.5 Hz), 5.57 (1H, d, *J* = 7.6 Hz), 6.42 (1H, d, *J* = 8.1 Hz), 6.55 (1H, dd, *J* = 14.2, 7.1 Hz), 6.80 (2H, d, *J* = 7.6 Hz), 7.08–7.15 (2H, m), 7.16–7.25 (4H, m), 7.28–7.39 (4H, m), 8.11 (2H, d, *J* = 7.3 Hz), 8.19 (1H, d, *J* = 7.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 20.0, 24.3, 30.7, 37.6, 57.1, 63.0, 70.3, 70.4, 120.6, 123.2, 126.1, 126.9, 127.4, 128.1, 128.4, 128.6, 128.8, 128.8, 128.9, 129.0, 131.4, 132.5, 133.2, 133.3, 133.9, 137.9, 142.3, 171.1, 178.9, 180.0. MS *m/z*: 615 (M^+).

5a: Yield 6%, mp 290–292 °C (EtOH) [lit.,[7] 295–297 °C]. $[\alpha]_D^{26}$ +2061° (*c* = 1.0 in $CHCl_3$). IR (KBr) cm^{-1}: 3426, 2973, 1674, 1641, 1164, 1078, 756. ^{1}H-NMR ($CDCl_3$) δ: 1.87 (1H, m), 1.98 (6H, s), 2.21–2.34 (1H, m), 2.40–2.43 (1H, m), 2.85–2.92 (1H, m), 3.37 (1H, dd, *J* = 17.8, 3.5 Hz), 3.44 (1H, d, *J* = 12.9 Hz), 3.92–3.93 (1H, m), 3.96–4.07 (1H, m), 4.26–4.39 (3H, m), 5.41 (1H, d, *J* = 7.3 Hz), 6.55 (1H, d, *J* = 10.0 Hz), 6.61–6.67 (1H, m), 6.81 (1H, d, *J* = 7.6 Hz), 6.92–6.98 (1H, m), 7.00–7.03 (1H, m), 7.10–7.14 (1H, m), 7.20–7.26 (1H, m), 7.20–7.26 (1H, m), 7.29–7.38 (2H, m), 7.44–7.57 (3H, m), 7.91 (2H, d, *J* = 9.4 Hz), 8.61 (1H, d, *J* = 9.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 19.8, 22.8, 29.7, 36.9, 58.7, 60.1, 68.6, 70.6, 120.7, 123.2, 125.8, 126.9, 127.3, 128.2, 128.6, 128.6, 128.8, 129.0, 129.2, 129.3, 129.4, 132.0, 132.6, 132.8, 133.4, 133.5, 134.4, 142.9, 171.6, 179.2, 181.2. MS *m/z*: 615 (M^+).

Reaction of (*S*)-Gly-Ni(II)-BPB (2) with 2',5'-dimethylbenzyl bromide (3b)

4b: Yield 87%, mp 215–216 °C (EtOH). $[\alpha]_D^{24}$ +2515° (*c* = 1.0 in $CHCl_3$). IR (KBr) cm^{-1}: 3440, 2944, 1685, 1634, 1164, 1065, 758. ^{1}H-NMR ($CDCl_3$) δ: 1.87–2.10 (2H, m), 2.08 (3H, s), 2.14 (3H, s), 2.38–2.62 (2H, m), 2.95–3.09 (1H, m), 3.25 (1H, dd, *J* = 5.6, 13.8 Hz), 3.29 (1H, dd, *J* = 2.5, 14.5 Hz), 3.37–3.51 (3H, m), 4.20 (1H, dd, *J* = 5.7, 6.7 Hz), 4.34 (1H, d, *J* = 12.5 Hz), 6,36 (1H, dd, *J* = 1.1, 6.7 Hz), 6.56–6.67 (2H, m), 6.79 (1H, s), 6.96–7.04 (2H, m), 7.08–7.17 (2H, m), 7.20–7.33 (4H, m), 7.41–7.52 (2H, m), 8.05 (2H, dd, *J* = 1.1, 8.1 Hz), 8.25 (1H, dd, *J* = 0.7, 8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 19.0, 20.9, 23.6, 30.8, 38.9, 57.2, 63.2, 70.5, 71.6, 120.5, 123.3, 126.1, 127.5, 128.0, 128.1, 128.7, 128.7, 128.8, 129.5, 130.7, 131.5, 132.1, 132.4, 133.3, 133.6, 134.0, 142.7, 170.8, 178.6, 180.2. MS *m/z*: 615 (M^+). *Anal.* Calcd $C_{36}H_{35}N_3O_3Ni$: C, 70.15; H, 5.72; N, 6.82. Found: C, 69.98; H, 5.65; N, 6.77.

6b: Yield 11%, mp 150–153 °C (EtOH). $[\alpha]_D^{23}$ +1810° (*c* = 1.0 in $CHCl_3$). IR (KBr) cm^{-1}: 3445, 2964, 1679, 1651, 1629, 1164, 1064, 749. ^{1}H-NMR ($CDCl_3$) δ: 1.53–1.70 (1H, m), 1.81 (3H, s), 2.04–2.23 (5H, m), 2.27 (3H, s), 2.29 (3H, s), 2.46 (3H, s), 3.14–3.23 (3H, m), 3.30–3.49 (3H, m), 4.53 (1H, d, *J* = 12.7 Hz), 6.40 (1H, d, *J* = 7.8 Hz), 6.43–6.57 (2H, m), 6.90–7.13 (6H, m), 7.19–7.35 (7H, m), 7.43 (1H, t, *J* = 7.4 Hz), 8.07 (1H, d, *J* = 8.6 Hz), 8.18 (2H, d, *J* = 7.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 18.4, 19.4, 21.7, 23.1, 30.2, 44.1, 57.3, 63.0, 68.8, 80.1, 120.3, 123.5, 126.4, 126.8, 127.2, 127.6, 126.7, 127.9, 128.1, 128.5, 128.7, 128.8, 129.1, 130.3, 131.1, 131.8, 131.9, 132.7, 132.9, 133.7, 133.8, 134.8, 134.9, 135.4, 135.5, 135.8, 136.6, 142.5, 171.2, 179.8, 180.6. MS *m/z*: 733 (M^++1). *Anal.* Calcd $C_{45}H_{44}N_3O_3Ni$: C, 73.68; H, 6.05; N, 5.73. Found: C, 73.43; H, 6.27; N, 5.52.

Reaction of (*S*)-Gly-Ni(II)-BPB (2) with 2',4'-dimethylbenzyl bromide (3c)

4c: Yield 82%, mp 122–124 °C (EtOH). $[\alpha]_D^{20}$ +2406° (*c* = 1.3 in $CHCl_3$). IR (KBr) cm^{-1}: 3428, 2921, 1674, 1642, 1165, 1066, 753. ^{1}H-NMR ($CDCl_3$) δ: 1.86–2.10 (2H, m), 2.01 (3H, s), 2.30 (3H, s), 2.44–2.62 (2H, m), 2.90–3.02 (1H, m), 3.20–3.30 (2H, m), 3.39–3.48 (3H, m), 4.21 (1H, dd, *J* = 5.6, 6.6 Hz), 4.33 (1H, d, *J* = 12.5 Hz), 6.40 (1H, d, *J* = 7.6 Hz), 6.55–6.66 (2H, m), 6.90–6.98 (2H, m), 7.07–7.16 (2H, m), 7.21–7.33 (4H, m), 7.43–7.51 (2H, m), 8,07 (2H, d, *J* = 7.8 Hz), 8.21 (1H, d, *J* = 8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 19.4, 21.0, 23.5, 30.8, 38.6, 57.3, 63.2, 70.5, 71.4, 120.6, 123.3, 126.2, 127.0, 127.5, 127.9, 128.7, 128.8, 129.5, 131.0, 131.3, 131.5, 131.6, 132.3, 133.3, 133.6, 133.7, 137.0, 137.5, 142.7, 170.8, 178.7, 180.3. MS *m/z*: 615 (M^+). *Anal.* Calcd $C_{36}H_{35}N_3O_3Ni$: C, 70.15; H, 5.72; N, 6.82. Found: C, 69.89; H, 5.85; N, 6.57.

6c: Yield 13%, mp 234–237 °C (EtOH). $[\alpha]_D^{20}$ +2400° (*c* = 1.1 in $CHCl_3$). IR (KBr) cm^{-1}: 3432,

2924, 1668, 1642, 1164, 1033, 749. ^{1}H-NMR ($CDCl_3$) δ: 1.53–1.67 (1H, m), 1.81 (3H, s), 1.90–2.17 (3H, m), 2.20–2.30 (2H, m), 2.34 (6H, s), 2.38 (3H, s), 3.12–3.22 (2H, m), 3.06–3.41 (4H m), 4.34 (1H, d, *J* = 12.5 Hz), 6.30 (1H, d, *J* = 7.9 Hz), 6.39–6.53 (2H, m), 6.97–7.10 (4H, m), 7.16–7.21 (4H, m), 7.28–7.53 (6H, m), 7.93 (1H, d, *J* = 7.8 Hz), 8.26 (2H, d, *J* = 7.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 19.8, 20.4, 21.0, 22.9, 30.4, 43.4, 58.5, 64.3, 70.2, 80.1, 120.2, 123.6, 126.4, 126.9, 127.2, 127.3, 127.6, 127.7, 128.1, 128.8, 128.9, 129.1, 131.3, 131.5, 131.5, 131.9, 132.0, 132.1, 132.9, 133.7, 134.2, 135.4, 136.5, 136.6, 137.0, 138.7, 142.3, 171.1, 179.8, 180.4. MS *m/z*: 733 (M^++1). *Anal.* Calcd $C_{45}H_{44}N_3O_3Ni$: C, 73.68; H, 6.05; N, 5.73. Found: C, 73.50; H, 5.80; N, 5.49.

Reaction of (*S*)-Gly-Ni(II)-BPB (2) with 2',3'-dimethylbenzyl bromide (3d)

4d: Yield 72%, mp 229–230 °C (EtOH). $[\alpha]_D^{24}$ +2215° (*c* = 1.0 in $CHCl_3$). IR (KBr) cm^{-1}: 3432, 2924, 1668, 1642, 1164, 1033, 749. ^{1}H-NMR ($CDCl_3$) δ: 1.78 (3H, s), 1.98–2.13 (2H, m), 2.19 (3H, s), 2.17–2.32 (1H, m), 2.46–2.78 (2H, m), 3.25–3.51 (5H, m), 3.72 (1H, dd, *J* = 8.1, 13.9 Hz), 4.25 (1H, dd, *J* = 4.8, 7.9 Hz), 4.36 (1H, d, *J* = 12.7 Hz), 6.00 (1H, d, *J* = 7.8 Hz), 6.50 (1H, d, *J* = 6.8 Hz), 6.61 (1H, dd, *J* = 7.3, 7.6 Hz), 6.93–7.21, (7H, m), 7.25–7.33 (2H, m), 7.36–7.46 (2H, m), 8.05 (2H, d, *J* = 7.4 Hz), 8.20 (1H, d, *J* = 8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 15.0, 20.8, 23.8, 30.9, 40.8, 57.2, 63.1, 70.6, 71.3, 120.6, 123.2, 125.7, 127.6, 128.1, 128.4, 128.5, 128.8, 128.9, 129.2, 129.3, 131.5, 132.3, 133.3, 133.5, 133.6, 133.7, 136.4, 137.4, 142.7, 170.7, 178.7, 180.3. MS *m/z*: 615 (M^+). *Anal.* Calcd $C_{36}H_{35}N_3O_3Ni$: C, 70.15; H, 5.72; N, 6.82. Found: C, 69.85; H, 5.72; N, 6.68.

5d: Yield 6%, mp 256–258 °C (EtOH). $[\alpha]_D^{25}$ –1569° (*c* = 1.0 in $CHCl_3$). IR (KBr) cm^{-1}: 3444, 1688, 1636, 1164, 761. ^{1}H-NMR ($CDCl_3$) δ: 1.98–2.35 (4H, m), 2.17 (3H, s), 2.20 (3H, s), 2.60–2.71 (1H, m), 3.17 (1H, dd, *J* = 5.4, 14.1 Hz), 3.32 (1H, d, J = 6.7, 13.9 Hz), 3.49 (1H, d, *J* = 13.5 Hz), 3.60 (1H, dd, *J* = 3.6, 9.4 Hz), 3.99 (1H, d, *J* = 13.5 Hz), 4.03–4.11 (1H, m), 4.22 (1H, dd, *J* = 5.3, 6.6 Hz), 6.32 (1H, d, *J* = 7.4 Hz), 6.65–6.73 (2H, m), 6.93–7.30 (6H, m), 7.40–7.48 (5H, m), 7.68 (2H, d, *J* = 6.4 Hz), 8.54 (1H, d, *J* = 8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 15.3, 20.9, 23.5, 30.9, 39.1, 57.4, 60.3, 69.2, 71.6, 120.7, 123.3, 125.6, 126.0, 127.5, 128.1, 128.5, 128.8, 129.0, 129.1, 129.2, 129.4, 129.9, 131.5, 132.7, 133.1, 133.8, 134.0, 134.2, 137.0, 137.5, 143.2, 171.1, 178.7, 206.9. MS *m/z*: 615 (M^+). HRMS calcd for $C_{36}H_{35}N_3O_3Ni$: 615.2032, Found: 615.2001.

6d: Yield 10%, mp 281–283 °C (EtOH). $[\alpha]_D^{21}$ +1665° (*c* = 1.0 in $CHCl_3$). IR (KBr) cm^{-1}: 3429, 1667, 1644, 1245, 1163, 747. ^{1}H-NMR ($CDCl_3$) δ: 1.53–1.67 (1H, m), 1.61 (3H, s), 1.74 (3H, s),

2.01–2.30 (5H, m), 2.25 (3H, s), 2.29 (3H, s), 2.37 (3H, s), 3.15–3.47 (6H, m), 4.31 (1H, d, *J* = 12.5 Hz), 6.20 (1H, d, *J* = 7.9 Hz), 6.40 (1H, dd, *J* = 1.7, 8.5 Hz), 6.46–6.52 (1H, m), 6.94–7.46 (14H, m), 7.95 (1H, dd, *J* = 0.9, 8.7 Hz), 8.22 (2H, d, *J* = 7.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 15.1, 16.0, 20.8, 21.4, 30.5, 44.1, 44.2, 58.2, 64.1, 70.3, 80.3, 120.2, 123.6, 125.1, 125.5, 125.6, 126.4, 126.9, 127.6, 127.9, 128.2, 128.9, 129.0, 129.1, 130.0, 131.4, 131.5, 133.7, 134.1, 134.9, 135.2, 135.9, 136.5, 137.4, 137.9, 142.3, 170.9, 179.5, 180.4. MS *m/z*: 733 (M^++1). *Anal.* Calcd $C_{45}H_{44}N_3O_3Ni$: C, 73.68; H, 6.05; N, 5.73. Found: C, 73.70; H, 6.16; N, 5.89.

Reaction of (*S*)-Gly-Ni(II)-BPB (2) with 3',5'-dimethylbenzyl bromide (3e)

4e: Yield 68%, mp 211–212 °C (AcOEt). $[\alpha]_D^{27}$ +2644° (*c* = 1.1 in $CHCl_3$). IR (KBr) cm^{-1}: 3428, 2920, 1675, 1640, 1164, 754. ^{1}H-NMR ($CDCl_3$) δ: 1.65–1.75 (1H, m), 1.92–2.02 (2H, m), 2.20–2.48 (3H, m), 2.27 (6H, s), 2.79 (1H, dd, *J* = 5.8, 13.6 Hz), 3.02 (1H, dd, *J* = 4.3, 13.7 Hz), 3.08–3.16 (1H, m), 3.32 (1H, dd, *J* = 7.9, 8.9 Hz), 3.47 (1H, d, *J* = 12.5 Hz), 4.22 (1H, dd, *J* = 4.3, 5.9 Hz), 4.27 (1H, d, *J* = 12.5 Hz), 6.65–6.74 (4H, m), 6.87 (1H, d, *J* = 7.4 Hz), 7.01 (1H, s), 7.11–7.17 (2H, m), 7.27–7.30 (3H, m), 7.32–7.47 (1H, m), 7.49–7.57 (2H, m), 8.01 (2H, d, *J* = 7.1 Hz), 8.26 (1H, d, *J* = 8.6 Hz). ^{13}C-NMR ($CDCl_3$) δ: 18.4, 21.3, 23.0, 30.5, 39.7, 57.2, 58.5, 63.3, 70.3, 120.5, 123.3, 126.1, 127.2, 128.0, 128.5, 128.7, 128.8, 129.0, 129.1, 129.7, 131.5, 132.4, 133.3, 133.5, 134.2, 135.6, 138.3, 142.9, 170.9, 178.7, 180.2. MS *m/z*: 615 (M^+). HRMS calcd for $C_{36}H_{35}N_3O_3Ni$: 615.2032, Found : 615.2009.

6e: Yield 12%, mp 240–241 °C (AcOEt). $[\alpha]_D^{27}$ +1915° (*c* = 1.1 in $CHCl_3$). IR (KBr) cm^{-1}: 3448, 2917, 1673, 1632, 1164, 751. ^{1}H-NMR ($CDCl_3$) δ: 1.53–1.58 (1H, m), 1.95–2.25 (4H, m), 2.33 (12H, s), 2.56 (1H, d, *J* = 16.7 Hz), 3.00 (2H, s), 3.13–3.40 (4H, m), 4.44 (1H, d, *J* = 12.9 Hz), 6.57 (2H, d, *J* = 4.0 Hz), 6.83–7.39 (14H, m), 7.49 (1H, t, *J* = 7.5 Hz), 7.92 (1H, d, *J* = 8.6 Hz), 8.07 (2H, d, *J* = 6.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.5, 22.8, 30.3, 45.4, 46.0, 57.5, 63.1, 68.8, 81.1, 120.3, 123.7, 127.1, 127.2, 127.4, 127.8, 127.9, 128.2, 128.6, 128.7, 128.8, 129.0, 129.1, 129.5, 131,6, 131.8, 132.9, 133.6, 136.6, 136.8, 136.9, 137.6, 138.2, 142.3, 171.9, 180.0, 180.5. MS *m/z*: 733 (M^++1). *Anal.* Calcd $C_{45}H_{44}N_3O_3Ni$: C, 73.68; H, 6.05; N, 5.73. Found: C, 73.39; H, 6.16; N, 5.94.

Reaction of (*S*)-Gly-Ni(II)-BPB (2) with 3',4'-dimethylbenzyl bromide (3f)

4f: Yield 57%, mp 144—146 °C (EtOAc). $[\alpha]_D^{28}$ +2139° (*c* = 1.0 in $CHCl_3$). IR (KBr) cm^{-1}: 3442, 2921, 1669, 1642, 1164, 756. ^{1}H-NMR ($CDCl_3$) δ: 1.86–2.00 (1H, m), 2.08–2.38 (3H, m), 2.22 (3H, s), 2.29 (3H, s), 2.77 (1H, dd, *J* = 5.7, 13.8 Hz), 2.92 (1H, d, *J* = 19.5 Hz), 3.30 (1H, dd, *J* = 7.1, 8.6 Hz), 2.97–3.08 (2H, m), 3.46 (1H, d, *J* = 12.7 Hz), 4.18–4.32 (2H, m), 6.67 (2H, d, *J*

= 4.0 Hz), 6.83–6.97 (3H, m), 7.10–7.20 (3H, m), 7.23–7.37 (3H, m), 7.40–7.46 (1H, m), 7.46–7.63 (2H, m), 8.00 (2H, d, *J* = 7.6 Hz), 8.24 (1H, d, *J* = 8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ: 19.5, 19.8, 22.8, 30.5, 39.3, 57.2, 63.3, 70.3, 71.6, 120.5, 123.4, 126.2, 127.2, 128.0, 128.1, 128.7, 128.8, 129.1, 129.7, 130.0, 131.5, 131.9, 132.0, 132.3, 133.2, 133.3, 133.5, 134.3, 135.6, 137.0, 142.9, 170.9, 178.7, 180.2. MS *m/z*: 615 (M^+). HRMS calcd for $C_{36}H_{35}N_3O_3Ni$: 615.2032, Found : 615.2010.

6f: Yield 18%, mp 234—236 °C (EtOAc). $[\alpha]_D^{26}$ +2011° (*c* = 1.1 in $CHCl_3$). IR (KBr) cm^{-1}: 3443, 2932, 1667, 1644, 1164, 748. ^{1}H-NMR ($CDCl_3$) δ: 1.49–1.60 (1H, m), 1.86–2.07 (3H, m), 2.17–2.38 (1H, m), 2.25 (3H, s), 2.27 (3H, s), 2.29 (3H, s), 2.33 (3H, s), 2.66 (1H, d, *J* = 16.8 Hz), 2.95 (1H, d, *J* = 14.5 Hz), 3.06–3.15 (2H, m), 3.20–3.31 (3H, m), 4.32 (1H, d, *J* = 12.5 Hz), 6.51–6.56 (2H, m), 6.92 (1H, s), 6.99–7.08 (2H, m), 7.16–7.40 (11H, m), 7.49 (1H, t, *J* = 7.4 Hz), 7.86 (1H, d, *J* = 8.6 Hz), 8.10 (2H, d, *J* = 7.1 Hz). ^{13}C-NMR ($CDCl_3$) 8: 19.4, 19.5, 20.0, 22.6, 30.3, 44.9, 45.6, 58.1, 63.8, 69.7, 81.3, 120.3, 123.8, 126.2, 127.1, 127.5, 127.8, 128.2, 128.3, 128.7, 128.8, 129.2, 129.5, 129.5, 130.0, 131.2, 131.5, 131.7, 132.5, 133.5, 133.6, 134.1, 134.3, 134.4, 135.6, 136.5, 136.8, 137.0, 142.2, 171.9, 180.0, 180.5. MS *m/z*: 733 (M^++1). *Anal.* Calcd $C_{45}H_{44}N_3O_3Ni$: C, 73.68; H, 6.05; N, 5.73. Found: C, 73.41; H, 6.24; N, 5.81.

General procedure for the synthesis of *N*-Boc-dimethyldiphenylalanines (1a–f) by decomposition of Ni(II)-complex (4a–f)

A solution of 3*N* HCl (6 mL) in MeOH (6 mL) was added dropwise to a stirred solution of **4a**–**f** (2.46 g, 4 mmol) in MeOH (15 mL) at 70 °C. The mixture was stirred at 70 °C until disappearance of the red color (*ca.* 3 h). After cooling to rt, the mixture was concentrated *in vacuo* and the residue was dissolved in H_2O (50 mL). To the solution were successively added Na_2CO_3 (2.65g, 25 mmol), dioxane (40 mL), and $(Boc)_2O$ (4.4 g, 20 mmol), and the mixture was stirred at rt for overnight. The mixture was concentrated *in vacuo*. A solution of water (50 mL) and $CHCl_3$ (50 mL) were added to the residue, and the aqueous layer was separated and extracted with $CHCl_3$ (20 mL x 3). The combined organic solvents were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and the residue was purified by recrystallization from ethanol to recover the (*S*)-BPB in 90–96% yields. The aqueous layer was adjusted to pH 3 by addition of 20% citric acid and extracted with $CHCl_3$ (50 mL x 3). The combined $CHCl_3$ extracts were dried over $MgSO_4$, filtered, concentrated *in vacuo*, and the residue was purified by silica gel flash column chromatography ($CHCl_3$: MeOH : AcOH = 4 : 1 : 0.01) to afford *N*-Boc-(*S*)-dimethylphenylalanine (**1a**–**f**) in 66–89% yield.

N-Boc-(*S*)-2',6'-dimethylphenylalanine (1a)

Yield 83%, mp 134–136 °C (hexane–AcOEt) [lit.,[4g] mp 122–124 °C]. $[\alpha]_D^{30}$ –25.2° (*c* = 1.02 in $CHCl_3$) [lit.,[6] $[\alpha]_D^{20}$ –25° (*c* = 1 in $CHCl_3$)]. IR (KBr) cm^{-1}: 3421, 2981, 1709, 784. ^{1}H-NMR ($CDCl_3$) δ: 1.04 and 1.35 (9H, s x 2), 2.41 (6H, s), 3.07–3.25 (2H, m), 4.54–4.60 (1H, m), 6.98–7.08 (3H, m), 7.41 (1H, d, *J* = 7.9 Hz), 12.77 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 20.3, 27.6, 34.6, 53.9, 81.2, 126.6, 128.4, 134.3, 137.4, 156.5, 175.5. MS *m/z*: 293 (M^+).

N-Boc-(*S*)-2',5'-dimethylphenylalanine (1b)

Yield 66%, mp 95–97 °C (hexane–AcOEt). $[\alpha]_D^{21}$ +13.9° (*c* = 1.14 in $CHCl_3$). IR (KBr) cm^{-1}: 3348, 2977, 1690, 776. ^{1}H-NMR ($CDCl_3$) δ: 1.15 and 1.40 (9H, s x 2), 2.28 (3H, s), 2.30 and 2.33 (3H, s x 2), 2.79–2.97 (1H, m), 3.18–3.30 (1H, m), 4.37–4.62 (1H, m), 4.93 (0.5H, d, *J* = 7.6 Hz), 6.93-7.06 (3.5H, m), 12.30 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 18.9, 20.9, 28.3, 35.3, 53.7, 83.4, 127.9, 130.5, 130.6, 133.6, 134.0, 135.5, 155.7, 164.60, 175.7. MS *m/z*: 293 (M^+). *Anal.* Calcd $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.45; H, 8.10; N, 4.71.

N-Boc-(*S*)-2',4'-dimethylphenylalanine (1c)

Yield 70%, oil. $[\alpha]_D^{18}$ +10.8° (*c* = 1.10 in $CHCl_3$). IR (neat) cm^{-1}: 3641, 2980, 1721, 756. ^{1}H-NMR ($CDCl_3$) δ: 1.05 and 1.39 (9H, s x 2), 2.28 (3H, s), 2.31 and 2.34 (3H, s x 2), 2.79–2.97 (1H, m), 3,18–3.27 (1H, m), 4.38–4.60 (1H, m), 4.99 (0.5H, d, *J* = 7.9 Hz), 6.91–7.10 (3.5H, m), 11.46 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 19.3, 20.9, 28.3, 35.0, 53.7, 80.3, 126.7, 129.8, 130.6, 131.1, 131.4, 136.6, 155.4, 176.9. MS *m/z*: 293 (M^+). HRMS calcd for $C_{16}H_{23}NO_4$: 293.1627, Found: 293.1654.

N-Boc-(*S*)-2',3'-dimethylphenylalanine (1d)

Yield 89%, oil. $[\alpha]_D^{22}$ –6.2° (*c* = 1.00 in $CHCl_3$). IR (neat) cm^{-1}: 3432, 2978, 1721, 758. ^{1}H-NMR ($CDCl_3$) δ: 1.12 and 1.39 (9H, s x 2), 2.28 (6H, s), 2.82–3.03 (1H, m), 3.26–3.37 (1H, m), 4.40–4.62 (1H, m), 5.00 (0.5H, d, *J* = 8.2 Hz), 6.95–7.18 (3.5H, m), 11.11 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 15.1, 20.7, 27.7, 36.12, 38.7, 54.9, 81.1, 125.5, 128.0, 128.7, 130.1, 135.2, 136.8, 156.7, 175.8. MS *m/z*: 293 (M^+). HRMS calcd for $C_{16}H_{23}NO_4$: 293.1627, Found: 293.1631.

N-Boc-(*S*)-3',5'-dimethylphenylalanine (1e)

Yield 86%, mp 106–110 °C (hexane–AcOEt). $[\alpha]_D^{24}$ +37.7° (*c* = 1.10 in $CHCl_3$). IR (KBr) cm^{-1}: 3346, 2981, 1689, 754. ^{1}H-NMR ($CDCl_3$) δ: 1.30 and 1.42 (9H, s x 2), 2.27 (6H, s), 2.90–3.20 (2H, m), 4.32–4.62 (1H, m), 4.92 (0.5H, d, *J* = 7.9 Hz), 6.21 (0.5H, br s), 6.79 (2H, s), 6.88 (1H, s), 10.05 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 21.3, 28.3, 37.4, 54.4, 80.4, 127.1, 128.8, 135.6, 138.2,

155.6, 175.3. MS *m/z*: 293 (M^+). *Anal.* Calcd $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.37; H, 7.99; N, 4.77.

N-Boc-(*S*)-3',4'-dimethylphenylalanine (1f)

Yield 74%, oil. $[\alpha]_D^{23}$ +27.5° (*c* = 1.00 in $CHCl_3$). IR (neat) cm^{-1}: 3320, 2979, 1720, 757. ^{1}H-NMR ($CDCl_3$) δ: 1.31 and 1.41 (9H, s x 2), 2.21 (6H, s), 2.93–3.18 (2H, m), 4.26–4.40 (1H, m), 5.02 (0.5H, d, *J* = 8.1 Hz), 6.02 (0.5H, br s), 6.86–7.04 (3H, m), 9.18 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 19.3, 19.7, 28.3, 37.2, 54.3, 80.2, 126.6, 129.8, 130.6, 133.0, 135.3, 136.7, 155.4, 176.7. MS *m/z*: 293 (M^+). HRMS calcd for $C_{16}H_{23}NO_4$: 293.1627, Found: 293.1654.

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