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Practical, asymmetric synthesis of aromatic-substituted bulky and hydrophobic tryptophan and phenylalanine derivatives

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Abstract—Aromatic ring substituted tryptophans and phenylalanines can provide valuable tools in developing highly potent and selective peptide ligands with specific structural features in addition to providing a large lipophilic surface for binding to receptors and for crossing membrane barriers. An efficient method for the synthesis of these novel amino acids has been developed. In the approach, asymmetric hydrogenations of α-enamides using Burk's DuPHOS-based Rh (I) catalysts generated high enantiomerically pure α-amino acid derivatives, which subsequently underwent Suzuki cross couplings with boronic acid derivatives to afford these aromatic substituted amino acids in high yields and high enantioselectivity. The method can allow for the preparation of such amino acids in large scales for extensive structure–activity studies.

1. Introduction

The aromatic moieties of peptide side chain groups play important roles in the molecular recognition processes between peptide ligands and specific receptors as well as receptor subtypes. Aromatic ring substituted amino acids can provide valuable tools in developing highly selective peptide ligands with specific structural features. In addition, they can provide a large lipophilic surface for binding to receptors, and for crossing membrane barriers (e.g. blood brain barriers (BBB) and intestinal mucosa), which provide an opportunity to address three issues simultaneously. In our continuing α- and γ-melanocyte stimulating hormone (MSH) project, there are many aromatic amino acids in the sequences of these peptides. For example, three such amino acids (His, Phe and Trp) are in the core sequence, His-Phe-Arg-Trp, of α-MSH peptides, which plays a key role in biological activity and selectivity.[1,2] The modification and substitution of His with Pro and L-Phe with D-Phe or D-Nal (2′) in the core sequence of the peptide has led to potent and selective α-MSH peptide ligands.[1,2] More recently,[3] we identified a potent γ-MSH peptide with high selectivity for hMC3R (human melanocortin receptor 3) by replacing L-Trp[8] with D-Trp.[8] In our efforts to further enhance potency and selectivity of α and γ-MSH peptide ligands, we have proposed to use more bulky and hydrophobic amino acids including aromatic-substituted tryptophans **1** and phenylalanines **2** to substitute for Trp and Phe, respectively (Fig. 1).

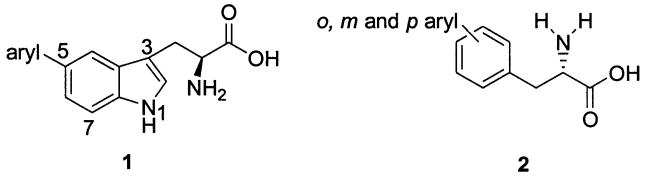

Figure 1. Structures of 5-aryl typtophans and *o*, *m*, and *p* substituted-aryl phenylalanines.

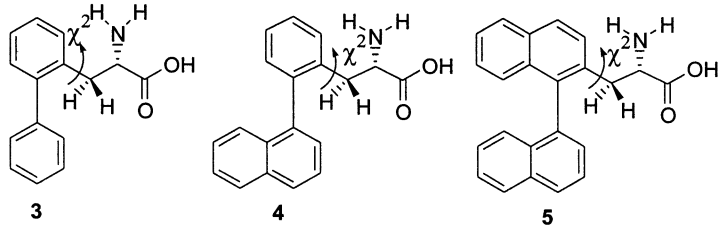

Figure 2. *o*-Substituted phenylalanine derivatives.

Keywords: asymmetric hydrogenation; DuPHOS; amino acids; tryptophan; phenylalanine.
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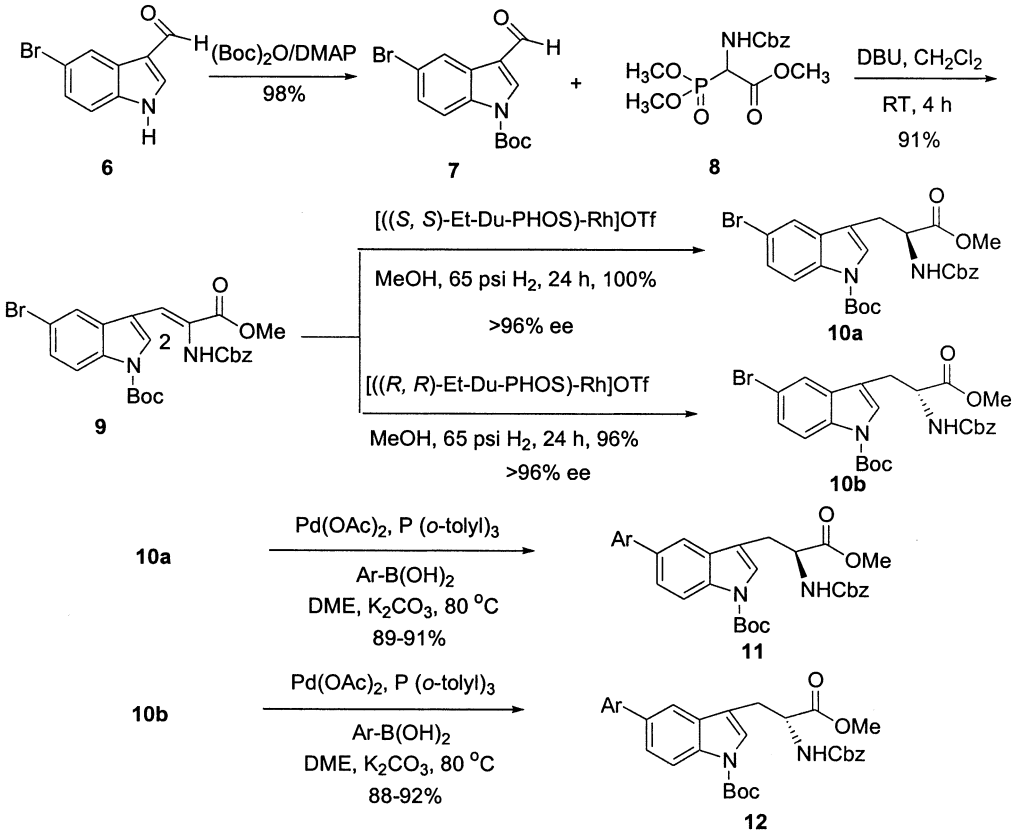


Scheme 1. Synthesis of 5-aryl-substituted tryptophan derivatives.

In these novel amino acids, the 2′-substituted phenylalanine derivatives **3** and **4** are of special interest since the χ^2 torsional angle can be efficiently restricted by the interaction between the aryl moiety and the β-hydrogens of the amino side chain (Fig. 2). Furthermore, some of the amino acids themselves are important biological compounds and synthetic intermediates.[4,5] Therefore, there is a need to develop an efficient method for the synthesis of such amino acids, particularly large-scale synthesis allowing for extensive structure–activity studies.

Our group has been long interested in the design and synthesis of unnatural amino acids,[6–8] and we have developed several methods for the synthesis of β-substituted constrained amino acids including tryptophan, phenylalanine, tyrosine, and glutamic acid derivatives.[9–15] Furthermore we have demonstrated that the incorporation of these unnatural amino acids into biologically active peptides and peptidomimetics can enhance the potency and selectivity significantly.[1,7,8,16–18] In a survey of literature, we were surprised to find, however, that few methods have been reported for the syntheses of aryl-substituted aromatic amino acids.[5,19–23] Herein we would like to report an efficient method for the asymmetric synthesis of both D and L aromatic substituted tryptophan and phenylalanine derivatives from readily available starting materials under very mild reaction conditions (Schemes 1, 3, and 4). The general strategy involves the asymmetric hydrogenation of α-enamides to generate functional α amino acids in high optical purity which serve as common intermediates from which a variety of substituted amino acid derivatives may be readily obtained through Suzuki-type cross couplings (Schemes 1, 3, and 4).

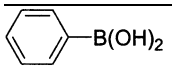
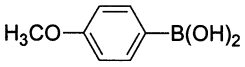
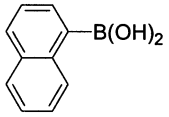
2. Results and discussion

2.1. Synthesis of 5-aryl tryptophan derivatives

A few methods have been reported for the synthesis of the aromatic substituted tryptophan analogues.[5,9–21] The synthetic approach used for the preparation of these unusual amino acids started with tryptophan. However, the route was somewhat lengthy and sometimes used harsh conditions.[5] Here we have developed an efficient method for the synthesis of these amino acids under very mild conditions, which allows for the preparation of both D and L 5-aryl tryptophan analogues from readily available starting materials (Scheme 1).

The synthesis of the 5-aryl substituted tryptophans started from commercially available 5-bromoindole-3-carboxaldehyde **6**. The indole amino group in the aldehyde was protected as Boc (*t*-butoxycarbonyl) using $(Boc)_2O$ (di-*t*-butyldicarbonate) in the presence of dimethylaminopyridine (DMAP) in 98% yield. Then the Horner–Emmons olefination of aldehyde **7** with phosphonate $(MeO)_2P(O)CH(NHCbz)COOMe$ **8** gave the dehydroamino acid derivative **9** with *Z*-configuration as a major product (*Z*/*E*>95/5) in 91% yield.[24] Compound **8** was synthesized in three steps following literature procedures.[25] The amino group in **8** was protected by Cbz (benzyloxycarbonyl), which was

Table 1. Suzuki cross coupling of **10** with aryl boronic acids

Boronic acids	Yields with **10a**	Yields with **10b**
	**11a**, 91%	**12a**, 89%
	**11b**, 90%	**12b**, 92%
	**11c**, 89%	**12c**, 88%

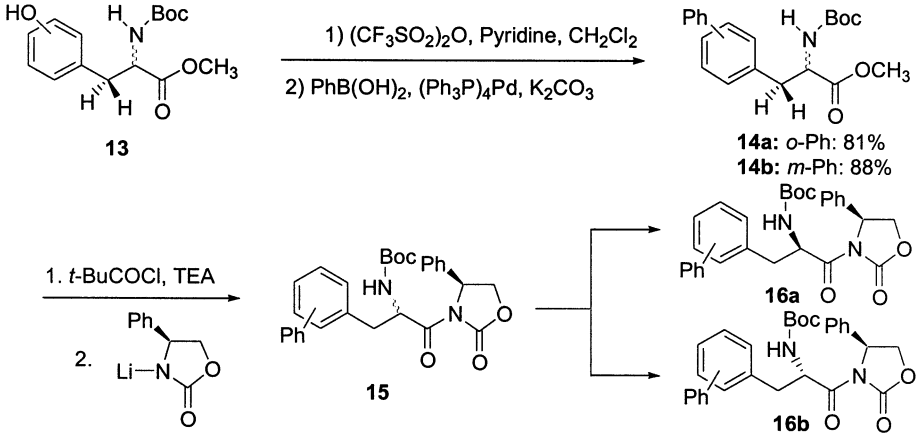
orthogonal to the Boc protected amino group in the indole ring of compound **7**. The dehydroamino ester **9** underwent asymmetric hydrogenations to give α-amino acid derivatives. We chose 1,2-bis ((2*S*,5*S*)/(2*R*,5*R*)-2,5-diethylphospholano)benzene(cyclooctadiene) rhodium (I) trifluoromethane sulfonate ((*S*,*S*)/(*R*,*R*) [Et-DuPHOS-Rh] OTf) as catalysts for the asymmetric hydrogenations since they give almost exclusively single enantiomers (>97% ee) in high yields (>95%).[26,27] The catalysts showed high efficiency (at a ratio of catalyst to substrate up to 1/2500)[27] and are commercially available.[28] Furthermore, both *Z* and *E* dehydroamino acids using this type of catalysts gave one single isomer.[27] In this case, we separated the two isomers (*Z* and *E*) by column chromatography. The isolated (*Z*)-dehydroamino acid ester **9** was used for asymmetric hydrogenations with a higher ee than that of (*E*) isomer. The (*S*,*S*) catalyst afforded the amino acid derivative **10a** with an absolute *S* configuration based on the selectivity of the (*S*,*S*)-Et-DuPHOS ligand in a high yield and high ee (>96%).[27] The (*R*) amino acid **10b** was also obtained using (*R*,*R*)-Et-DuPHOS as a ligand in a high yield and high ee as well. 5-Bromotryptophans **10** were subjected to Suzuki cross couplings with a variety of boronic acids to give amino acid derivatives **11** and **12** in 88–92% yields (Table 1). We have tried several Suzuki cross coupling reaction conditions and found the following reaction conditions to give the best yields without any racemization: 5 mol% $Pd(OAc)_2$ and 10 mol% tri(*o*-tolyl)phosphine as a catalyst, 1.5 equiv. boronic acid and 2.0 equiv. Na_2CO_3 in a mixture of ethylene glycol dimethyl ether (DME) and H_2O at 80°C for 3–4 h.[29] The enantiomeric purity was determined by the Mosher's agent[30] and the conversion of compound **11a** to 5-phenyl-L-tryptophan methyl ester, a known compound $[\alpha]_{24}^{D}=+42.6$ (*c* 1.06, MeOH), lit.[5] $[\alpha]_{25}^{D}=+42.4$ (*c* 1.24, MeOH), indicated that no racemization occurred during the cross couplings.

2.2. Synthesis of biphenylalanine derivatives

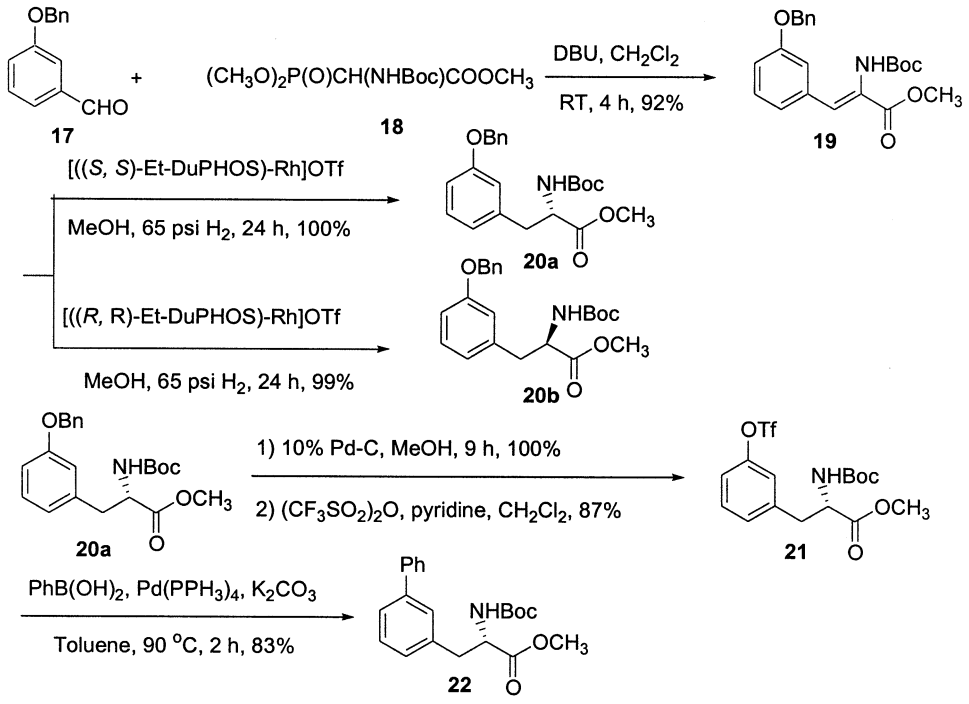
Earlier our laboratory developed an approach to the synthesis of unusual aromatic amino acids **16** using an Evans-type auxiliaryfor the resolution of racemic amino acids **15** (Scheme 2).[23,31] The synthesis started from N^{α}-Boc tyrosine derivatives **13** (some of the amino acids are commercially available), which were converted to tyrosine triflates with trifluoromethanesulfonic anhydride. The resulting tyrosine triflates were then coupled with arylboronic acids to give N^{α}-Boc amino acid methyl esters **16** in high yields (Scheme 2). However, the method involved more synthetic steps, and in some cases, multiple-step recrystallizations of the diastereomers were required to obtain optically pure forms. Using a similar synthetic strategy, Shieh and Carlson asymmetrically synthesized 4′-arylphenylalanines from N^{α}-Boc-(*S*)-tyrosine triflate in high optical purity (>99% ee).[22]

In our initial study, we applied a similar strategy for the synthesis of *m*-phenylphenylalanine derivative **22** (Scheme 3). The enantiopure (*R*) or (*S*) *m*-tyrosine derivatives **20a**, **b** were used as starting materials instead of racemic forms. They were prepared by asymmetric hydrogenations (Scheme 3).

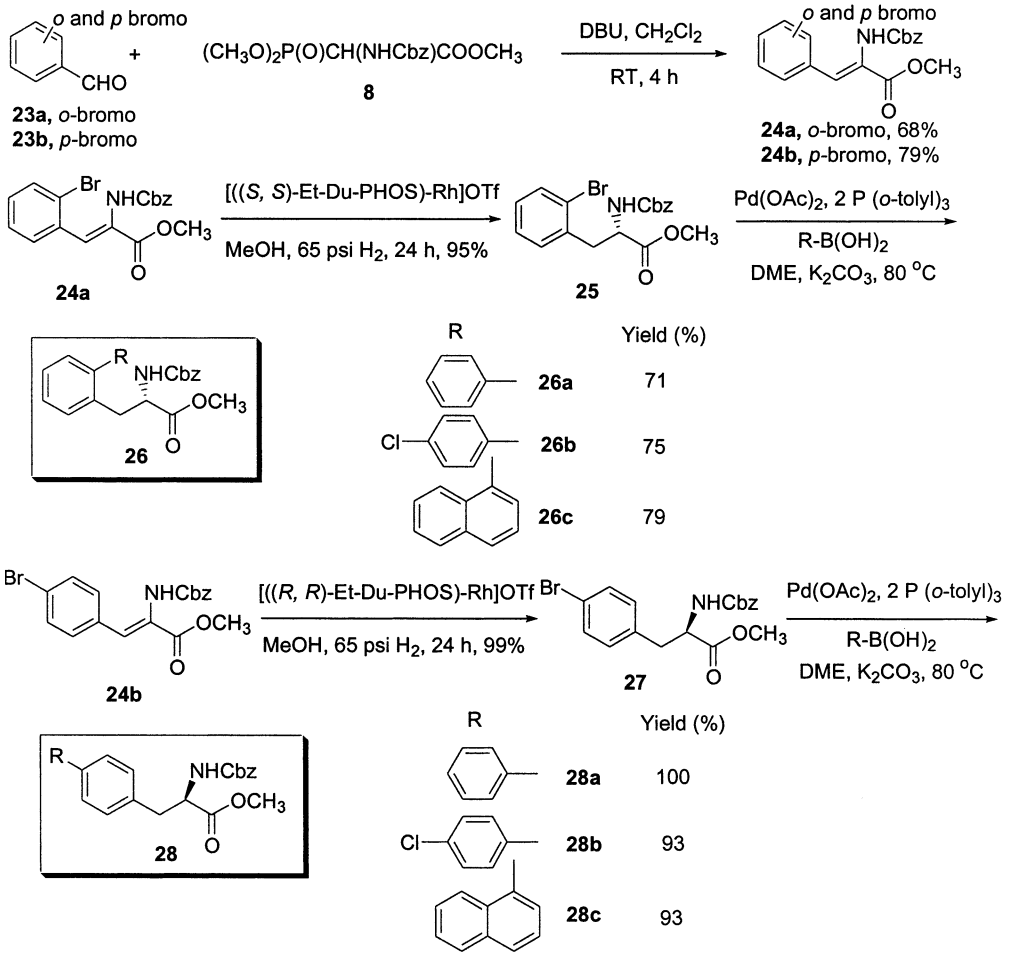
Commercially available 3-benzyloxybenzaldehyde **17** was reacted with phosphonate $(MeO)_2P(O)CHNH(Boc)COOMe$ **18** in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base to give the dehydroamino acid derivative **19** with >95/5 ratio of *Z*/*E* isomers in 92% yield. The amino group in **18** was protected as Boc, which was orthogonal to the benzyl-protected phenol hydroxyl group in **17**. (*S*) and (*R*) amino acid esters **20** were obtained via asymmetric hydrogenations of the isolated (*Z*) isomer **19** using (*S*,*S*) or (*R*,*R*) [Et-DuPHOS-Rh (I)] OTf, respectively, in high yields and high ee.[27] The benzyl protecting group in **20a** was cleaved by Pd-catalyzed hydrogenation, and then the resulting free hydroxyl group was acylated with trifluoromethanesulfonic anhydride to afford N^{α}-Boc-(*S*)-tyrosine



Scheme 2. Synthesis of *o* and *m* biphenylalanines.



Scheme 3. Synthesis of *m*-biphenylalanine.



Scheme 4. Synthesis of *o* and *p* aromatic substituted phenylalanine derivatives.

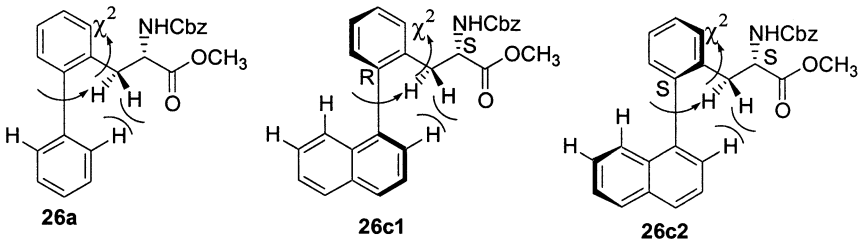


Figure 3.

triflate **21** in 87% yield, a precursor for the Suzuki coupling. The final product, *m*-phenylphenylalanine derivative **22** was obtained by reacting the triflate **21** with phenylboronic acid in 83% yield under the heterogeneous conditions of 3 mol% $Pd(PPh_3)_4$ and anhydrous K_2CO_3 in toluene at 90°C for 2 h following the literature procedure.[22] No detectable racemization of the starting N^{α}-Boc-(*S*)-tyrosine triflate **13** or product *m*-phenylphenylalanine **22** was observed in the reaction under these reaction conditions.[22]

We synthesized *m*-phenylphenylalanine **22** by coupling N^{α}-Boc-(*S*)-tyrosine triflate **21** with phenylboronic acid. However, by using bromo-substituted (*o* and *p*) phenylalanine derivatives rather than tyrosine triflates, we can synthesize aromatic substituted phenylalanines in two fewer steps. Therefore, we prepared enantiometrically pure (*S*) and (*R*)-N^{α}-Cbz methyl esters of *o* and *p*-bromophenylalanines **25** and **27**, respectively, which subsequently were employed in Sukuzi-type cross coupling reactions with a variety of boronic acid derivatives (Scheme 4). It should be mentioned that Burk and co-workers recently reported a similar strategy for the synthesis of such amino acids.[29] In their approach, the α-amino groups of amino acids were protected with an acetyl group, which generally is cleaved under rather harsh acidic hydrolysis conditions. In certain cases, significant racemization occurred during the hydrolysis step.[29] Therefore in our approach, we used Cbz as a protecting group, which is easily removed under mild conditions by Pd-catalyzed hydrogenations without causing racemization.

The isolated (*Z*) α-enamides **24a** and **24b** were obtained as major products by the condensation of *o*-bromo and *p*-bromo benzaldehydes **23a** and **23b**, respectively with **8** in the presence of DBU in CH_2Cl_2 in 68 and 79% yields, respectively. Asymmetric hydrogenation of α-enamides **24a** and **24b** in the presence of 5 mol% catalysts, Rh(I)-(*S*,*S*)-Et-DuPHOS or Rh(I)-(*R*,*R*)-Et-DuPHOS,[27] 65 psi of H_2, 24 h in methanol gave N^{α}-Cbz-(*S*)-*o*-bromophenylalanine methyl ester **25** in 95% yield and N^{α}-Cbz-(*R*)-*p*-bromophenylalanine methyl ester **27** in 99% yield and >96% ee in both cases, respectively. The bromophenylalanines **25** and **27** were reacted with various boronic acids through the Suzuki cross coupling reactions. We employed the same coupling reaction conditions as used before in high yields, and no racemization occurred.[32] A longer reaction time (6–10 h) was required for *o*-bromophenylalanine and naphthylboronic acid couplings and the yields were lower than those of *p*-bromophenylalanine.

As mentioned earlier, we are particularly interested in *o*-aromatic substituted phenylalanine derivatives (Fig. 2). The side chain conformations of these *o*-aromatic substituted phenylalanine amino acids can be restricted due to the interaction between the aryl moieties and the β-hydrogens of amino side chain. In the preliminary studies of compounds **26** using ^{1}H NMR (Fig. 3), we found that the *o*-phenyl group in **26a** rotated freely, indicating that the interaction between the phenyl moiety and the β-hydrogen's of amino side chain was small. However, a larger naphthyl group resulted in two isomers in **26c**, detected by ^{1}H NMR with two groups of proton signals. The ratio was about 1/1 based on integrations of ^{1}H NMR spectra. We assumed the two isomers with (*S*,*S*) and (*S*,*R*) configurations, respectively (Fig. 3). The naphthyl groups in **26c** were away from the two β-hydrogens of amino side chain to reduce steric hindrance. Similar interactions in *m* and *p*-substituted naphthyl phenylalanine analogues **22** and **28** were not observed. The detailed conformation studies of these amino acids including the more steric 1-(1-naphthyl)-2-naphthylalanine **5** (Fig. 2) will be reported in due course based on X-ray crystal structures, NMR, and computer modeling. It is also realized that these conformationally constrained amino acids carrying fluorophores are very useful in structure–activity studies of peptides and receptors.

3. Conclusion

An efficient method has been developed for the synthesis of aromatic-substituted phenylalanine and tryptophan derivatives. These amino acids were synthesized through asymmetric hydrogenations using Burk's DuPHOS-based catalysts with high ee (>96%), followed by Suzuki crossing couplings also in high yields. The method can be easily scaled up for the synthesis of a large amount of these amino acids. We have synthesized multi-grams of some of these amino acids. The incorporation of the amino acids into biologically active peptides and peptidomimetics, biological evaluation, and structure–biological activity relationship study of the peptides and peptidomimetics are in progress.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR were performed on a Varian Unity-300 and Brukers AM-250 and DRX-500 and 600 spectrometers using TMS and $CDCl_3$ as internal standards. High Resolution Mass Spectra (HRMS) were recorded on a JEOL HX110A instrument in the University of Arizona Mass

Spectrum Laboratory. Optical rotations were measured on a JASCO-1020 polarimeter. Melting points (mp) are uncorrected and were obtained on a Thomas–Hoover apparatus in open capillaries. Commercially available starting materials and reagents were purchased from Aldrich used as received. THF was distilled from Na and benzophenone; methylene chloride (CH_2Cl_2) was distilled from CaH_2; HPLC grade methanol was used for hydrogenations. Column chromatography was performed using silica gel (230–400 mesh) from EM science. Thin layer chromatography (TLC) was performed on 13181 silica gel-based sheet with fluorescent indicator from Kodak. Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as estimated by ^1H and ^{13}C NMR spectroscopy. All new compounds were characterized by ^1H, ^{13}C, and HRMS or elemental analysis.

4.1.1. 1-(*tert*-Butoxycarbonyl)-5-bromo-indol-3-carboxaldehyde 7. To a solution of 5-bromo-indole-3-carboxaldehyde **6** (3.36 g, 15 mmol) in dry CH_2Cl_2 (30 mL) was added di-*t*-butyldicarbonate (4.58 g, 21 mmol). The mixture was stirred at RT for 4 h. Evaporation of the solvent followed by flash column chromatography, eluting with ethyl acetate/hexanes (1/5) to give a white solid (4.74 g, 98%). Mp 162–163°C; ^1H NMR (500 MHz, $CDCl_3$) δ 10.07 (1H, s), 8.46 (1H, d, J=1.5 Hz), 8.22 (1H, s), 8.03 (1H, d, J=7.0 Hz), 7.52 (1H, dd, J_1=1.5 Hz, J_2=7.0 Hz), 1.71 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.5, 148.6, 137.1, 134.8, 129.2, 127.8, 125.0, 120.8, 118.4, 116.8, 86.4, 28.3; HRMS (FAB) calcd for $C_{14}H_{15}BrNO_3$ 324.0235 (Br 79), 326.0216 (Br 81), found 324.0238 (Br 79), 326.0206 (Br 81).

4.1.2. Methyl (*Z*)-2-(benzyloxycarbonyl)amino-3-[(1-*tert*-butoxycarbonyl-5-bromo)indol] acrylate 9. To a solution of $(MeO)_2P(O)CH(NHCbz)COOMe$ **8** (5.25 g, 15.85 mmol) in 10 mL of dry CH_2Cl_2 under an argon atmosphere was added DBU (2.2 mL, 14.53 mmol). After 10 min stirring, compound **7** (4.28 g, 13.21 mmol) in 10 mL of dry CH_2Cl_2 was added slowly. After the reaction mixture was stirred for 5 h, the solvent was evaporated under reduced pressure. The residue was dissolved in 250 mL of ethyl acetate, then the organic solution was washed with 1N HCl (2×80 mL) and brine (80 mL), dried ($MgSO_4$), and evaporated. The crude product was purified by flash column chromatography (ethyl acetate/hexanes: 1/5) to give a white solid. The solid was recrystallized from ethyl acetate and hexanes to give a white crystal (6.37 g, 91%). Mp 146–148°C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (1H, d, J=8.7 Hz), 7.91 (1H, s), 7.83 (1H, d, J=1.5 Hz), 7.55 (1H, s), 7.44 (1H, dd, J_1=1.5 Hz, J_2=8.7 Hz), 7.32–7.36 (5H, m), 6.45 (brs, 1H), 5.14 (2H, s), 3.84 (3H, s), 1.64 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 153.9, 148.9, 135.9, 133.8, 131.2, 128.7, 128.5, 128.3, 128.2, 127.8, 127.1, 123.8, 123.1, 122.1, 117.0, 113.6, 85.2, 67.8, 52.9, 28.3; HRMS (FAB) calcd for $C_{25}H_{26}BrN_2O_6$ 529.0974 (Br 79), 531.0958 (Br 81), found 529.0985 (Br 79), 531.0941 (Br 81).

4.1.3. (*S*) 5-Bromo-1-*tert*-butoxycarbonyl-N^{α}-benzyloxycarbonyl-tryptophan methyl ester 10a. A hydrogenation bottle charged with **9** (2.116 g, 4.0 mmol) in degassed methanol (30 mL) was purged by argon for about 30 min, followed by adding (*S*,*S*) (COD) Et-DuPHOS Rh (I) OTf (6.0 mg, 0.008 mmol). After five vacuum/hydrogen cycles, the reaction bottle was pressurized to an initial pressure of 65 psi. The reaction was allowed to proceed for 24 h. After the evaporation of solvent, the crude produce was passed through a short silica gel column, eluting with methylene chloride/ethyl acetate (4/1) to remove the catalyst. The removal of the solvent afforded a white solid (2.121 g, 100%). $[\alpha]_D^{25}$=+43.4 (*c* 1.48, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.98 (1H, brs), 7.61 (1H, brs), 7.30–7.41 (7H, m), 5.40 (1H, d, J=7.8 Hz), 5.13 (2H, dd, J_1=12.6 Hz, J_2=18.0 Hz), 4.71 (1H, dd, J_1=5.4 Hz, J_2=12.6 Hz), 3.72 (3H, s), 3.25 (1H, dd, J_1=5.4 Hz, J_2=12.6 Hz), 3.19 (1H, dd, J_1=5.4 Hz, J_2=12.6 Hz), 1.66 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 155.8, 149.3, 136.3, 134.2, 132.3, 128.7, 128.4, 128.3, 127.6, 125.5, 121.8, 117.0, 116.2, 114.3, 84.4, 67.3, 60.6, 54.1, 52.7, 28.3; HRMS (FAB) calcd for $C_{25}H_{27}BrN_2O_6$ 530.1052, (Br 79), 532.1036 (Br 81), found 530.1052 (Br 79), 530.1057 (Br 81).

4.2. General procedures for palladium-catalyzed Suzuki coupling reactions

A reaction flask fitted with a Teflon valve was charged with bromoarylalanine derivatives, boronic acid (1.5 equiv.), Na_2CO_3 (2.0 equiv.), $Pd(OAc)_2$ (5 mol%), P(*o*-tolyl)$_3$ (10 mol%), DME (6 mL/mmol), degassed water (1 mL/mmol) was heated to 80°C for 4–6 h. The reaction mixture was passed through a short column containing a bottom 1″ layer of silica gel (230–400 mesh) and a top 1″ layer of $NaHCO_3$ using ethyl acetate as eluent. The solvent was removed under reduced pressure with a rotary evaporator. The crude product was purified by flash column chromatography using an appropriate mixture of ethyl acetate and hexanes as eluent.

4.2.1. (*S*) 1-*tert*-Butoxycarbonyl-5-phenyl-N^{α}-benzyloxycarbonyl-tryptophan methyl ester 11a. 91% Yield, $[\alpha]_D^{22}$=+22.5 (*c* 1.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, J=8.4 Hz), 7.63–7.69 (3H, m), 7.56 (1H, dd, J_1=1.5 Hz, J_2=8.4 Hz), 7.40–7.45 (3H, m), 7.24–7.35 (6H, m), 5.43 (1H, d, J=8.1 Hz), 5.07 (2H, dd, J_1=12.3 Hz, J_2=31.5 Hz), 4.77 (1H, dd, J_1=5.7 Hz, J_2=13.5 Hz), 3.67 (3H, s), 3.34 (1H, dd, J_1=5.1 Hz, J_2=14.7 Hz), 3.26 (1H, dd, J_1=5.7 Hz, J_2=14.7 Hz), 1.67 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 171.3, 155.8, 149.6, 141.7, 136.2, 134.9, 131.2, 128.9, 128.7, 128.3, 128.2, 127.5, 127.1, 124.9, 124.3, 17.5, 115.7, 115.3, 84.0, 67.3, 60.6, 54.4, 52.6, 28.4; HRMS (FAB) calcd for $C_{31}H_{32}N_2O_6$ 528.2260, found 528.2246.

4.2.2. (*S*) 1-*tert*-Butoxycarbonyl-5-(*p*-methoxyphenyl)-N^{α}-benzyloxycarbonyl-tryptophan methyl ester 11b. 90% Yield, $[\alpha]_D^{24}$=+20.5 (*c* 1.72, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (1H, d, J=8.1 Hz), 7.63 (1H, brs), 7.54–7.58 (2H, m), 7.51 (1H, dd, J_1=1.8 Hz, J_2=8.7 Hz), 7.41 (1H, s), 7.28–7.30 (5H, m), 6.95 (2H, d, J=8.4 Hz), 5.41 (1H, d, J=8.1 Hz), 5.08 (2H, dd, J_1=12.3 Hz, J_2=27.3 Hz), 4.76 (1H, dd, J_1=5.4 Hz, J_2=13.2 Hz), 3.84 (3H, s), 3.67 (3H, s), 3.33 (1H, dd, J_1=5.4 Hz, J_2=14.7 Hz), 3.25 (1H, dd, J_1=5.7 Hz, J_2=14.7 Hz), 1.67 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 159.1, 155.9, 149.7,

136.2, 135.9, 134.6, 134.3, 131.2, 128.7, 128.4, 128.3, 128.2, 124.9, 124.0, 117.0, 115.7, 115.2, 114.4, 84.0, 67.3, 60.6, 55.6, 54.4, 52.7, 28.4; HRMS (FAB) calcd for $C_{32}H_{34}N_2O_7$ 558.2366, found 558.2370.

4.2.3. (*S*)-1-*tert*-Butoxycarbonyl-5-(1-naphthyl)-N^{α}-benzyloxycarbonyl-tryptophan methyl ester 11c. 89% Yield, $[\alpha]_D^{22}=+36.9$ (*c* 0.73, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (1H, d, *J*=8.1 Hz), 7.84–7.91 (3H, m), 7.57 (1H, s), 7.35–7.51 (5H, m), 7.23–7.27 (5H, m), 5.41 (1H, d, *J*=8.1 Hz), 5.00 (2H, dd, J_1=12.6 Hz, J_2=42.3 Hz), 4.72 (1H, dd, J_1=5.4 Hz, J_2=12.9 Hz), 3.63 (3H, s), 3.31 (1H, dd, J_1=5.4 Hz, J_2=14.7 Hz), 3.22 (1H, dd, J_1=5.7 Hz, J_2=14.7 Hz), 1.69 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 155.9, 149.7, 140.6, 136.3, 135.5, 134.8, 133.9, 132.1, 130.8, 128.7, 128.4, 128.3, 128.1, 127.7, 127.3, 127.1, 126.3, 126.2, 125.9, 125.5, 125.0, 120.3, 115.1, 115.0, 84.1, 67.2, 60.6, 54.3, 52.6, 28.4; HRMS (FAB) calcd for $C_{35}H_{34}N_2O_6$ 578.2417, found 578.2412.

4.2.4. (*R*)-5-Bromo-1-*tert*-butoxycarbonyl-N^{α}-benzyloxycarbonyl-tryptophan methyl ester 10b. In a manner similar to the preparation of **10a**, compound **9** with (*R*,*R*) (COD)-Et-DuPHOS Rh (I) OTf as a catalyst provided **10b** in a 96% yield. $[\alpha]_D^{25}=-42.2$ (*c* 1.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (1H, brs), 7.60 (1H, s), 7.39 (1H, dd, J_1=1.8 Hz, J_2=9.0 Hz), 7.29–7.36 (6H, m), 5.38 (1H, d, *J*=7.8 Hz), 5.13 (2H, dd, J_1=12.6 Hz, J_2=18.0 Hz), 4.71 (1H, dd, J_1=5.4 Hz, J_2=12.6 Hz), 3.72 (3H, s), 3.24 (1H, dd, J_1=5.4 Hz, J_2=15.0 Hz), 3.18 (1H, dd, J_1=5.4 Hz, J_2=15.0 Hz), 1.65 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 155.8, 149.3, 136.3, 134.2, 132.4, 128.7, 128.4, 128.3, 127.6, 125.5, 121.8, 117.0, 116.2, 114.3, 84.4, 67.4, 60.6, 54.1, 52.7, 28.3; HRMS (FAB) calcd for $C_{25}H_{27}BrN_2O_6$ 530.1052 (Br 79), 532.1036 (Br 81), found 530.1046 (Br 79), 532.1021 (Br 81).

4.2.5. (*R*)-1-*tert*-Butoxycarbonyl-5-phenyl-N^{α}-benzyloxycarbonyl-tryptophan methyl ester 12a. 89% Yield, $[\alpha]_D^{23}=-22.2$ (*c* 1.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, *J*=8.1 Hz), 7.55–7.69 (4H, m), 7.40–7.45 (3H, m), 7.24–7.35 (6H, m), 5.42 (1H, d, *J*=7.8 Hz), 5.07 (2H, dd, J_1=12.0 Hz, J_2=31.5 Hz), 4.77 (1H, dd, J_1=5.4 Hz, J_2=12.9 Hz), 3.67 (3H, s), 3.34 (1H, dd, J_1=5.1 Hz, J_2=15.0 Hz), 3.26 (1H, dd, J_1=5.4 Hz, J_2=15.0 Hz), 1.67 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 171.3, 155.9, 149.6, 141.7, 136.2, 134.9, 131.2, 128.9, 128.7, 128.3, 128.2, 127.5, 127.1, 124.9, 124.3, 117.5, 115.7, 115.2, 84.1, 67.3, 60.5, 54.4, 52.6, 28.4; HRMS (FAB) calcd for $C_{31}H_{32}N_2O_6$ 528.2260, found 528.2274.

4.2.6. (*R*)1-*tert*-Butoxycarbonyl-5-(*p*-methoxyphenyl)-N^{α}-benzyloxycarbonyl-tryptophan methyl ester 12b. 92% Yield, $[\alpha]_D^{24}=-20.2$ (*c* 1.46, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (1H, d, *J*=8.1 Hz), 7.63 (1H, s), 7.56 (2H, d, *J*=8.7 Hz), 7.51 (1H, dd, J_1=1.2 Hz, J_2=8.7 Hz), 7.41 (1H, s), 7.25–7.29 (5H, m), 6.95 (2H, d, *J*=8.7 Hz), 5.42 (1H, d, *J*=8.1 Hz), 5.07 (2H, dd, J_1=12.3 Hz, J_2=30.0 Hz), 4.76 (1H, dd, J_1=5.4 Hz, J_2=13.2 Hz), 3.84 (3H, s), 3.67 (3H, s), 3.33 (1H, dd, J_1=5.4 Hz, J_2=15.0 Hz), 3.25 (1H, dd, J_1=6.0 Hz, J_2=15.0 Hz), 1.67 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 159.1, 155.9, 149.7, 136.2, 135.9, 134.6, 134.2, 131.2, 128.7, 128.4, 128.3, 128.2, 124.9, 124.0, 117.0, 115.6, 115.2, 114.4, 84.0, 67.3, 60.4, 55.6, 54.4, 52.7, 28.4; HRMS (FAB) calcd for $C_{32}H_{34}N_2O_7$ 558.2366, found 558.2380.

4.2.7. (*R*)-1-*tert*-Butoxycarbonyl-5-(1-naphthyl)-N^{α}-benzyloxycarbonyl-tryptophan methyl ester 12c. 88% Yield, $[\alpha]_D^{22}=-36.5$ (*c* 1.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.20 (1H, d, *J*=8.1 Hz), 7.84–7.92 (3H, m), 7.57 (1H, s), 7.36–7.51 (6H, m), 7.25–7.28 (5H, m), 5.38 (1H, d, *J*=8.1 Hz), 5.01 (2H, dd, J_1=12.0 Hz, J_2=43.2 Hz), 4.73 (1H, dd, J_1=5.7 Hz, J_2=13.2 Hz), 3.64 (3H, s), 3.31 (1H, dd, J_1=5.1 Hz, J_2=14.7 Hz), 3.23 (1H, dd, J_1=5.7 Hz, J_2=14.7 Hz), 1.70 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 155.9, 149.8, 140.7, 136.3, 135.6, 134.8, 134.0, 132.2, 130.8, 128.7, 128.4, 128.3, 128.2, 127.7, 127.4, 127.1, 126.4, 126.2, 125.9, 125.5, 125.0, 120.3, 115.2, 115.1, 84.1, 67.2, 60.6, 54.3, 52.7, 28.4; HRMS (FAB) calcd for $C_{35}H_{34}N_2O_6$ 578.2417, found 578.2412.

4.2.8. Methyl (*Z*)-2-(*tert*-butoxycarbonyl)amino-3-[(3-benzyloxy)phenyl]acrylate 19. To a solution of $(MeO)_2CH$ (NHBoc)COOMe **18** (3.27 g, 11 mmol) in 20 mL of dry methylene chloride was added DBU (1.65 mL, 11 mmol) slowly under an argon atmosphere with stirring. After ca. 10 min, *m*-benzyloxybenzaldehyde **17** (2.12 g, 10 mmol) was added slowly to the above mixture. After 4 h, the solvent was evaporated and the residue was dissolved in 180 mL of ethyl acetate. The organic solution was washed with 1N HCl (40 mL) and brine (45 mL), dried over ($MgSO_4$) and evaporated. The crude product was purified by flash column chromatography on silica gel, eluting with ethyl acetate and hexanes (1/6) to give a white solid (3.52 g, 92%). Mp 10–102°C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.12–7.44 (9H, m), 6.93 (1H, dd, J_1=2.4 Hz, J_2=8.1 Hz), 6.19 (1H, brs), 5.05 (2H, s), 3.84 (3H, s), 1.40 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 158.9, 152.9, 136.9, 135.6, 129.9, 129.7, 128.8, 128.2, 127.7, 125.0, 122.7, 116.1, 115.9, 81.2, 70.2, 52.8, 28.3; HRMS (FAB) calcd for $C_{22}H_{26}NO_5$ 384.1811, found 384.1807; Anal. calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 69.18; H, 6.49; N, 3.76.

4.2.9. (*S*)-N^{α}-*tert*-Butoxycarbonyl-*m*-(3-benzyloxy)phenylalanine methyl ester 20a. A hydrogenation bottle charged with **19** (1.53 g, 3.13 mmol) in degassed methanol (20 mL) was purged by argon for about 30 min, followed by adding catalyst (*S*,*S*) (COD) Et-DuPHOS Rh (I) OTf (4.5 mg, 0.0063 mmol). After five vacuum/hydrogen cycles, the reaction bottle was pressurized to an initial pressure of 65 psi. The reaction was allowed to proceed for 24 h. After evaporation of the solvent, the crude product was passed through a short silica gel column, eluting with methylene chloride/ethyl acetate (4/1) to remove the catalyst. The removal of the solvent afforded a white solid (1.538 g, 100%). Mp 80.0–82.0°C; $[\alpha]_D^{25}=+39.1$ (*c* 1.21, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.44 (5H, m), 7.18–7.26 (1H, m), 6.84–6.88 (1H, m), 6.72–6.76 (2H, m), 5.04 (2H, s), 4.98 (1H, d, *J*=8.1 Hz), 4.58 (1H, dd, J_1=6.0 Hz, J_2=13.8 Hz), 3.70 (3H, s), 3.09 (1H, dd, J_1=6.0 Hz, J_2=13.8 Hz), 3.02 (1H, dd, J_1=6.0 Hz, J_2=

13.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 159.1, 155.3, 137.8, 137.1, 129.8, 128.8, 128.2, 127.7, 122.1, 116.1, 113.5, 80.2, 70.1, 54.5, 52.4, 38.5, 28.6; HRMS (FAB) calcd for $C_{22}H_{28}NO_5$ 386.1967, found 386.1974; Anal. calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.53; H, 7.01; N, 3.61.

4.2.10. (*R*)-*N*$^{\alpha}$-*tert*-Butoxycarbonyl-*m*-(3-benzyloxy)-phenylalanine methyl ester 20b. In a manner similar to the preparation of **20a**, compound **19** with (*R*,*R*) (COD)-Et-DuPHOS Rh (I) OTf as a catalyst provided **20b** in 99% yield. Mp 80.5–82.0°C; $[\alpha]_D^{25}=-38.5$ (*c* 1.21, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.45 (5H, m), 7.18–7.27 (1H, m), 6.84–6.88 (1H, m), 6.72–6.76 (2H, m), 5.03 (2H, s), 4.98 (1H, d, J=8.1 Hz), 4.58 (1H, dd, J_1=5.7 Hz, J_2=13.8 Hz), 3.70 (3H, s), 3.09 (1H, dd, J_1=5.7 Hz, J_2=13.8 Hz), 3.04 (1H, dd, J_1=5.7 Hz, J_2=13.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 159.1, 155.3, 137.8, 137.1, 129.8, 128.8, 128.2, 127.7, 122.1, 116.1, 113.5, 80.1, 70.1, 54.5, 52.4, 38.5, 28.5; HRMS (FAB) calcd for $C_{22}H_{28}NO_5$ 386.1967, found 386.1960; Anal. calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.71; H, 7.31; N, 3.61.

4.2.11. (*S*)-*N*$^{\alpha}$-*tert*-Butoxycarbonyl-*m*-tyrosine methyl ester. A mixture of **20a** (1.26 g, 3.27 mmol) and 10% Pd–C (100 mg) in 20 mL of HPLC grade methanol was hydrogenated under a hydrogen atmosphere at 60 psi for 9 h. After the removal of the catalyst by filtration, the evaporation of the solvent gave a clear oil (0.94 g, 99%). $[\alpha]_D^{25}=+34.2$ (*c* 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12–7.17 (1H, m), 6.64–6.75 (3H, m), 5.07 (1H, d, J=8.1 Hz), 4.57 (1H, dd, J_1=6.0 Hz, J_2=13.8 Hz), 3.71 (3H, s), 3.05 (1H, dd, J_1=6.0 Hz, J_2=13.8 Hz), 2.97 (1H, dd, J_1=6.6 Hz, J_2=13.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 156.4, 155.6, 137.7, 129.9, 121.4, 116.3, 114.4, 80.5, 54.5, 52.5, 38.4, 28.5; HRMS (FAB) calcd for $C_{15}H_{22}NO_5$ 296.1498, found 296.1492.

4.2.12. (*S*)-*N*$^{\alpha}$-*tert*-Butoxycarbonyl-*m*-{[(trifluoromethyl)-sulfonyl]oxy}phenylalanine methyl ester 21. A solution of the above tyrosine derivative (0.93 g, 3.15 mmol) and pyridine (1.27 mL, 15.57 mmol) in 5 mL of dry methylene chloride was cooled to 0°C. $(CF_3SO_2)_2O$ (0.64 mL, 3.78 mol) was added at this temperature, and the reaction mixture was stirred for another 30 min. The reaction mixture was diluted with water (10 mL) and methylene chloride (50 mL) and washed sequentially with 0.5N NaOH solution (8 mL), water (10 mL), 5% citric acid (2×15 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and evaporated to give an oil. The crude product was purified by flash column chromatography (ethyl acetate/hexanes: 1/5) to afford a slightly yellow oil (1.25 g, 93%). $[\alpha]_D^{26}=+42.3$ (*c* 1.70, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.41 (2H, m), 7.15–7.19 (2H, m), 7.05 (1H, s), 5.04 (1H, d, J=8.1 Hz), 4.61 (1H, dd, J_1=5.7 Hz, J_2=13.8 Hz), 3.73 (3H, s), 3.20 (1H, dd, J_1=5.7 Hz, J_2=13.8 Hz), 3.09 (1H, dd, J_1=5.7 Hz, J_2=13.8 Hz), 1.43 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 155.1, 149.7, 139.4, 130.4, 129.6, 122.5, 120.1, 118.9 (q, $J_{c,f}$=318.5 Hz), 80.4, 54.3, 52.7, 38.2, 28.4; HRMS (FAB) calcd for $C_{16}H_{22}F_3NO_7S$ 428.0991, found 428.1006.

4.2.13. (*S*)-*N*$^{\alpha}$-*tert*-Butoxycarbonyl-*m*-(phenyl)phenylalanine methyl ester 22. Argon was passed through a suspension of triflate **21** (415 mg, 0.97 mmol), phenylboronic acid (177 mg, 1.46 mmol) and K_2CO_3 (268 mg, 1.94 mmol) in toluene (15 mL) for 15 min $Pd(PPh_3)_4$ (56 mg, 0.049 mmol) was added and the reaction mixture was heated at 90°C for 2 h. The reaction mixture was passed through a short column containing a bottom 1″ layer of silica gel (230–400 mesh) and a top 1″ layer of $NaHCO_3$ using ethyl acetate as eluent. The solvent was removed under reduced pressure with a rotary evaporator. The crude product was purified by flash column chromatography using ethyl acetate and hexanes (1/8) as eluent to give a white solid (287 mg, 83%). Mp 85–87°C; $[\alpha]_D^{26}=+49.7$ (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.58 (8H, m), 7.11 (1H, d, J=7.5 Hz), 5.02 (1H, d, J=7.8 Hz), 4.64 (1H, dd, J_1=6.0 Hz, J_2=13.8 Hz), 3.20 (1H, dd, J_1=5.7 Hz, J_2=13.8 Hz), 3.11 (1H, dd, J_1=6.0 Hz, J_2=13.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 155.2, 141.6, 141.1, 136.7, 129.2, 128.9, 128.4, 128.3, 127.5, 127.3, 126.1, 80.2, 54.6, 52.5, 38.6, 28.5; HRMS (FAB) calcd for $C_{21}H_{26}NO_4$ 356.1862, found 356.1860.

4.2.14. Methyl (*Z*)-2-(benzyloxycarbonyl)amino-3-(*o*-bromophenyl)acrylate 24a. To a solution of $(MeO)_2CH(NHCbz)COOMe$ **8** (1.98 g, 6 mmol) in 15 mL of dry methylene chloride was added DBU (0.9 mL, 6 mmol) slowly under an argon atmosphere with stirring. After ca. 10 min, *o*-bromobenzaldehyde **23a** (0.93 g, 5 mmol) was added slowly into the above mixture. After 4 h, the solvent was evaporated, and the residue was dissolved in 120 mL of ethyl acetate. The organic solution was washed with 1N HCl (30 mL) and brine (30 mL), dried over $MgSO_4$ and evaporated. The crude product was purified by flash column chromatography, eluting with ethyl acetate and hexanes (1/6) to give an oil (1.33 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13–7.61 (10H, m), 6.44 (1H, s), 5.04 (2H, s), 3.85 (3H, s); ^{13}C NMR δ (75 MHz, $CDCl_3$) δ 165.4, 153.4, 135.9, 134.7, 133.1, 130.3, 129.6, 128.7, 128.6, 128.5, 128.4, 127.4, 126.1, 124.7, 67.7, 53.1; HRMS (FAB) calcd for $C_{18}H_{17}BrNO_4$ 390.0341 (Br 79), 392.0323 (Br 81), found 390.0340 (Br 79), 392.0330 (Br 81).

4.2.15. (*S*)-*N*$^{\alpha}$-Benzyloxycarbonyl-*o*-bromophenylalanine methyl ester 25. A hydrogenation bottle charged with **24a** (1.26 g, 2.33 mmol) in degassed methanol (20 mL) was purged with argon for about 30 min, followed by adding (*S*,*S*) (COD) Et-DuPHOS Rh (I) OTf 2.3 mg, 0.0065 mmol). After five vacuum/hydrogen cycles, the reaction bottle was pressurized to an initial pressure of 65 psi. The reaction was allowed for 24 h. After the evaporation of solvent, the crude produce was passed through a short silica gel column, eluting with methylene chloride/ethyl acetate (4/1) to remove the catalyst. The removal of the solvent afforded a white solid (1.213 g, 95%). Mp 81.5–83.5°C; $[\alpha]_D^{26}=+3.9$ (*c* 1.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, d, J=7.8 Hz), 7.07–7.34 (8H, m), 5.32 (1H, d, J=8.1 Hz), 5.06 (2H, s), 4.72 (1H, dd, J_1=8.1 Hz, J_2=13.8 Hz), 3.72 (3H, s), 3.33 (1H, dd, J_1=6.0 Hz, J_2=13.8 Hz), 3.15 (1H, dd, J_1=8.1 Hz, J_2=13.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 155.8, 136.4, 135.9, 133.2, 131.5, 129.0, 128.7, 128.3, 128.2,

127.7, 125.2, 67.1, 54.2, 52.7, 38.7; HRMS (FAB) calcd for $C_{18}H_{19}BrNO_4$ 392.0497 (Br 79), 394.0479 (Br 81), found 392.0486 (Br 79), 394.0485 (Br 81).

4.2.16. (*S*)-*N*$^{\alpha}$-Benzyloxycarbonyl-*o*-(phenyl)phenylalanine methyl ester 26a. 71% Yield, $[\alpha]_D^{26}=+16.0$ (*c* 1.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–7.41 (14H, m), 4.98 (2H, dd, J_1=12.3 Hz, J_2=21.6 Hz), 4.79 (1H, d, J=11.1 Hz), 4.41 (1H, dt), 3.56 (3H, s), 3.22 (1H, dd, J_1=5.7 Hz, J_2=13.8 Hz), 3.00 (1H, dd, J_1=8.4 Hz, J_2=13.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 155.6, 142.9, 141.3, 136.4, 133.6, 130.6, 130.1, 129.5, 128.6, 128.5, 128.2, 128.1, 127.7, 127.3, 127.1, 66.9, 54.8, 52.4, 35.3; HRMS (FAB) calcd for $C_{24}H_{24}NO_4$ 390.1705, found 390.1710.

4.2.17. (*S*)-*N*$^{\alpha}$-Benzyloxycarbonyl-*o*-(*p*-chlorophenyl)-phenylalanine methyl ester 26b. 75% Yield, $[\alpha]_D^{26}=+13.6$ (*c* 1.46, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.14–7.37 (13H, m), 4.98 (2H, s), 4.43 (1H, dt), 3.60 (3H, s), 3.22 (1H, dd, J_1=5.4 Hz, J_2=14.1 Hz), 2.96 (1H, J_1=8.1 Hz, J_2=14.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 155.6, 141.7, 139.8, 136.4, 133.6, 133.4, 130.9, 130.5, 130.3, 128.7, 128.3, 128.2, 128.1, 127.3, 67.0, 54.8, 52.5, 35.5; HRMS (FAB) calcd for $C_{24}H_{23}ClNO_4$ 424.1316 (Cl 35) 426.1297 (Cl 37), found 424.1322 (Cl 35), 426.1292 (Cl 37).

4.2.18. (*S*)-*N*$^{\alpha}$-Benzyloxycarbonyl-*o*-(1-naphthyl)phenylalanine methyl ester 26c. 79% Yield, two diastereomers (1/1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84–7.89 (4H, m), 7.23–7.52 (28H, m), 4.86–5.02 (4H, m), 4.33–4.47 (2H, m), 3.50 (3H, s), 3.47 (3H, s), 3.03 (1H, dd, J_1=5.1 Hz, J_2=14.4 Hz), 2.88 (1H, dd, J_1=5.1 Hz, J_2=14.4 Hz), 2.75 (1H, dd, J_1=8.7 Hz, J_2=14.1 Hz), 2.59 (1H, dd, J_1=8.7 Hz, J_2=14.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 155.7, 155.6, 140.8, 140.7, 138.8, 138.5, 136.4, 135.2, 135.0, 133.7, 133.6, 132.3, 132.2, 131.3, 131.2, 129.7, 129.6, 128.6, 128.5, 128.2, 128.1, 128.0, 127.5, 127.3, 127.1, 127.0, 126.5, 126.4, 126.1, 126.0, 125.9, 125.5, 125.4, 66.9, 55.1, 54.7, 52.3, 35.7, 35.6, 29.9; HRMS (FAB) calcd for $C_{28}H_{26}NO_4$ 440.1862, found 440.1875.

4.2.19. Methyl (*Z*)-2-(benzyloxycarbonyl)amino-3-(4-bromophenyl)acrylate 24b. To a solution of $(MeO)_2CH(NHCbz)COOMe$ **8** (3.97 g, 12 mmol) in 15 mL of dry methylene chloride was added DBU (1.64 mL, 11 mmol) slowly under an argon atmosphere with stirring. After ca. 10 min, *p*-bromobenzaldehyde **23b** (1.85 g, 10 mmol) was added slowly into the above mixture. After 4 h, the solvent was evaporated, the residue was dissolved in 180 mL of ethyl acetate. The organic solution was washed with 1N HCl (2×40 mL) and brine (45 mL), dried over $MgSO_4$ and evaporated. The crude product was purified by flash column chromatography, eluting with ethyl acetate and hexanes (1/5) to give a white solid (3.095 g, 79%). Mp 101–102.5°C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.19 (10H, m), 6.40 (1H, s), 5.02 (2H, s), 3.74 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 153.6, 135.9, 132.9, 131.9, 131.2, 130.3, 128.7, 128.5, 124.5, 123.7, 98.7, 67.8, 53.0; HRMS (FAB) calcd for $C_{18}H_{17}BrNO_4$ 390.0341 (Br 79), 392.0323 (Br 81), found 390.0341 (Br 79), 392.0333 (Br 81).

4.2.20. (*R*)-*N*$^{\alpha}$-Benzyloxycarbonyl-*p*-bromophenylalanine methyl ester 27. In a similar manner to the preparation of **25**, using (*R*,*R*) (COD)Et-DuPHOS Rh (I) OTf as a catalyst gave **27** in 99% yield. Mp 96–98°C; $[\alpha]_D^{26}=-43.7$ (*c* 1.28, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41–7.26 (7H, m), 6.94–6.98 (2H, m), 5.24 (1H, d, J=7.8 Hz), 5.09 (2H, dd, J_1=12.1 Hz, J_2=17.8 Hz), 4.64 (1H, dd, J_1=6.0 Hz, J_2=13.8 Hz), 3.73 (3H, s), 3.11 (1H, dd, J_1=5.4 Hz, J_2=13.8 Hz), 3.01 (1H, J_1=6.0 Hz, J_2=13.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 155.7, 136.3, 134.9, 131.9, 131.2, 128.7, 128.5, 128.3, 121.3, 67.2, 54.8, 52.6, 37.9; HRMS (FAB) calcd for $C_{18}H_{19}BrNO_4$ 392.0497 (Br 79), 394.0479 (Br 81), found 392.0486 (Br 79), 394.0462 (Br 81).

4.2.21. (*R*)-*N*$^{\alpha}$-Benzyloxycarbonyl-*p*-(phenyl)phenylalanine methyl ester 28a. 100% Yield, mp 83–85°C; $[\alpha]_D^{23}=-55.2$ (*c* 1.14, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.57–7.58 (2H, m), 7.52–7.50 (2H, m), 7.43–7.46 (2H, m), 7.30–7.37 (6H, m), 7.17–7.19 (2H, m), 5.26 (1H, d, J=7.8 Hz), 5.12 (2H, dd, J_1=12.0 Hz, J_2=20.4 Hz), 4.71 (1H, dd, J_1=6.0 Hz, J_2=13.8 Hz), 3.76 (3H, s), 3.20 (1H, dd, J_1=5.4 Hz, J_2=13.8 Hz), 3.14 (1H, dd, J_1=6.0 Hz, J_2=13.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 155.8, 140.8, 140.2, 136.4, 134.9, 129.9, 129.2, 128.9, 128.7, 128.4, 128.3, 127.5, 127.2, 67.2, 54.9, 52.6, 38.0; HRMS (FAB) $C_{24}H_{24}NO_4$ 390.1705, found 390.1708.

4.2.22. (*R*)-*N*$^{\alpha}$-Benzyloxycarbonyl-*p*-(*p*-chlorophenyl)-phenylalanine methyl ester 28b. 93% Yield, mp 103–106°C; $[\alpha]_D^{23}=-54.4$ (*c* 0.768, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.29–7.45 (11H, m), 7.12 (2H, d, J=8.1 Hz), 5.28 (1H, d, J=8.1 Hz), 5.06 (2H, dd, J_1=12.2 Hz, J_2=14.4 Hz), 4.66 (1H, dd, J_1=6.0 Hz, J_2=14.0 Hz), 3.70 (3H, s), 3.15 (1H, dd, J_1=5.8 Hz, J_2=14.0 Hz), 3.06 (1H, dd, J_1=6.0 Hz, J_2=14.0 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.9, 155.6, 139.1, 138.7, 136.2, 135.1, 133.3, 129.8, 128.9, 128.5, 128.2, 128.1, 127.1, 67.0, 54.7, 52.3, 37.8; HRMS (FAB) for $C_{24}H_{23}ClNO_4$ 424.1316 (Cl 35), 426.1297 (Cl 37), found 424.1305 (Cl 35), 426.1316 (Cl 37).

4.2.23. (*R*)-*N*$^{\alpha}$-Benzyloxycarbonyl-*p*-(1-naphthyl)phenylalanine methyl ester 28c. 93% Yield, $[\alpha]_D^{24}=-48.0$; (*c* 2.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.82–7.89 (3H, m), 7.28–7.52 (11H, m), 7.21 (2H, d, J=8.1 Hz), 5.38 (1H, d, J=8.1 Hz), 5.12 (2H, dd, J_1=12.3 Hz, J_2=15.3 Hz), 4.74 (1H, dd, J_1=6.0 Hz, J_2=13.8 Hz), 3.23 (1H, dd, J_1=6.0 Hz, J_2=13.8 Hz), 3.16 (1H, J_1=6.0 Hz, J_2=13.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 155.8, 139.9, 139.7, 136.4, 134.9, 133.9, 131.7, 130.4, 129.3, 128.7, 128.4, 128.3, 128.2, 127.8, 127.1, 126.2, 126.0, 125.9, 125.5, 67.2, 55.0, 52.6, 38.1; HRMS (FAB) calcd for $C_{28}H_{26}NO_4$ 440.1862, found 440.1855.

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