

Ag(I)/TiO₂-Photocatalyzed N-Methylation of Amino Acids with Methanol

Yuna Morioka,^[a] Ivven Huang,^[a] Susumu Saito,^{*[a][b]} and Hiroshi Naka^{*[b]}

Dedicated to Professor Akihiko Kudo on the occasion of his 60th birthday

[a] Y. Morioka, I. Huang, Prof. Dr. S. Saito
Graduate School of Science, Nagoya University
Chikusa, Nagoya 464-8602 (Japan)

[b] Prof. Dr. S. Saito, Prof. Dr. H. Naka
Research Center for Materials Science, Nagoya University
Chikusa, Nagoya 464-8602 (Japan)
E-mail: saito.susumu@f.mbox.nagoya-u.ac.jp
E-mail: h_naka@nagoya-u.jp

Abstract: Silver(I)-loaded titanium dioxide (AgNO₃/TiO₂) catalyzes the direct N-methylation of amino acids with methanol under irradiation with UV light. This method produces a variety of *N*-methyl and *N,N*-dimethyl amino acids with retention of their optical purity.

N-Methylated amino acids are important structural features in non-ribosomal peptides.^[1,2] *N,N*-Dimethyl amino acids derived from valine, leucine, isoleucine, and phenylalanine are residues commonly encountered in bioactive natural products. Representative examples include dolastatin 10^[3,4] and coibamide A,^[5,6] both of which are natural products with potent antitumor activity (Figure 1). Moreover, *N,N*-dimethyl amino acids serve as isobaric tags for proteomics research.^[7,8]

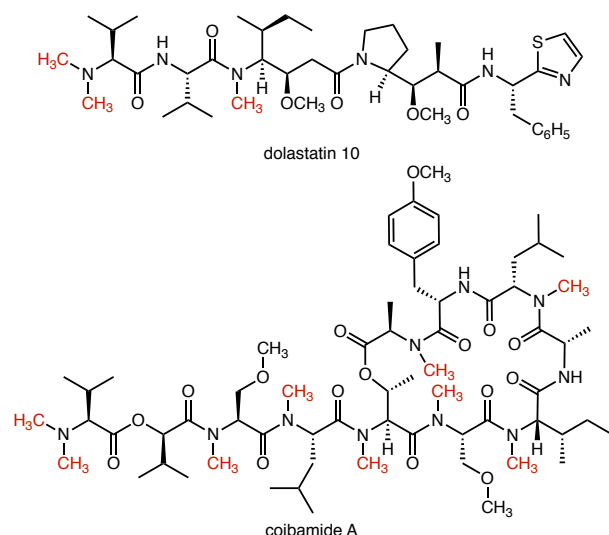
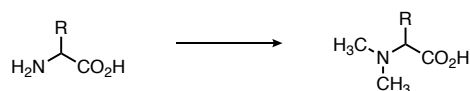


Figure 1. Representative, naturally occurring *N*-methyl amino acids.

Direct N-methylation of primary or secondary amino acids is a powerful tool for the synthesis of *N*-methylated amino acids.^[9] Classical methods include the direct N-methylation of amino acids with alkyl halides (CH₃I/Ag₂O),^[10] and the reductive amination with formaldehyde and sodium

borohydrides^[11] (Scheme 1A). However, these methods are limited, mostly due to the relatively low stability of the starting materials, and the formation of stoichiometric salt by-products that are inseparable from the charged amino acid products. The N-methylation of amino acids with methanol represents an attractive alternative process, considering that only the desired *N*-methyl amino acids and water are generated. In 2010, Huang reported the direct N-methylation of hydrophobic amino acids such as proline, leucine, and phenylalanine with methanol under an H₂ atmosphere at room temperature using palladium on charcoal (Pd/C) as a catalyst (Scheme 1B).^[12] The reductive methylation of amino acids with formaldehyde and H₂ over Pd/C is also possible.^[6,13,14]



A Conventional method (reliable but generates salt waste)

direct: CH₃I, Ag₂O; NaOH, ethanol
reductive: HCHO, NaBH₄, CF₃CH₂OH, reflux, 24 h

B Catalytic (clean but requires hazardous reagents)

direct: CH₃OH, H₂, Pd/C, rt, 76 h
reductive: HCHO, H₂, Pd/C, H₂O, rt, 5 d; reflux, 10 min

C Photocatalytic (this work) (clean and safe)

direct: CH₃OH, AgNO₃/TiO₂, *hν*, rt, 15 h

Scheme 1. N-Methylation of amino acids.

In the context of our program on the photocatalytic conversion of alcohols with metal-loaded titanium dioxide for N-alkylation of amines with alcohols,^[15–17] dehydrogenation of primary alcohols,^[18] and hydrogenolysis of allyl alcohols,^[19,20] we have reported that L-proline can be N-methylated with methanol using a silver-loaded titanium dioxide (Ag/TiO₂) photocatalyst.^[15] This was accomplished under irradiation with near UV-light and retention of the chirality at the α-position.^[15] Based on this previous preliminary result, we report herein a versatile method for the direct N-methylation of amino acids with methanol at room temperature using an AgNO₃-loaded TiO₂ (AgNO₃/TiO₂) photocatalyst (Scheme 1C). It should be

noted here that this method does not require any hazardous stoichiometric reducing reagents such as NaBH₄ or H₂.

Table 1. Photocatalytic Methylation of L-Valine (**1**).^[a]

$\text{H}_2\text{N}-\text{CH}(\text{CH}_3)-\text{CO}_2\text{H} \xrightarrow[\text{CH}_3\text{OH}, 35^\circ\text{C}, 3\text{ h}]{\text{UV-LEDs } (\lambda_0 = 365\text{ nm}), \text{AgNO}_3/\text{TiO}_2, -n\text{H}_2\text{O}} \text{H}_3\text{C}-\text{N}(\text{H})-\text{CH}(\text{CH}_3)-\text{CO}_2\text{H} \text{ or } \text{H}_3\text{C}-\text{N}(\text{CH}_3)_2-\text{CH}(\text{CH}_3)-\text{CO}_2\text{H}$			
<div style="display: flex; justify-content: space-around;"> 1 (L-Val) 2 3 </div>			
entry	changes in conditions	yield (%) ^[b]	
		2	3
1	none	45	36
2	15 h	<1	98 [88] ^[c]
3	CH ₃ OH/H ₂ O (1:1, 10 mL)	23	2
4	none ^[d]	45	33
5	CH ₃ OH/H ₂ O (1:1, 10 mL) ^[d]	13	<1
6	with NaOAc ^[e]	49	42
7	with NaOAc, 6 h ^[e]	<1	98 [72] ^[c]
8	with NaOAc, in the dark ^[e]	<1	<1
9	without AgNO ₃ /TiO ₂ , with NaOAc ^[e]	<1	<1

^[a]Conditions: **1** (0.10 mmol), CH₃OH (10 mL, 240 mmol), AgNO₃/TiO₂ (10 mg, 5 mol% Ag), UV-LEDs ($\lambda_0 = 365$ nm, 32 W), Ar (1 atm), 35 °C (stirred at rt, warmed by exposure to UV irradiation), 3 h. ^[b]Determined by ¹H NMR using maleic acid as the internal standard. ^[c]Isolated yields in brackets. ^[d]With Ag/TiO₂ (10 mg, 5 mol% Ag) prepared from AgNO₃/TiO₂, NaOAc, and NaBH₄ in H₂O. ^[e]With NaOAc (0.23 mmol).

Initially, we investigated the N-methylation of L-valine (**1**) because this reaction produces *N*-methyl valine (**2**) and *N,N*-dimethyl valine (**3**), which are often found in bioactive natural products. For that purpose, silver was loaded on a TiO₂ surface by impregnating TiO₂ (Aeroxide® P25) with an aqueous solution of silver nitrate (AgNO₃/TiO₂). The desired methyl amino acids **2** and **3** were obtained after mixing AgNO₃/TiO₂ (10 mg, 5 mol% Ag) and **1** (0.10 mmol) in dehydrated CH₃OH (10 mL, 240 mmol), and exposing the stirred reaction mixture for 3 h to irradiation from UV-LEDs ($\lambda_0 = 365$ nm, 32 W). A ¹H NMR analysis (internal standard: maleic acid) of the thus obtained mixture revealed the formation of **2** and **3** in 45% and 36% yield, respectively (Table 1, entry 1). The conversion of **1** to **3** was completed after 15 h of continuous irradiation (entry 2). Significant side reactions did not occur upon over-irradiation (Table S1). Product **3** was isolated in the form of the 0.58 hydrate after removing the solid photocatalyst by filtration, concentrating the filtrate, and drying under reduced pressure (88% yield). The obtained $[\alpha]_D^{21}$ value (+36.8 °; *c* 2.1; ethanol) is consistent with literature values ($[\alpha]_D^{26} = +38.6$ °; *c* 2.1; ethanol)^[6], which confirms the retention of the chirality at the α -carbon atom (Table 2, entry 1).

The photocatalytic N-methylation of **1** decelerated in the presence of water (Table 1, entry 3). The performance of the current Ag(I)/TiO₂ system is broadly the same as the original Ag(0)/TiO₂ system,^[15] for which the reduction of AgNO₃/TiO₂ with NaBH₄ in an aqueous NaOAc solution is conducted separately before the photon-promoted N-methylation starts

(Table 1, entries 1 and 3 vs 4 and 5, respectively). The presence of NaOAc enhances the reactivity (entry 6). However, the removal of NaOAc from **3** requires preparative HPLC separation (entry 7). The current photocatalytic reaction does not proceed in the dark, nor in the absence of the photocatalyst (Table 1, entries 8 and 9).

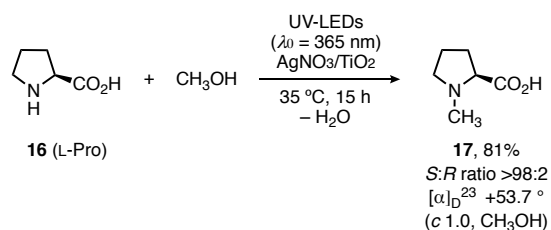
Table 2. N,N-Dimethylation of Amino Acids.^[a]

$\text{H}_2\text{N}-\text{CH}(\text{R})-\text{CO}_2\text{H} + 2\text{CH}_3\text{OH} \xrightarrow[\text{35 } ^\circ\text{C}, 15\text{ h}]{\text{UV-LEDs } (\lambda_0 = 365\text{ nm}), \text{AgNO}_3/\text{TiO}_2, -2\text{H}_2\text{O}} \text{H}_3\text{C}-\text{N}(\text{CH}_3)_2-\text{CH}(\text{R})-\text{CO}_2\text{H}$			
entry	reactant	product	yield, ^[b] S/R or dr [α] _D ^[c]
1	1 (L-Val)		3 88% $[\alpha]_D^{21} +36.8^\circ$ (<i>c</i> 2.1, ethanol)
2	4 (Gly)		5 80%
3	6 (L-Ala)		7 94%, S/R ratio >98:2 ^[c] $[\alpha]_D^{23} -0.293^\circ$ (<i>c</i> 0.3, CH ₃ OH)
4	8 (L-Phe)		9 97% $[\alpha]_D^{21} +29.8^\circ$ (<i>c</i> 1.0, CH ₃ OH)
5	10 (L-Ile)		11 92%, dr >98:2 ^[d] $[\alpha]_D^{23} +47.8^\circ$ (<i>c</i> 1.0, CH ₃ OH)
6	12 (L-Leu)		13 82% $[\alpha]_D^{21} +47.6^\circ$ (<i>c</i> 1.0, CH ₃ OH)
7	14 (L-Met)		15 68% $[\alpha]_D^{23} +53.7^\circ$ (<i>c</i> 1.0, CH ₃ OH)

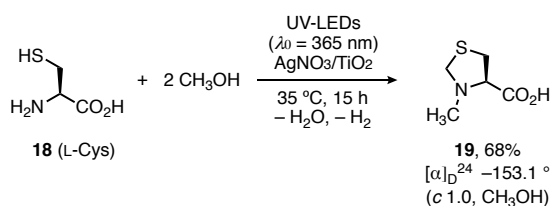
^[a]Conditions: **1** (0.10 mmol), CH₃OH (10 mL, 240 mmol), AgNO₃/TiO₂ (10 mg, 5 mol% Ag, 5 wt%), UV-LEDs ($\lambda_0 = 365$ nm, 32 W), Ar (1 atm), 35 °C, 15 h. ^[b]Isolated yield. ^[c]Determined by chiral GC/MS. ^[d]The diastereomeric ratio (dr) was determined by ¹H NMR spectroscopy.

Table 2 summarizes the results of the photocatalytic N-methylation of various amino acids under the optimized reaction conditions (Table 1, entry 2). The conversions and yields of each compound were determined by NMR analysis using 1,4-dioxane as an internal standard. Simple amino acids such as L-valine (**1**), glycine (**4**), L-alanine (**6**), L-phenylalanine (**8**), L-isoleucine (**10**), and L-leucine (**12**) were smoothly converted into the corresponding dimethyl amino acids without producing any side products (Table 2, entries 1–6).

Retention of the stereochemistry at the α -carbon atoms in **7** and **11** was unambiguously confirmed by chiral GC/MS and NMR (diastereomeric ratio) analysis, respectively. In contrast to previously reported catalytic methods, the presence of a sulfur atom in L-methionine (**14**) was compatible (Table 2, entry 7). Unfortunately, irradiation of polar amino acids such as lysine, serine, threonine, arginine, tyrosine, asparagine, glutamine, aspartic acid, and glutamic acid (without protection of the corresponding side chains) under the standard conditions resulted in the formation of complex mixtures. As in the case of our previous work, the N-methylation of L-proline (**16**) proceeded smoothly to give **17** in 81% yield (*S/R* ratio >98:2, Scheme 2).



Scheme 2. N-Methylation of L-proline.



Scheme 3. N-Methylation and N,S-acetalization of L-cysteine.

A trial on the dimethylation of L-cysteine (**18**) furnished mono-methylated *N,S*-acetal **19** in 68% yield (Scheme 3).^[21] It should be noted here that **19** is a protected form of *N*-monomethyl cysteine, which is potentially usable in the Kent ligation (native chemical ligation).^[22,23]

In summary, we found a straightforward system for the photocatalytic N-methylation and N,N-dimethylation of amino acids with methanol at ambient temperature using a silver(I)-loaded TiO_2 photocatalyst. Further applications of this method to natural amino acids with protected side chains currently under investigation.

Experimental Section

Preparation of the photocatalyst. Silver nitrate (78.7 mg, 0.46 mmol) was dissolved in deionized water (30.0 mL) in a 100-mL round bottom flask wrapped in aluminum foil. Subsequently, TiO_2 (950 mg) was added to the solution. The resulting suspension was rotated at 50 °C for 30 min on a rotary evaporator, before the solvent was removed under reduced pressure (20 mmHg) to give $\text{AgNO}_3/\text{TiO}_2$. The preparative method and the characterization data for Ag/TiO_2 have previously been reported.^[14]

Photocatalytic N-methylation of 1 to afford 3. $\text{AgNO}_3/\text{TiO}_2$ (10 mg, 5 mol% Ag), L-valine (**1**, 11.8 mg, 0.10 mmol), and dehydrated CH_3OH (10 mL) were added to a 30-mL Pyrex® test tube equipped with a magnetic stirring bar and a rubber septum. After sonication for 15 s, the resulting mixture was

sparged with argon (cannula, 5 min) and stirred at rt for 15 h under exposure to UV light (UV-LEDs; $\lambda_0 = 365 \text{ nm}$; 32 W). Then, the mixture was filtered through a membrane filter (pore size: 0.45 μm) and the solvent was evaporated. The residue was dissolved in D_2O and examined by NMR spectroscopy (Table 1), using maleic acid as an internal standard (98%). During isolation and characterization (Table 2), the residue was dried under reduced pressure (0.01 mmHg, 10 h) to give **3**·0.58 H_2O (14.1 mg, 88% yield). Analytical data: white solid, Mp 123.4–127.8 °C; ^1H NMR (600 MHz, D_2O , 1,4-dioxane) δ 0.96 (d, $J = 6.6 \text{ Hz}$, 3H), 1.08 (d, $J = 6.6 \text{ Hz}$, 3H), 2.31–2.39 (m, 1H), 2.89 (s, 6H), 3.41 (d, $J = 6.0$, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, D_2O) δ 16.4, 19.9, 26.6, 40.7, 43.7, 76.8, 172.3; elemental analysis calcd for C, 53.98; H, 10.46; N, 8.99, found C, 53.98; H, 10.45; N, 8.64; $[\alpha]_{\text{D}}^{21} +36.8^\circ$ (*c* 2.1, ethanol) [lit.^[6] $[\alpha]_{\text{D}}^{26} +38.6^\circ$ (*c* 2.1, ethanol)]; HRMS (ESI) calcd for $[\text{C}_7\text{H}_{14}\text{NO}_2]^-$ ($[\text{M}-\text{H}]^-$) 144.1030, found 144.1053.

Supporting Information

Supplementary table; experimental procedures; spectral data (PDF)

^1H and ^{13}C NMR spectra; chromatographic charts (PDF)

Acknowledgments

This work was supported by JSPS KAKENHI Grant Number JP26410115 (to H.N.), JGC Scholarship Foundation (to H.N.), Iwatani Foundation (to H.N.), and Fukuoka Naohiko Memorial Foundation (to H.N.). Y.M. and I.H. are grateful to financial support from JSPS fellowship (DC) and GTR program (Nagoya Univ.), respectively. We sincerely thank Prof. S. Oishi (Nagoya Univ.) for his help on preparative HPLC isolation of **3**. We are grateful to Prof. R. Noyori (Nagoya Univ.), Prof. A. Kudo (Tokyo Univ. of Sci), Dr. A. E. H. Wheatley (Univ. of Cambridge), and Dr. M. Inoue (AIST) for their encouragement and suggestions.

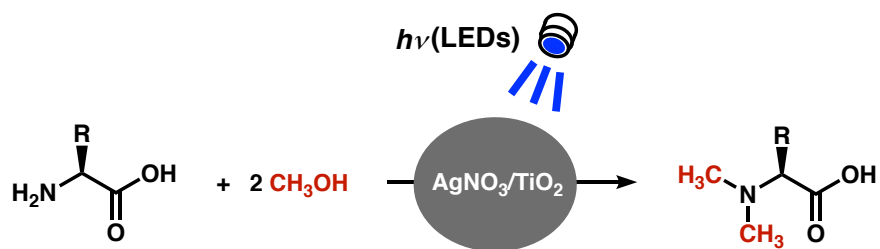
Keywords: amino acid • methylation • photocatalysis • silver • methanol

References

- [1] D. C. Gournelis, G. G. Laskaris, R. Verpoorte, *Nat. Prod. Rep.* **1997**, 14, 75–82.
- [2] M. M. Jourli, D. J. Richard, *Chem. Commun.* **2004**, 2011–2015.
- [3] G. R. Pettit, Y. Kamano, C. L. Herald, A. A. Tuinman, F. E. Boettner, H. Kizu, J. M. Schmidt, L. Baczyński, K. B. Tomer, R. J. Bontems, *J. Am. Chem. Soc.* **1987**, 109, 6883–6885.
- [4] W. Zhou, X.-D. Nie, Y. Zhang, C.-M. Si, Z. Zhou, X. Sun, B.-G. Wie, *Org. Biomol. Chem.* **2017**, 15, 6119–6131.
- [5] R. A. Medina, D. E. Goeger, P. Hills, S. L. Mooberry, N. Huang, L. I. Romero, E. Ortega-Barria, W. H. Gerwick, K. L. McPhail, *J. Am. Chem. Soc.* **2008**, 130, 6324–6325.
- [6] G. Yao, Z. Pan, C. Wu, W. Wang, L. Fang, W. Su, *J. Am. Chem. Soc.* **2015**, 137, 13488–13491.
- [7] F. Xiang, H. Ye, R. B. Chen, Q. Fu, L. J. Li, *Anal. Chem.* **2010**, 82, 2817–2825.
- [8] Q. Yu, X. Shi, T. Greer, C. B. Lietz, K. C. Kent, L. Li, *J. Proteome Res.* **2016**, 15, 3420–3431.
- [9] L. Aurelio, A. B. Hughes, *Synthesis of N-Alkyl Amino Acids*. In *Amino Acids, Peptides, and Proteins in Organic Chemistry: Origins and Synthesis of Amino Acids*; A. B. Hughes Ed.; Wiley-VCH, **2009**, Chapter 6.
- [10] B. C. Das, S. D. Gero, E. Lederer, *Biochem. Biophys. Res. Commun.* **1967**, 29, 211–215.
- [11] M. Tajbakhsh, R. Hosseinzadeh, H. Alinezhad, S. Ghahari, A. Heydari, S. Khaksar, *Synthesis* **2011**, 490.

- [12] C.-P. Xu, Z.-H. Xiao, B.-Q. Zhuo, Y.-H. Wang, P.-Q. Huang, *Chem. Commun.* **2010**, 46, 7834–7836.
- [13] A. M. King, M. De Ryck, R. Kaminski, A. Valade, J. P. Stables, H. Kohn, *J. Med. Chem.* **2011**, 54, 6432–6442.
- [14] M. Stodulski, A. Maminska, J. Mlynarski, *Tetrahedron: Asymmetry*, **2011**, 22, 464–467.
- [15] V. N. Tsarev, Y. Morioka, J. Caner, Q. Wang, R. Ushimaru, A. Kudo, H. Naka, S. Saito, *Org. Lett.* **2015**, 17, 2530–2533.
- [16] L.-M. Wang, K. Jenkinson, A. E. H. Wheatley, K. Kuwata, S. Saito, H. Naka, *ACS Sustainable Chem. Eng.* **2018**, 6, 15419–15424.
- [17] L.-M. Wang, Y. Morioka, K. Jenkinson, A. E. H. Wheatley, S. Saito, H. Naka, *Sci. Rep.* **2018**, 8, 6931.
- [18] M. Shibata, R. Nagata, S. Saito, H. Naka, *Chem. Lett.* **2017**, 46, 580–582.
- [19] J. Caner, Z. Liu, Y. Takada, A. Kudo, H. Naka, S. Saito, *Catal. Sci. Technol.* **2014**, 4, 4093–4098.
- [20] Y. Takada, J. Caner, S. Kaliyamoorthy, H. Naka, S. Saito, *Chem. - Eur. J.* **2017**, 23, 18025–18032.
- [21] W. Ando, T. Takata, L. Huang, Y. Tamura, *Synthesis*, **1986**, 139–140.
- [22] P. E. Dawson, *Isr. J. Chem.* **2011**, 51, 862–867.
- [23] M. Jbara, S. K. Maity, M. Seenaiiah, A. Brik, *J. Am. Chem. Soc.* **2016**, 138, 5069–5075.

Entry for the Table of Contents



Silver-nitrate-loaded titanium dioxide ($\text{AgNO}_3/\text{TiO}_2$) promotes the direct N-methylation of amino acids with methanol under UV light irradiation. This method produces a variety of *N,N*-dimethyl amino acids under retention of their optical purity.

Twitter username: @hirosh_naka

Supporting Information for

Ag(I)/TiO₂-Photocatalyzed N-Methylation of Amino Acids with Methanol

Yuna Morioka,[†] Ivven Huang,[†] Susumu Saito,^{†,#,*} and Hiroshi Naka^{#,*}

[†]Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan

[#]Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan

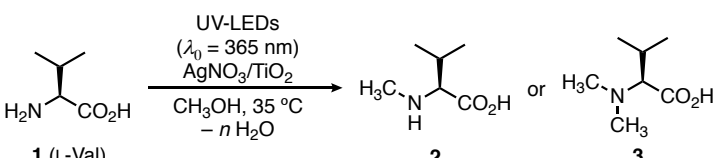
saito.susumu@f.mbox.nagoya-u.ac.jp; h_naka@nagoya-u.jp

Table of Contents

1. Supplementary Table	...S2
2. General Comments	...S2
3. Materials	...S2
4. Preparation of Photocatalyst	...S3
5. Photocatalytic Reactions	...S4
6. References	...S6

1. Supplementary Table

Table S1. Reaction Progress in the Photocatalytic Methylation of **1** ^[a].

				
1 (L-Val)		2	or	3
		molar ratio (%) ^[b]		
entry	time (h)	1	2	3
1	3	18	45	36
2	5	<1	27	72
3	7	<1	16	84
4	10	<1	3	97
5	13	<1	2	98
6	15	<1	<1	99
7	19	<1	1	99
8	25	<1	1	99

^[a]Conditions are analogous to those in Table 1. ^[b]Determined by ¹H NMR.

2. General Comments

GC/MS analyses were performed on Agilent 7820A series network GC systems and Agilent 5977E series Mass Selective Detectors (EI). The following conditions were used unless otherwise noted: [column: CYCLOSIL-B capillary column ($l = 30$ m, $d = 0.25$ mm, film thickness = 0.25 μ m), carrier gas: He (1.5 mL/min, at 27 psi)]. ¹H and ¹³C{¹H} NMR spectra were recorded on a JEOL ECA-600 (600 MHz for ¹H, 150 MHz for ¹³C{¹H}) at 27 °C. Chemical shifts are reported as δ in ppm and are referenced to 1,4-dioxane ($\delta 3.76$ ppm for ¹H, internal reference) or tetramethylsilane (TMS, $\delta 0.68$ ppm for ¹³C{¹H}, external reference)]. The following abbreviations are used: s = singlet, d = doublet, dd = doublet of doublets, and m = multiplet. High-resolution mass spectra (HRMS) were obtained from micrOTOF-QII (ESI, Bruker). Low-resolution mass spectra (LRMS) were obtained from Agilent 5973 MSD (EI). Preparative reverse phase high performance liquid chromatography (PREP-HPLC) was conducted using JASCO preparative instruments equipped with UV-2077 plus detector, PU 2080 plus and 2087 plus pumps.

3. Materials

The following reagents were purchased from commercial suppliers and used as received unless otherwise noted.

Preparation of Photocatalyst

titanium(IV) dioxide (Aeroxide P25)	Sigma-Aldrich
silver(I) nitrate	Wako Chemicals
sodium acetate	Wako Chemicals
sodium borohydride	Tokyo Chemical Industry

Photocatalytic Reactions

L-valine (1)	Wako Chemicals
dehydrated methanol (CH ₃ OH)	KANTO Chemicals
deuterium oxide (D ₂ O, 99.8%)	KANTO Chemicals
DL-valine	Tokyo Chemical Industry
DL-phenylalanine	KANTO Chemicals
DL-proline	Tokyo Chemical Industry
DL-alanine	Tokyo Chemical Industry
<i>N,O</i> -bis(trimethylsilyl)acetamide (BSA)	Tokyo Chemical Industry
glycine (4)	Tokyo Chemical Industry
L-alanine (6)	Wako Chemicals
L-phenylalanine (8)	Sigma-Aldrich
L-isoleucine (10)	KANTO Chemicals
L-leucine (12)	Tokyo Chemical Industry
L-methionine (14)	Wako Chemicals
L-proline (16)	Sigma-Aldrich
L-cysteine (18)	Sigma-Aldrich
acetic acid	Wako Chemicals
1,4-dioxane	Wako Chemicals
maleic acid	Tokyo Chemical Industry
dehydrated toluene	KANTO Chemicals.
chloroform- <i>d</i> (CDCl ₃ , 99.8% + 0.05% v/v TMS)	Cambridge Isotope Laboratory Inc.
HCl (2 M in diethyl ether)	Sigma-Aldrich

4. Preparation of the Photocatalyst

Silver nitrate (78.7 mg, 0.46 mmol) was dissolved in deionized water (30.0 mL) in a 100-mL round bottom flask wrapped with aluminum foil. Subsequently, TiO₂ (950 mg) was added to the solution. The resulted suspension was rotated at 50 °C for 30 min on a rotary evaporator, before the solvent was removed under vacuum (20 mmHg) to give AgNO₃/TiO₂. The preparative method and the characterization data for Ag/TiO₂ have previously been reported.¹

5. Photocatalytic Reactions

General Procedure: AgNO₃/TiO₂ (10 mg, 5 mol% Ag), amino acid (0.10 mmol), and dehydrated CH₃OH (10 mL) were added to a 30-mL Pyrex test tube (IWAKI TE-32) equipped with a magnetic stirring bar and a rubber septum. After sonication for 15 s, the resulting mixture was sparged with argon (cannula, 5 min) and stirred at rt under exposure to UV light [λ_0 = 365 nm, 32 W UV-LEDs (2 × 16W LN-128UV2-365 model provided by CCS Inc.)] (mixture temperature = ~35 °C) for indicated periods. The reaction mixture was filtered through a 0.45 μ m membrane filter (Merck Millipore SLLHH13NK 0.45 μ m pore size, hydrophilic PTFE membrane, 13 mm diameter) and the solvent was evaporated. The residue was analyzed by ¹H NMR in D₂O using maleic acid (0.1 M) as an internal standard (Table 1). During isolation and characterization (Table 2), the residue was dried under reduced pressure (0.01 mmHg, 10 h) using an oil pump to give products as hydrates. The degrees of hydrate were determined by NMR using 1,4-dioxane (8.8 mg, 100 μ mol, 3.77 ppm, 8H) as an internal standard.

3: Substrate: L-valine (**1**, 11.8 mg, 0.10 mmol). The product was dried to give **3**•0.58H₂O (14.1 mg, 88% yield). Analytical data: white solid, Mp 123.4–127.8 °C; ¹H NMR (600 MHz, D₂O, 1,4-dioxane) δ 0.96 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H), 2.31–2.39 (m, 1H), 2.89 (s, 6H), 3.41 (d, J = 6.0 Hz, 1H); ¹³C{¹H} NMR (150 MHz, D₂O) δ 16.4, 19.9, 26.6, 40.7, 43.7, 76.8, 172.3; elemental analysis calcd for C, 53.98; H, 10.46; N, 8.99, found C, 53.98; H, 10.45; N, 8.64; [α]_D²¹ +36.8 ° (c 2.1, ethanol) [lit.² [α]_D²⁶ +38.6° (c 2.1, ethanol)]; HRMS (ESI) calcd for [C₇H₁₄NO₂][−] ([M-H][−]) 144.1030, found 144.1053.

PREP-HPLC purification of 3: A crude mixture of **3** that contains NaOAc (after reaction using AgNO₃/TiO₂ and NaOAc for 6 h) was purified by PREP-HPLC [column: C18-20-4 (OD-S), H₂O/CH₃CN + 0.1% TFA = 9:1–2:3 (gradient), 10 mL/min] to give **3** (72% yield). Analytical data: ¹H NMR (600 MHz, D₂O) δ 0.95 (d, J = 9.0 Hz, 3H), 1.08 (d, J = 9.0 Hz, 3H), 2.40 (octet, J = 5.5 Hz, 1H), 2.89 (d, J = 10.3 Hz, 6H), 3.63 (d, J = 4.9 Hz, 1H); ¹³C{¹H} NMR (150 MHz, D₂O) δ 15.5, 19.1, 26.1, 40.2, 43.2, 74.6, 170.6.

5: Substrate: glycine (**4**, 7.5 mg, 0.10 mmol). The product was dried to afford **5**•2.6H₂O (12.2 mg, 80% yield). Analytical data: pale yellow oil; ¹H NMR (600 MHz, D₂O, 1,4-dioxane) δ 2.93 (s, 6H), 3.72 (s, 2H); ¹³C{¹H} NMR (150 MHz, D₂O) δ 44.2, 60.5, 170.9; HRMS (ESI) calcd for [C₄H₈NO₂][−] ([M-H][−]) 102.0561, found 102.0566.

7: Substrate: L-alanine (**6**, 9.0 mg, 0.10 mmol). The product was dried to afford **7**•0.22H₂O (11.5 mg, 94% yield). Analytical data: white solid; ¹H NMR (600 MHz, D₂O,

1,4-dioxane) δ 1.49 (d, J = 7.2 Hz, 3H), 2.86 (s, 6H), 3.72 (dd, J = 14.4, 6.6 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, D_2O) δ 12.6, 39.5, 43.3, 66.6, 174.6; HRMS (ESI) calcd for $[\text{C}_5\text{H}_{10}\text{NO}_2^-]$ ($[\text{M}-\text{H}]^-$) 116.0717, found 116.0738; $[\alpha]_{\text{D}}^{23}$ -0.293° (c 0.3, CH_3OH); chiral GC/MS (Agilent Cyclosil-B, chromatographic elution: isothermal at 50°C for 1.0 min, 50 – 70°C at a rate of $0.1^\circ\text{C min}^{-1}$, isothermal at 70°C for 0 min, 70 – 230°C at a rate of $20^\circ\text{C min}^{-1}$, isothermal at 230°C for 4 min, after silylation with BSA [70°C , 150 min]): t_{R} 36.6 min (S), S : R ratio $>98:2$. A racemic sample was prepared using the same procedure (48% yield): t_{R} 36.7 min (S), t_{R} 37.2 min (R).

9: Substrate: L-phenylalanine (**8**, 16.5 mg, 0.10 mmol). The product was dried to afford **9**• $0.24\text{H}_2\text{O}$ (18.8 mg, 97% yield). Analytical data: white solid; ^1H NMR (600 MHz, D_2O , 1,4-dioxane) δ 2.93 (s, 6H), 3.12 (dd, J = 13.8, 9.6 Hz, 1H), 3.34 (dd, J = 15.0, 7.2 Hz, 1H), 3.84 (dd, J = 9.6, 6.6 Hz, 1H), 7.32–7.41 (m, 5H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, D_2O) δ 34.7, 41.8, 43.5, 72.8, 128.1, 129.6, 129.8, 135.9, 172.9; HRMS (ESI) calcd for $[\text{C}_{11}\text{H}_{14}\text{NO}_2^-]$ ($[\text{M}-\text{H}]^-$) 192.1030, found 192.1047; elemental analysis calcd for C, 66.84; H, 7.89; N, 7.08, found C, 66.84; H, 7.96; N, 6.99; $[\alpha]_{\text{D}}^{21}$ $+29.8^\circ$ (c 1.0, CH_3OH).

11: Substrate: L-isoleucine (**10**, 13.1 mg, 0.10 mmol). The product was dried to afford **11**• $1.0\text{H}_2\text{O}$ (16.4 mg, 92% yield). Analytical data: white solid; ^1H NMR (600 MHz, D_2O , 1,4-dioxane) δ 0.93–0.98 (m, 6H), 1.29–1.36 (m, 1H), 1.49–1.56 (m, 1H), 2.03–2.10 (m, 1H), 2.88 (s, 6H), 3.50 (d, J = 4.8 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, D_2O) δ 11.9, 13.7, 27.3, 33.4, 40.4, 44.2, 75.4, 172.2; HRMS (ESI) calcd for $[\text{C}_8\text{H}_{16}\text{NO}_2^-]$ ($[\text{M}-\text{H}]^-$) 158.1187, found 158.1198; $[\alpha]_{\text{D}}^{23}$ $+47.8^\circ$ (c 1.0, CH_3OH).

13: Substrate: L-leucine (**12**, 13.1 mg, 0.10 mmol). The product was dried to afford **13**• $2.8\text{H}_2\text{O}$ (17.0 mg, 82% yield). Analytical data: white solid; ^1H NMR (600 MHz, D_2O , TMS) δ 0.95–0.97 (m, 6H), 1.63–1.75 (m, 3H), 2.88 (s, 6H), 3.55–3.57 (m, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, D_2O) δ 21.2, 23.4, 25.7, 37.4, 40.8, 43.0, 70.9, 174.2; HRMS (ESI) calcd for $[\text{C}_8\text{H}_{16}\text{NO}_2^-]$ ($[\text{M}-\text{H}]^-$) 158.1187, found 158.1215; $[\alpha]_{\text{D}}^{21}$ $+47.6^\circ$ (c 1.0, CH_3OH) [lit.³ $[\alpha]_{\text{D}}^{26}$ $+35.1^\circ$ (c 1.0, CH_3OH)].

15: Substrate: L-methionine (**14**, 14.9 mg, 0.10 mmol). The product was dried to afford **15**• $2.3\text{H}_2\text{O}$ (17.7 mg, 81% yield). Analytical data: pale yellow solid; ^1H NMR (600 MHz, D_2O , 1,4-dioxane) δ 2.11–2.23 (m, 5H), 2.53–2.60 (m, 1H), 2.62–2.67 (m, 1H), 2.90 (s, 6H), 3.69 (dd, J = 9.0, 4.2 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, D_2O , TMS) δ 14.8, 27.8, 29.8, 40.6, 43.6, 70.5, 173.1; HRMS (ESI) calcd for $[\text{C}_7\text{H}_{14}\text{NO}_2\text{S}^-]$ ($[\text{M}-\text{H}]^-$) 176.0751, found 175.0750; $[\alpha]_{\text{D}}^{23}$ $+53.7^\circ$ (c 1.0, CH_3OH).

17: Substrate: L-proline (**16**, 11.5 mg, 0.10 mmol). The product was dried to afford **17**•1.9H₂O (14.0 mg, 79% yield). Analytical data: pale yellow solid; ¹H NMR (600 MHz, D₂O, 1,4-dioxane) δ 1.96–2.02 (m, 1H), 2.06–2.12 (m, 1H), 2.13–2.19 (m, 1H), 2.47–2.54 (m, 1H), 2.94 (s, 3H), 3.14–3.18 (m, 1H), 3.70–3.80 (m, 1H), 3.80–3.91 (m, 1H); ¹³C{¹H} NMR (150 MHz, D₂O) δ 23.5, 29.4, 41.4, 57.0, 71.3, 174.3; HRMS (ESI) calcd for [C₆H₁₀NO₂[−]] ([M-H][−]) 128.0717, found 128.0742; [α]_D²¹ −92.2 ° (*c* 1.5, CH₃OH) [lit.¹ [α]_D²³ −78° (*c* 1.5, CH₃OH)]; chiral GC/MS (Agilent Cyclosil-B, chromatographic elution: isothermal at 50 °C for 1.0 min, 50–70 °C at a rate of 0.2 °C min^{−1}, isothermal at 70 °C for 0 min, 70–230 °C at a rate of 20 °C min^{−1}, isothermal at 230 °C for 4 min, after silylation with BSA [70°C, 150 min]): *t*_R 87.6 min (*S*), *S*:*R* ratio >98:2. A racemic sample was prepared using the same procedure (54% yield): *t*_R 89.2 min (*S*), *t*_R 87.7 min (*R*).

19: Substrate: L-cysteine (**18**, 12.1 mg, 0.10 mmol). The product was dried to afford **19**•3.7H₂O (14.6 mg, 68% yield). Analytical data: pale yellow solid; ¹H NMR (600 MHz, D₂O, 1,4-dioxane) δ 3.05 (s, 3H), 3.40 (dd, *J* = 11.4, 6.0 Hz, 1H), 3.59 (dd, *J* = 11.4, 8.4 Hz, 1H), 4.20 (dd, *J* = 8.4, 6.0 Hz, 1H), 4.27 (d, *J* = 10.2 Hz, 1H), 4.68 (d, *J* = 10.8 Hz, 1H); ¹³C{¹H} NMR (150 MHz, D₂O) δ 33.3, 41.4, 58.8, 72.9, 172.0; HRMS (ESI) calcd for [C₅H₈NO₂S[−]] ([M-H][−]) 146.0281, found 146.0287; [α]_D²⁴ −153.1 ° (*c* 1.0, CH₃OH).

6. References

- ¹ Tsarev, V, N.; Morioka, Y.; Caner, J.; Wang, Q.; Ushimaru, R.; Kudo, A.; Naka, H.; Saito, S. N-Methylation of Amines with Methanol at Room Temperature. *Org. Lett.* **2015**, *17*, 2530–2533.
- ² Yao, G.; Pan, Z.; Wu, C.; Wang, W.; Fang, L.; Su, W. Efficient Synthesis and Stereochemical Revision of Coibamide A. *J. Am. Chem. Soc.* **2015**, *137*, 13488–13491.
- ³ Barcelo, V, S.; Bienz, S. Synthesis of Highly Substituted 3-Pyrrolin-2-ones from *N,N*-Disubstituted α -Amino Acids. *J. Org. Chem.* **2018**, *83*, 2734–2743.

Supporting Information (NMR and Chromatographic Charts) for

Ag(I)/TiO₂-Photocatalyzed N-Methylation of Amino Acids with Methanol

Yuna Morioka,[†] Ivven Huang,[†] Susumu Saito,^{†, #, *} and Hiroshi Naka^{#, *}

[†]Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan

[#]Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan

saito.susumu@f.mbox.nagoya-u.ac.jp; h_naka@nagoya-u.jp

