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PAPER

Palladium-catalyzed mono-*N*-allylation of unprotected amino acids with 1,1-dimethylallyl alcohol in water†

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Palladium-catalyzed *N*-allylation of unprotected amino acids with 1,1-dimethylallyl alcohol were carried out. The reaction in the presence of $Pd(OAc)_2$ (5 mol%), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 10 mol%), and AcONa (2 equiv) in water at 120 °C for 16 h in a sealed tube gave only mono-*N*-allylated amino acids in good yield.

Introduction

Biologically active natural products containing *N*-1,1-dimethylallylated amino acids such as fumitremorgin B,[1] fumitremorgin C,[2] (+)-austamide,[3] okaramine N[4] and aeruginosamide[5] have been reported (Fig. 1). Reductive amination[1–4] and *N*-alkylation[5] of ester **1** were used for formation of *N*-1,1-dimethylallylated amino acids (Scheme 1).

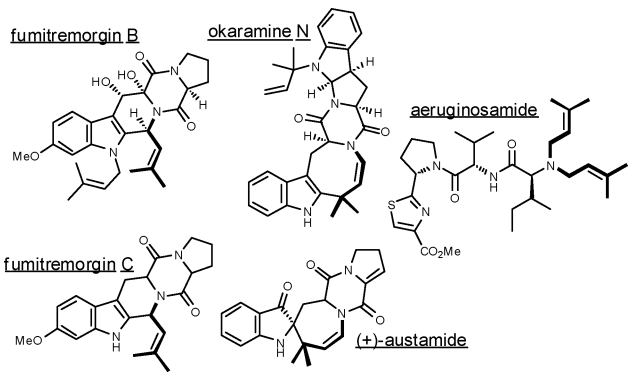
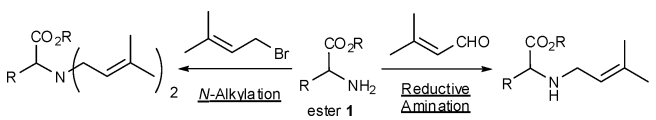


Fig. 1 Biologically active natural products.



Scheme 1 Formation of *N*-allylated amino acids.

Since 1999, we have been investigating the total synthesis of ergot alkaloids from tryptophan derivatives.[6] During the synthesis of clavicipitic acid, palladium-catalyzed *N*-allylation of unprotected 4-bromotryptophan with 1,1-dimethylallyl alcohol was observed. In general, palladium-catalyzed allylations with allylic alcohols are difficult because the reactivity of allylic alcohols towards Pd(0) is poor, and compared with allylic carbonates or acetates, the reaction does not easily lead to the formation of the π-allyl complex. Therefore, Lewis acids,[7] cationic Pd^{II} catalysts,[8] Pt catalysts,[9] or Pd-$P(OPh)_3$ catalysts[10] were used for *N*-allylations with allylic alcohols in organic solvents. On the other hand, recent studies indicated that palladium-catalyzed *N*-allylation with allylic alcohols proceeded in water, which played an important role in the activation of the allylic alcohol to form the π-allyl complex.[11] In these reports, hydrophobic substrates were often tested on the *N*-allylation in a two-phase system. However, there has been no investigation of water-soluble starting materials such as amino acids using only water as a solvent. We have already reported the palladium-catalyzed chemoselective reaction of 4-bromotryptophan or haloanilines with 1,1-dimethylallyl alcohol in aqueous media.[6,11c] Changing the pH affected which site in the molecule was reactive: *N*-allylation occurred under weakly basic conditions, while the Heck reaction occurred selectively under strongly basic conditions. It should be emphasized that this reaction only occurred when water was used as the solvent. It is very interesting that pH plays a critical role in the chemoselectivity of palladium-catalyzed reactions in aqueous media.

Herein, we report a palladium-catalyzed mono-*N*-allylation of unprotected amino acids with 1,1-dimethylallyl alcohol in water.

Results and discussion

To evaluate the *N*-allylation of unprotected amino acids with 1,1-dimethylallyl alcohol **2a**, we treated a mixture of tryptophan **1a** and **2a** (5 equiv) in the presence of $Pd(OAc)_2$ (5 mol%), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 10 mol%), and AcONa (2 equiv) in water at 120 °C for 16 h in a sealed tube. After work-up, the mixture was subjected to ODS silica gel chromatography to give the desired product **3a** in 70% yield along with recovery of starting material **1a** (entry 1 in Table 1,

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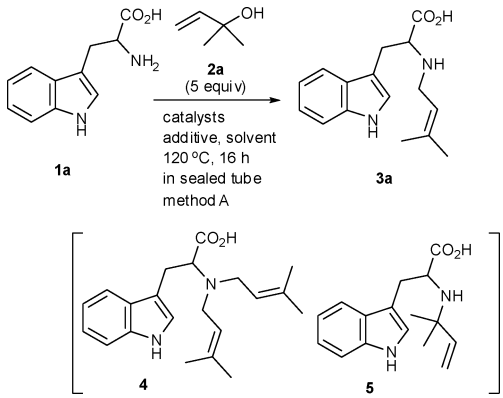
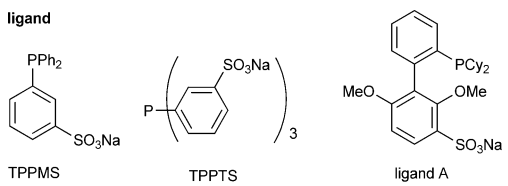
† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra of the new products and HPLC analytical data of (*S*)-**3a** methyl ester. See DOI: 10.1039/c1ob05238a

Table 1 Effects of catalyst, additive and solvent on *N*-allylation of **1a**



				Yield (%)	
Entry	Catalysts	Additive (equiv)	Solvent	**3a**	Recov. of **1a**
1	$Pd(OAc)_2$/TPPMS	AcONa (2)	H_2O	70	27
2[a]	$Pd(OAc)_2$/TPPMS	AcONa (2)	H_2O	85	trace
3	Pd_2dba_3/TPPMS	AcONa (2)	H_2O	69	25
4	$Pd(tppts)_3$	AcONa (2)	H_2O	48	28
5	$Pd(OAc)_2$/Ligand A	AcONa (2)	H_2O	53	32
6	None	AcONa (2)	H_2O	No reaction	
7	$PdCl_2(PPh_3)_2$	AcONa (2)	DMF	No reaction	
8	$Pd(OAc)_2$/TPPMS	AcONa (2)	DMF, DMSO or EtOH	No reaction	
9	$Pd(OAc)_2$/TPPMS	None	H_2O	32	33
10	$Pd(OAc)_2$/TPPMS	K_2CO_3 (2)	H_2O	20	68
11	$Pd(OAc)_2$/TPPMS	AcOH (2)	H_2O	No reaction	

[a] Method B: Amino acid **1**, $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), AcONa (2 equiv) and **2a** (5 equiv) in H_2O, 120 °C, 14 h. Then, $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%) and **2a** (5 equiv) were added, 120 °C, 1 d.

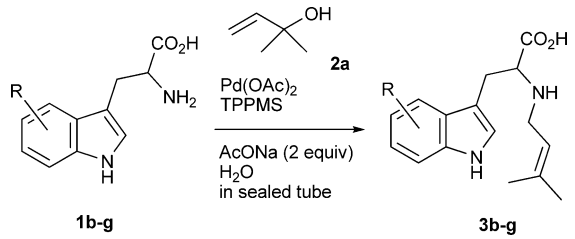


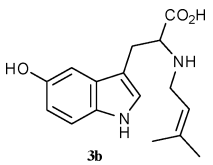
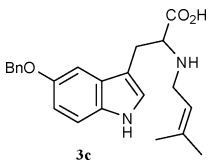
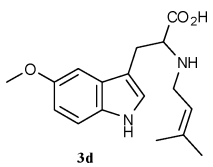
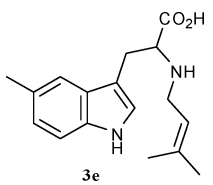
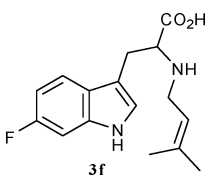
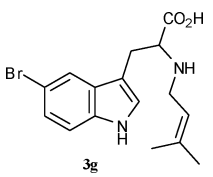
method A). The reaction did not go to completion, because the π-allyl palladium intermediate may be unstable in our catalytic system.[12]

Therefore, after the *N*-allylation of **1a** with 1,1-dimethylallylalcohol **2a** under the same reaction conditions as entry 1 for 14 h, fresh catalyst [$Pd(OAc)_2$ (5 mol%) and TPPMS(10 mol%)] and allylic alcohol **2a** (5 equiv) were added to the resulting solution. After 1 d, the yield improved up to 85% yield (entry 2, method B). It is noted that only mono-*N*-allylated product **3a** was obtained in good yield in spite of the possibility of forming by-products **4** and **5**. Thus, the reaction was considered sufficient for synthetic purposes. With regard to the catalyst, the use of $Pd_2(dba)_3$/TPPMS also resulted in the formation of **3a** in 69% yield (entry 3). Using $Pd(tppts)_3$ (tppts: triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt) or $Pd(OAc)_2$ with ligand A (ligand A: sodium 2′-dicyclohexylphosphino-2,6-dimethoxy-1,1′-biphenyl-3-sulfonate hydrate), the reaction proceeded slowly to give **3a** in 48–53% yield (entries 4 and 5). Since the reaction did not proceed without the palladium catalyst (entry 6), a S_N2' type reaction mechanism was excluded in the formation of the *N*-allylated product. Using $PdCl_2(PPh_3)_2$ instead of a water-soluble ligand, the reaction did not occur in DMF (entry 7). Using a water-soluble ligand, the use of organic solvents such as DMF, DMSO or EtOH also resulted in no reaction (entry 8), most likely due to the insolubility of the amino acid in the organic solvent. In addition, water may play an important role for the smooth generation of the π-allylpalladium species by hydration of the hydroxyl group. With regard to the additive, the absence of AcONa or switching to K_2CO_3 gave lower yields of **3a** (entries 9 and 10). AcOH also suppressed the *N*-allylation (entry 11).

Table 2 summarizes the results of *N*-allylation of tryptophan derivatives with allylic alcohol **2a**. At first, we tested the *N*-allylation of 5-hydroxytryptophan derivatives. 5-Hydroxytryptophan (5-HTP) is known as a chemical precursor as well as a metabolic intermediate in the biosynthesis of the neurotransmitters serotonin and melatonin from tryptophan. 5-HTP **1b** afforded only the *N*-allylated product **3b** in 57% yield (entry 1). *O*-Protected 5-HTP such as 5-benzyloxytryptophan **1c** and 5-methoxytryptophan **1d** gave the corresponding allylated products **3c** and **3d** in 70% and 80% yields, respectively (entries 2 and 3). Other tryptophans such as 5-methyltryptophan **1e**

Table 2 *N*-Allylation of tryptophans **1** with allylic alcohol **2a**



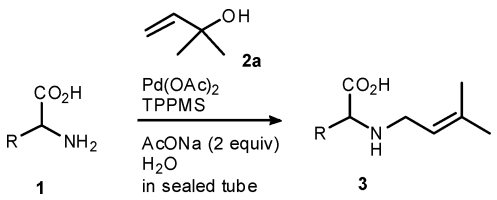
Entry	Tryptophan **1**	Product **3**	Method[a]	Yield (%) **3**	Yield (%) Recov. of SM **1**
1	5-Hydroxy tryptophan **1b**	 **3b**	B	57	—[b]
2	5-Benzyloxy tryptophan **1c**	 **3c**	A	70	21
3	5-Methoxy tryptophan **1d**	 **3d**	B	80	Trace
4	5-Methyl tryptophan **1e**	 **3e**	A	71	19
5	6-Fluoro tryptophan **1f**	 **3f**	B	86	Trace
6	5-Bromo tryptophan **1g**	 **3g**	A	58	32

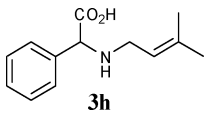
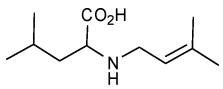
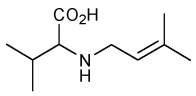
[a] Method A: Amino acid **1**, $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), AcONa (2 equiv) and **2a** (5 equiv) in H_2O, 120 °C, 16 h. Method B: Amino acid **1**, $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), AcONa (2 equiv) and **2a** (5 equiv) in H_2O, 120 °C, 14 h. Then, $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%) and **2a** (5 equiv) were added, 120 °C, 1 d. [b] Yield not determined.

and 6-fluorotryptophan **1f** afforded desired products **3e** and **3f** in 71% and 86% yields, respectively (entries 4 and 5). *N*-Allylation of 5-bromotryptophan **1g** occurred to give *N*-allylated 5-bromotryptophan **3g** in 58% yield selectively (entry 6). *N*-Allylated **3g** should be converted to the 5-substituted product using cross-coupling.[13]

We then investigated the scope and limitations of different amino acids **1** (Table 3). Phenylglycine **1h** afforded the

Table 3 *N*-Allylation of several amino acids **1**

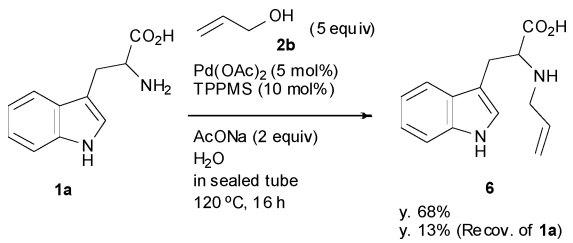


Entry	Amino acid **1**	Product **3**	Method[a]	Yield (%)[b]
1	Phenylglycine **1h**	 **3h**	B	60
2	Leucine **1i**	 **3i**	B	43
3	Valine **1j**	 **3j**	A	58

[a] Method A: Amino acid **1**, $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), AcONa (2 equiv) and **2a** (5 equiv) in H_2O, 120 °C, 16 h. Method B: Amino acid **1**, $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%), AcONa (2 equiv) and **2a** (5 equiv) in H_2O, 120 °C, 14 h. Then, $Pd(OAc)_2$ (5 mol%), TPPMS (10 mol%) and **2a** (5 equiv) were added, 120 °C, 1 d. [b] Incomplete conversion.

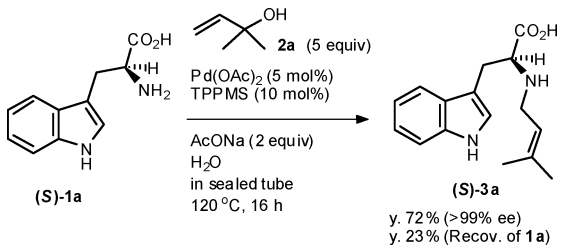
corresponding product **3h** in 60% yield (entry 1). Aliphatic amino acids such as leucine **1i** and valine **1j** gave the desired products **3i** and **3j** in 43% and 58% yields, respectively (entries 2 and 3). In all cases, the reaction did not go to completion, and starting material **1** was detected by TLC.

As shown in Scheme 2, allyl alcohol itself (**2b**) also gave the *N*-allylated product **6** in 68% yield.



Scheme 2 *N*-Allylation of tryptophan with allyl alcohol **2b**.

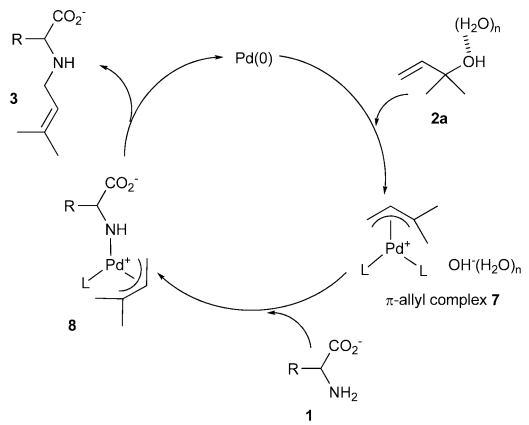
As shown in Scheme 3, *N*-allylation of (*S*)-**1a** occurred to give (*S*)-**3a** (>99% ee)[14] in 72% yield. In our previous report, we found



Scheme 3 *N*-Allylation of (*S*)-tryptophan.

that racemization did not occur during the Heck reaction of (*S*)-4-bromotryptophan with 1,1-dimethylallyl alcohol **2a** in spite of the strong basic conditions (3 equiv. of K_2CO_3, 130 °C, 8 h in H_2O),[6] and water suppressed the racemization and decomposition of amino acids.[15] Thus, this reaction will be applicable to the synthesis of optically active *N*-allylated amino acids.

A possible mechanism for the formation of *N*-1,1-dimethylallylamino acid **3** from amino acid **1** and 1,1-dimethylallyl alcohol **2a** is illustrated in Scheme 4. Oxidative addition of alcohol **2a** to a Pd(0) species affords the π-allyl palladium complex, and water may play an important role for the smooth generation of the π-allylpalladium species **7** by hydration of the hydroxyl group.[11a] Next, the ligand exchange of the π-allyl system with the amino



Scheme 4 A possible mechanism for the formation of *N*-1,1-dimethylallylamino acid **3**.

group of **1** takes place to generate intermediate **8**, followed by reductive elimination to give only the mono-*N*-allylated product **3**. On the other hand, *N*-alkylation with prenylbromide gives the di-*N*-allylated product in organic solvents.[5] In our catalytic system, *N*-allylated compound **3** does not react any further with the π-allyl complex **7**, because water suppresses the nucleophilicity of **3** by the hydration of the amino group. In addition, our method succeeds in the presence of AcONa as a base in good yield. AcOH suppressed the nucleophilicity of **1a** by protonation of the amino group. In strong basic conditions, the π-allyl palladium intermediate **7** is unstable.[12] Therefore, pH plays a critical role in the palladium-catalyzed *N*-allylation and the outcome of the *N*-allylation can be controlled simply by changing the basicity of the reaction media. Overall, water plays a key role as a solvent in our catalytic system.

Conclusions

In summary, we developed a methodology for achieving a palladium-catalyzed mono-*N*-allylation of unprotected amino acids **1** with 1,1-dimethylallyl alcohol **2a** in water. This methodology offers a new synthetic strategy for the chemical modification of amino acids into unnatural derivatives containing a 1,1-dimethylallyl moiety using the Tsuji–Trost reaction without activation of allylic alcohols in water. Water may play a key role as a solvent in the development of new synthetic reactions involving free amino acids. We are currently working on the development of new reactions involving water-soluble compounds in aqueous media.

Experimental

All reagents and anhydrous solvents were purchased from commercial suppliers and used without further purification. Melting points were determined on a Yanagimoto micro-melting hot stage apparatus and were uncorrected. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. NMR spectra were recorded on a JEOL GX-400 (400 MHz) spectrometer. For ^{1}H NMR, CD_3OD (δ = 3.30) or tetramethylsilane (TMS) (δ = 0) served as an internal standard. For ^{13}C NMR, CD_3OD (δ = 49.00) or tetramethylsilane (TMS) (δ = 0) served as an internal standard. Preparation of NMR samples for ^{1}H NMR and ^{13}C NMR: compound **3** and **6** (5 mg) were dissolved in CD_3OD (500 μL) and 20% DCl in D_2O (10 μL). FAB mass spectra were measured with a JEOL JMS-600H spectrometer. EI mass spectra were measured with a JEOL GCmate spectrometer. Separations were performed using ODS DM1020T (Fuji Silysia Chemical Ltd.) for silica gel column chromatography. Thin layer chromatography (TLC) was performed on precoated plates of silica gel 60F_{254} (Merck).

General procedure for the synthesis of *N*-allylated amino acids 3a–j, 6 and (*S*)-3a.

Method A. A mixture of amino acid **1** (0.5 mmol), palladium(II) acetate (6 mg, 0.025 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 18 mg, 0.05 mmol), AcONa·3H_2O (136 mg, 1.0 mmol) and 2-methyl-3-buten-2-ol **2a** or prop-2-en-1-ol **2b** (2.5 mmol) in H_2O (2 mL) was heated at 120 °C for 16 h in a sealed tube. The solvent was removed under reduced pressure, and the resulting residue was dissolved in AcOH (1 mL) and subjected to ODS silica gel column chromatography. A solvent gradient, starting with H_2O and with increasing proportions of MeOH, was used as the eluent.

Method B. A mixture of amino acid **1** (0.5 mmol), palladium(II) acetate (6 mg, 0.025 mmol), TPPMS (18 mg, 0.05 mmol), AcONa·3H_2O (136 mg, 1.0 mmol) and **2a** (260 μL, 2.5 mmol) in H_2O (2 mL) was heated at 120 °C for 14 h in a sealed tube. Next, palladium(II) acetate (6 mg, 0.025 mmol), TPPMS (18 mg, 0.05 mmol) and **2a** (260 μL, 2.5 mmol) were added to the resulting solution, which was heated at 120 °C for 1 d. The work-up and isolation were carried out as above.

Characterization of *N*-allylated amino acid 3a–j and 6

***dl*-*N*-(3-Methyl-2-buten-1-yl)tryptophan (3a) (Table 1, entries 1 and 2).** Off-white solid; mp 238–240 °C; IR (KBr) (cm^{-1}) 3419, 1618; ^{1}H NMR (400 MHz, CD_3OD+DCl): δ 1.63 (s, 3H), 1.76 (s, 3H), 3.48 (d, J = 6.1 Hz, 2H), 3.64 (d, J = 7.8 Hz, 2H), 4.23 (t, J = 6.1 Hz, 1H), 5.20 (t, J = 7.8 Hz, 1H), 7.04 (ddd, J = 7.8, 7.1, 1.0 Hz, 1H), 7.12 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 7.25 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H); ^{13}C NMR (400 MHz, CD_3OD + DCl): δ 18.2, 26.0, 27.2, 45.6, 60.1, 107.5, 112.6, 114.7, 119.1, 120.3, 122.9, 125.7, 128.3, 138.3, 144.7, 171.2; FAB-MS: m/z 273 [M + H]$^+$; Anal. Calcd for $C_{16}H_{20}N_2O_2$·0.3H_2O: C, 69.19; H, 7.48; N, 10.09. Found: C, 68.87; H, 7.24; N, 9.86%.

***dl*-5-Hydroxy-*N*-(3-methyl-2-buten-1-yl)tryptophan (3b) (Table 2, entry 1).** White solid; mp 195–196 °C; IR (KBr) (cm^{-1}) 3323, 1618; ^{1}H NMR (400 MHz, CD_3OD): δ 1.53 (s, 3H), 1.68 (s, 3H), 3.12 (dd, J = 15.2, 9.1 Hz, 1H), 3.30–3.60 (m, 3H), 3.81 (d, J = 9.1, 4.4 Hz, 1H), 4.90–5.10 (m, 1H), 6.69 (dd, J = 8.6, 2.0 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H), 7.14 (s, 1H), 7.18 (d, J = 8.6 Hz, 1H); ^{13}C NMR (400 MHz, CD_3OD + DCl): δ 18.2, 26.0, 27.3, 45.6, 59.9, 106.7, 113.0, 113.1, 114.7, 126.3, 128.9, 133.1, 144.8, 151.7, 171.2; FAB-MS: m/z 289 [M + H]$^+$; Anal. Calcd for $C_{16}H_{20}N_2O_3$·1.1H_2O: C, 62.36; H, 7.26; N, 9.09. Found: C, 62.18; H, 7.10; N, 8.71%.

***dl*-5-Benzyloxy-*N*-(3-methyl-2-buten-1-yl)tryptophan (3c) (Table 2, entry 2).** White solid; mp 236–238 °C; IR (KBr) (cm^{-1}) 3420, 3033, 1612; ^{1}H NMR (400 MHz, CD_3OD + DCl): δ 1.63 (s, 3H), 1.76 (s, 3H), 3.44 (d, J = 6.1 Hz, 2H), 3.63 (d, J = 7.5 Hz, 2H), 4.20 (t, J = 6.1 Hz, 1H), 5.10 (s, 2H), 5.21 (t, J = 7.5 Hz, 1H), 6.87 (dd, J = 8.7, 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 7.22 (s, 1H), 7.25–7.35 (m, 2H), 7.36 (t, J = 7.3 Hz, 1H), 7.46 (d, J = 7.3 Hz, 1H); ^{13}C NMR (400 MHz, CD_3OD + DCl): δ 18.2, 26.0, 27.2, 45.6, 60.0, 72.1, 107.3, 113.3, 113.8, 114.8, 126.5, 128.7, 128.8, 129.5, 133.7, 139.3, 144.7, 154.4, 171.2; FAB-MS: m/z 379 [M + H]$^+$; Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.89; H, 7.00; N, 7.25%.

***dl*-5-Methoxy-*N*-(3-methyl-2-buten-1-yl)tryptophan (3d) (Table 2, entry 3).** Pale yellow solid; mp 235–236 °C; IR (KBr) (cm^{-1}) 3353, 3056, 1627; ^{1}H NMR (400 MHz, CD_3OD+DCl): δ 1.63 (s, 3H), 1.76 (s, 3H), 3.46 (d, J = 6.2 Hz, 2H), 3.66 (d, J = 7.4 Hz, 2H), 3.83 (s, 3H), 4.20 (t, J = 6.2 Hz, 1H), 5.24 (t, J = 7.4 Hz, 1H), 6.77 (dd, J = 8.8, 2.2 Hz, 1H), 7.10 (d, J = 2.2 Hz, 1H),7.24 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H); ^{13}C NMR (400 MHz, CD_3OD+DCl): δ 18.2, 26.0, 27.2, 45.6, 56.4, 60.0, 101.2, 107.2, 113.2, 113.3, 114.8, 126.4, 128.6, 133.4, 144.7, 155.4, 171.2; FAB-MS: m/z 303

[M + H]$^+$; Anal. Calcd for $C_{17}H_{22}N_2O_3 \cdot 0.5H_2CO_3$: C, 63.05; H, 6.95; N, 8.40. Found: C, 63.32; H, 6.97; N, 8.08%.

***dl*-5-Methyl-*N*-(3-methyl-2-buten-1-yl)tryptophan (3e) (Table 2, entry 4).** Off-white solid; mp 240–242 °C; IR (KBr) (cm^{-1}) 3238, 3034, 1616; ^{1}H NMR (400 MHz, CD_3OD + DCl): δ 1.62 (s, 3H), 1.75 (s, 3H), 2.41 (s, 3H), 3.40–3.50 (m, 2H), 3.60–3.70 (m, 2H), 4.22 (t, J = 6.3 Hz, 1H), 5.19 (t, J = 7.3 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 7.20 (s, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.37 (s, 1H); ^{13}C NMR (400 MHz, CD_3OD + DCl): δ 18.1, 21.7, 26.0, 27.2, 45.6, 60.0, 107.0, 112.3, 114.8, 118.7, 124.6, 125.7, 128.5, 129.5, 136.6, 144.7, 171.2; FAB-MS: *m*/*z* 287 [M + H]$^+$; Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 70.90; H, 7.68; N, 9.53%.

***dl*-5-Fluoro-*N*-(3-methyl-2-buten-1-yl)tryptophan (3f) (Table 2, entry 5).** White solid; mp 248–250 °C; IR (KBr) (cm^{-1}) 3256, 3033, 1617; ^{1}H NMR (400 MHz, CD_3OD + DCl): δ 1.65 (s, 3H), 1.77 (s, 3H), 3.46 (t, J = 6.1 Hz, 2H), 3.65 (d, J = 7.6 Hz, 2H), 4.22 (t, J = 6.1 Hz, 1H), 5.22 (t, J = 7.6 Hz, 1H), 6.80–6.86 (m, 1H), 7.08 (dd, J = 9.8, 2.2 Hz, 1H), 7.20 (s, 1H), 7.54 (dd, J = 8.8, 5.1 Hz, 1H); ^{13}C NMR (400 MHz, CD_3OD + DCl): δ 18.1, 21.7, 26.0, 27.2, 45.6, 60.0, 107.0, 112.3, 114.8, 118.7, 124.6, 125.7, 128.5, 129.5, 136.6, 144.7, 171.2; FAB-MS: *m*/*z* 291 [M + H]$^+$; Anal. Calcd for $C_{16}H_{19}FN_2O_2$: C, 65.38; H, 6.65; N, 9.53. Found: C, 65.31; H, 6.53; N, 9.31%.

***dl*-5-Bromo-*N*-(3-methyl-2-buten-1-yl)tryptophan (3g) (Table 2, entry 6).** White solid; mp 251–253 °C; IR (KBr) (cm^{-1}) 3418, 1626; ^{1}H NMR (400 MHz, CD_3OD+DCl): δ 1.67 (s, 3H), 1.78 (s, 3H), 3.44 (t, J = 6.1 Hz, 2H), 3.67 (d, J = 7.8 Hz, 2H), 4.21 (t, J = 6.1 Hz, 1H), 5.23 (t, J = 7.8 Hz, 1H), 7.20 (dd, J = 8.5, 1.7 Hz, 1H), 7.29 (s, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 1.7 Hz, 1H); ^{13}C NMR (400 MHz, CD_3OD + DCl): δ 18.2, 26.0, 26.9, 45.7, 60.1, 107.4, 113.5, 114.3, 114.7, 121.7, 125.7, 127.3, 130.2, 136.8, 144.8, 171.1; FAB-MS: *m*/*z* 351 [M + H]$^+$, 353 [M + H + 2]$^+$; Anal. Calcd for $C_{16}H_{19}BrN_2O_2 \cdot 0.3CH_3CH_2OH$: C, 54.62; H, 5.74; N, 7.67. Found: C, 54.64; H, 5.41; N, 7.30%.

***dl*-*N*-(3-Methyl-2-buten-1-yl)phenylglycine (3h) (Table 3, entry 1).** White solid; mp 224–226 °C; IR (KBr) (cm^{-1}) 3422, 3063, 1579; ^{1}H NMR (400 MHz, CD_3OD+DCl): δ 1.63 (s, 3H), 1.81 (s, 3H), 3.50–3.70 (m, 2H), 4.95–5.05 (m, 1H), 5.29 (t, J = 7.3 Hz, 1H), 7.40–7.60 (m, 5H); ^{13}C NMR (400 MHz, CD_3OD+DCl): δ 18.2, 26.0, 45.0, 63.4, 114.6, 129.8, 130.7, 131.5, 132.2, 144.6, 170.2; FAB-MS: *m*/*z* 220 [M + H]$^+$; Anal. Calcd for $C_{13}H_{17}NO_2 \cdot 0.1H_2O$: C, 70.63; H, 7.84; N, 6.34. Found: C, 70.66; H, 7.80; N, 6.23%.

***dl*-*N*-(3-Methyl-2-buten-1-yl)leucine (3i) (Table 3, entry 2).** White solid; mp 197–200 °C; IR (KBr) (cm^{-1}) 3448, 2956, 1577; ^{1}H NMR (400 MHz, CD_3OD+DCl): δ 0.99 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 1.65–1.90 (m, 3H), 1.76 (s, 3H), 1.82 (s, 3H), 3.30–3.45 (m, 2H), 3.68 (d, J = 7.6 Hz, 2H), 3.89 (dd, J = 8.3, 5.4 Hz, 1H), 5.31 (t, J = 7.6 Hz, 1H); ^{13}C NMR (400 MHz, CD_3OD+DCl): δ 18.3, 21.9, 23.3, 25.9, 26.0, 40.1, 45.3, 58.7, 114.8, 144.9, 171.5; FAB-MS: *m*/*z* 200 [M + H]$^+$; Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 65.99; H, 10.51; N, 6.93%.

***dl*-*N*-(3-Methyl-2-buten-1-yl)valine (3j) (Table 3, entry 3).** White solid; mp 206–209 °C; IR (KBr) (cm^{-1}) 3422, 2967, 1578; ^{1}H NMR (400 MHz, CD_3OD+DCl): δ 1.05 (d, J = 7.1 Hz, 3H), 1.13 (d, J = 7.1 Hz, 3H), 1.74 (s, 3H), 1.82 (s, 3H), 2.20–2.40 (m, 1H), 3.60–3.80 (m, 2H), 3.80 (d, J = 3.6 Hz, 1H), 5.31 (t, J = 6.8 Hz, 1H); ^{13}C NMR (400 MHz, CD_3OD+DCl): δ 17.5, 18.2, 19.5, 19.6, 26.0, 30.7, 46.2, 65.4, 114.7, 145.0, 170.2; FAB-MS: *m*/*z* 186 [M + H]$^+$; Anal. Calcd for $C_{10}H_{19}NO_2 \cdot 0.1H_2O$: C, 64.21; H, 10.35; N, 7.49. Found: C, 63.85; H, 10.12; N, 7.44%.

***dl*-*N*-Allyltryptophan (6) (Scheme 2).** White solid; mp 226–229 °C (Lit.,[16] 247 °C); IR (KBr) (cm^{-1}) 3411 (OH), 1625 (C=O); ^{1}H NMR (400 MHz, CD_3OD+DCl): δ 3.50 (d, J = 6.0 Hz, 2H), 3.65 (d, J = 6.8 Hz, 2H), 4.26 (t, J = 6.0 Hz, 1H), 5.41 (dd, J = 7.8, 1.2 Hz, 1H), 5.44 (s, 1H), 5.80–5.95 (m, 1H), 7.04 (ddd, J = 8.0, 7.0, 1.2 Hz, 1H), 7.12 (dd, J = 8.0, 7.0, 1.2 Hz, 1H), 7.26 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H); ^{13}C NMR (400 MHz, CD_3OD+DCl): δ 26.9, 60.4, 107.4, 112.6, 119.1, 120.3, 122.9, 124.9, 125.7, 128.3, 128.8, 138.2, 171.0; FAB-MS: *m*/*z* 245 [M + H]$^+$; Anal. Calcd for $C_{14}H_{16}N_2O_2 \cdot 0.2H_2O$: C, 67.83; H, 6.67; N, 11.30. Found: C, 67.68; H, 6.54; N, 11.06%.

(*S*)-*N*-(3-Methyl-2-buten-1-yl)tryptophan (*S*)-3a[6b] (Scheme 3). Off-white solid; mp 228–229 °C (Lit. mp 224–225 °C); IR (KBr) (cm^{-1}) 3276, 3057, 1611; ^{1}H NMR (400 MHz, CD_3OD + DCl): δ 1.63 (s, 3H), 1.76 (s, 3H), 3.48 (d, J = 6.4 Hz, 2H), 3.64 (d, J = 7.8 Hz, 2H), 4.23 (t, J = 6.4 Hz, 1H), 5.20 (t, J = 7.8 Hz, 1H), 7.04 (ddd, J = 7.8, 7.1, 1.0 Hz, 1H), 7.12 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H), 7.24 (s, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H); ^{13}C NMR (400 MHz, CD_3OD + DCl): δ 18.1, 26.0, 27.2, 45.6, 60.1, 107.5, 112.6, 114.7, 119.1, 120.3, 122.9, 125.6, 128.3, 138.3, 144.7, 171.2; FAB-MS: *m*/*z* 273 [M + H]$^+$.

Determination of optical purity of (*S*)-3a. A mixture of (*S*)-**3a** (20 mg, 0.073 mmol), MeOH (160 μL), AcOEt (625 μL) and $TMSCHN_2$ (600 μL, 0.36 mmol) was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and the resulting residue was purified by preparative TLC (hexane : AcOEt = 2 : 1) to give (*S*)-*N*-(3-methyl-2-buten-1-yl)tryptophan methyl ester (16 mg, 77%) as a colorless oil, whose optical purity was >99% ee as determined by HPLC analysis [CHIRALCEL AD-H, n-hexane/EtOH = 97/3, 1.0 mL min^{-1}, 220 nm (UV), t (minor) = 23 min, t (major) = 29 min).

(*S*)-*N*-(3-Methyl-2-buten-1-yl)tryptophan methyl ester[1c]. IR (neat) (cm^{-1}) 3408, 2923, 1735; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 3H), 1.66 (s, 3H), 1.95 (brs, 1H), 3.11 (dd, J = 13.2, 6.8 Hz, 1H), 3.15 (d, J = 6.4 Hz, 1H), 3.16 (d, J = 6.4 Hz, 1H), 3.21 (dd, J = 13.0, 6.8 Hz, 1H), 3.62 (s, 3H), 3.66 (t, J = 6.4 Hz, 1H), 5.16 (t, J = 6.8 Hz, 1H), 7.04 (d, J = 2.2 Hz, 1H), 7.11 (ddd, J = 7.8, 6.8, 1.0 Hz, 1H), 7.18 (ddd, J = 7.8, 6.8, 1.0 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 8.15 (brs, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 17.8, 25.7, 29.3, 45.6, 51.7, 61.4, 111.1, 111.3, 118.8, 119.4, 122.1, 122.3, 122.8, 127.5, 135.1, 136.2, 175.4; EI-MS: *m*/*z* 286 (M$^+$, 22%), 130 (BP).

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