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

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Abstract—An efficient method for the synthesis of novel aromatic substituted, bulky and hydrophobic tryptophan derivatives has been developed. Asymmetric hydrogenations of α-enamide **5** using Burk's DuPHOS-based catalysts generated high enantiomerically pure D- and L-α-amino acid derivatives **6**, which subsequently underwent Suzuki cross couplings with boronic acid derivatives to afford aromatic substituted tryptophan derivatives **7** and **8** in high yields. The method can allow for the preparation of such amino acids in large-scales for extensive structure–activity studies. © 2001 Elsevier Science Ltd. All rights reserved.

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-melanocyte stimulating hormone (MSH) project, there are three aromatic amino acids (His, Phe and Trp) in the core sequence, His-Phe-Arg-Trp, of α-MSH peptides, which play a key role in biological activity and selectivity.[1,2] The modification and substitution of His and Phe in the core sequence of the peptide has led to potent and selective α-MSH peptide ligands.[1,2] In our efforts to further enhance potency and selectivity of α-MSH peptide ligands, we have proposed to use more bulky and hydrophobic amino acids aromatic-substituted tryptophan analogues to replace Trp (Fig. 1). 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.

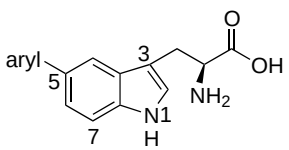

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Figure 1. Structures of 5-aryl tryptophans.

Our group has been long interested in the design and synthesis of novel unnatural amino acids,[3–5] and we have developed a few methods for the synthesis of β-substituted constrained amino acids including tryptophan, tyrosine, phenylalanine, and glutamic acid derivatives.[6–10] Furthermore, we have demonstrated that the incorporation of these novel amino acids into biologically active peptides and peptidomimetics can enhance the potency and selectivity significantly.[1,4,5,11,12] In a survey of literature, we were surprised to find that very few methods have been reported for the synthesis of the aromatic substituted tryptophan analogues.[13–16] For example, one of the synthetic approaches used for the preparation of these unusual amino acids started with tryptophan.[13] However, the route was somewhat lengthy and sometimes used harsh conditions. Herein, we would like to report an efficient method for the asymmetric synthesis of both D- and L-aromatic substituted tryptophan derivatives from readily available starting materials under very mild reaction conditions in four steps (Scheme 1). The general strategy involves the asymmetric hydrogenation of α-enamides **5** to generate functional α-amino acids **6** in high optical purity which serve as common intermediates from which a variety of substituted amino acid derivatives **7** and **8** may be readily obtained through Suzuki-type cross couplings (Scheme 1).

Keywords: amino acids; tryptophan; asymmetric hydrogenation; Suzuki cross coupling.

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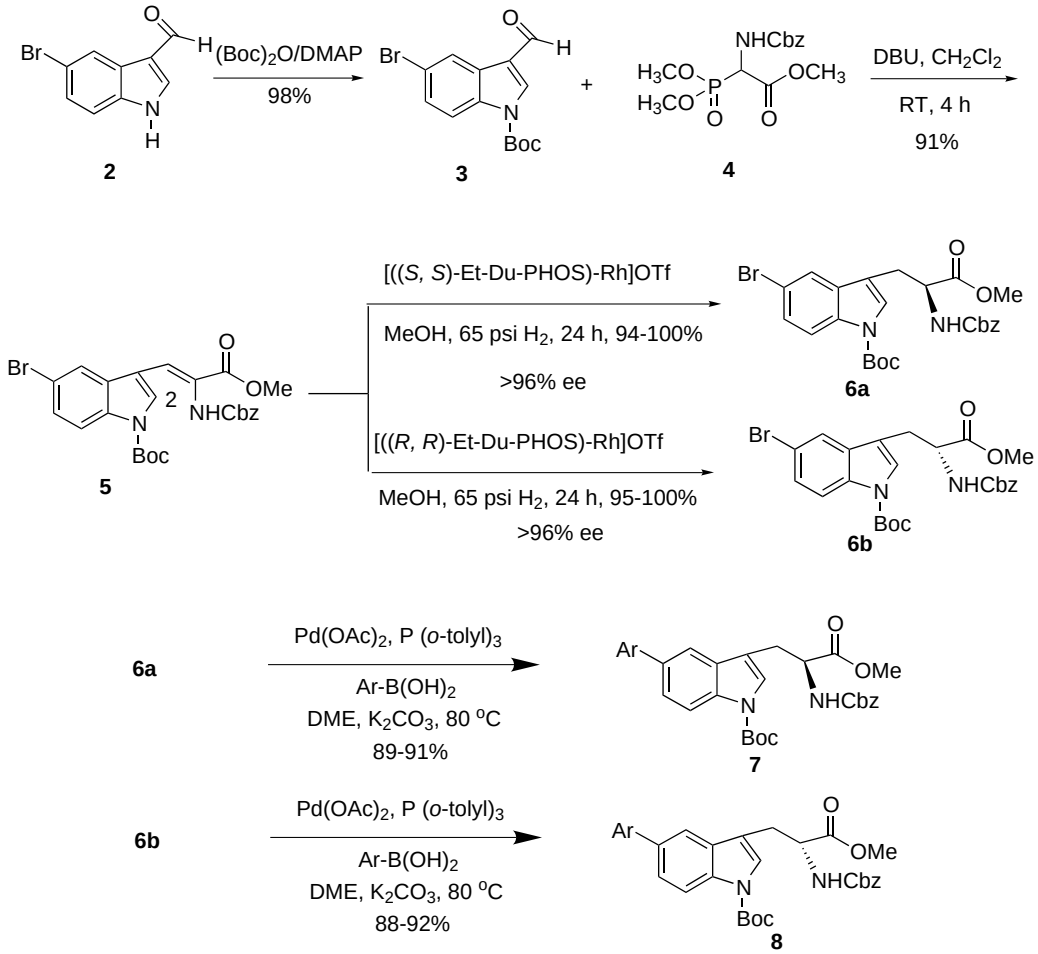
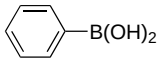
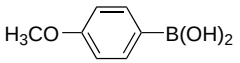
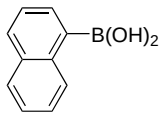


Scheme 1. Synthesis of 5-aryl-substituted tryptophan derivatives.

The synthesis of the 5-aryl substituted tryptophans started from commercially available 5-bromoindole-3-carboxaldehyde **2**. 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 **3** with phosphonate $(MeO)_2P(O)CH(NHCbz)COOMe$ **4** gave the dehydroamino acid **5** with *Z*-configuration as a major product (*Z*/*E*>95/5) in 91% yield.[17,18] Compound **4** was synthesized in three steps following literature procedures.[19] The amino group in **4** was protected by Cbz (benzyloxycarbonyl), which was orthogonal to Boc protected amino group on the indole ring of compound **5**. The dehydroamino ester **5** 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 enantiomer (>97% ee) in high yields (>95%).[20,21] The catalysts showed high efficiency (at a ratio of catalyst to substrate up to 1/2500)[21] and are commercially available.[22] Furthermore, both *Z* and *E* dehydroamino acids using this type of catalysts gave one single isomer.[21] In this case, we separated the two isomers by column chromatography. The isolated (*Z*)-dehydroamino acid ester **5** used for asymmetric hydrogenations with a higher ee than that of (*E*) isomer. The (*S*,*S*) catalyst afforded the amino acid derivative **6a** with an absolute *S* configuration based on the selectivity of the (*S*,*S*)-Et-DuPHOS ligand in a high yield and high ee (>96%).[21,23] The (*R*) amino acid **6b** was also obtained using (*R*,*R*)-Et-DuPHOS as a ligand in a high yield and high ee as well. 5-Bromotryptophans **6** were subjected to Suzuki cross couplings with a variety of boronic acids to give amino acid derivatives **7** and **8** 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.[24] The enantiomeric purity was determined by the Mosher's agent[25] and the conversion of compound **7a** to 5-phenyl-L-tryptophan methyl ester, a known compound ($[\alpha]_{24}^{D}$ +42.6 (*c* 1.06, MeOH), lit.[13] ($[\alpha]_{25}^{D}$ +42.4 (*c* 1.24, MeOH), indicating no racemization observed during the cross couplings.

In conclusion, we have developed an efficient method for the synthesis of aryl-substituted tryptophan derivatives. These amino acids were synthesized via asymmet-

Table 1. Suzuki cross coupling of **6** with aryl boronic acids

Boronic aicds	Yields with **6a**	Yields with **6b**
	**7a**, 91%	**8a**, 89%
	**7b**, 90%	**8b**, 92%
	**7c**, 89%	**8c**, 88%

ric 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 the amino acids. The incorporation of the amino acids into biologically active α-MSH peptides and peptidomimetics, biological evaluation, and structure-biological activity relationship studies of the bioactive peptides and peptidomimetics are in progress.

Acknowledgements

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23. Compound **6a**: $[\alpha]_D^{25}$ +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).
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