Catalytic Removal of *N*-Allyloxycarbonyl Groups Using the [CpRu(IV)(π -C₃H₅)(2-quinolinecarboxylato)]PF₆ Complex. A New Efficient Deprotecting Method in Peptide Synthesis.

Shinji Tanaka, Hajime Saburi, Takanori Murase, Masahiro Yoshimura, and
Masato Kitamura*

Research Center for Materials Science and Department of Chemistry, Nagoya
University, Japan. Fax: +81-52-789-2261; Tel: +81-52-789-2957; E-mail:
kitamura@os.rcms.nagoya-u.ac.jp

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(1) Instruments

Nuclear magnetic resonance (NMR) spectra were recorded on a 600-MHz spectrometer. The chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane or in ppm relative to CHCl_3 , $\text{CHD}_2\text{COCD}_3$, and CHD_2OD (δ 7.26, 2.05, and 3.31 in ^1H NMR and δ 77.0, 29.8, and 49.0 in ^{13}C NMR). Signal patterns of ^1H NMR are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Infrared (IR) spectra were measured by use of polytetrafluoroethylene (PTFE) film. Elemental analyses, high-resolution mass spectra (HRMS), and high performance liquid chromatography (HPLC) analyses were performed on standard laboratory instruments.

(2) Materials

Gas: Argon gas was purified by being passed through a column of the BASF R3-11 catalyst at 80 °C and then through a column of granular calcium sulfate.

Solvents: Methanol and ethanol were dried and degassed at the reflux temperature in the presence of magnesium (250 mg/100 mL) under a stream of argon for 6 h and distilled into Schlenk flasks. *iso*-Propyl alcohol, *tert*-butyl alcohol, DMF, acetonitrile, and dichloromethane were distilled from calcium hydride (250 mg/100 mL). THF was distilled from sodium benzophenone ketyl (250 mg/100 mL). Water was

purchased and used without further purification. All of the solvents were degassed by three freeze–thaw cycles before use.

Silica gel: Flash column chromatography was performed using Daiko AP 300 or nacalai tesque Silica Gel 60 (spherical, neutral).

Catalyst: [CpRu(IV)(π -C₃H₅)(2-quinolinecarboxylato)]PF₆ was synthesized according to a literature report.¹

Substrates: Allyl 2-phenylethyl carbonate (**1a**)², allyl *N*-(2-phenylethyl)carbamate (**1b**),³ allyl *N*-cyclohexylcarbamate (**1c**),⁴ allyl *N*-phenylcarbamate (**1e**),⁵ and allyl morpholine-4-carboxylate (**1f**)⁶ were synthesized according to published procedures. Allyl *N*-2-(2-methyl-3-phenylpropyl)carbamate (**1d**) and *N*-allyloxycarbonyl-(*S*)-proline *tert*-butyl ester (**1g**) were synthesized as follows.

Allyl *N*-2-(2-methyl-3-phenylpropyl)carbamate (**1d**)

A 100-mL flask connected to a supply of argon was equipped with a Teflon-coated magnetic stirring bar. The flask was charged with 1-phenyl-2-methyl-2-propanamine (1.10 g, 7.38 mmol). Through an inlet capped by a septum rubber, dry dichloromethane (25 mL), triethylamine (1.34 mL, 10.0 mmol), and allyl chloroformate (1.21 g, 10.0 mmol) were introduced. After the rubber was replaced with a glass stopper coated by silicon grease, the mixture was stirred at 30 °C for 24 h. A saturated

solution of aqueous ammonium chloride (15 mL) was added and the organic layer was washed successively with saturated aqueous sodium hydrogen carbonate (15 mL) and brine (15 mL). The pale yellow organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the filtrate concentrated under reduced pressure to give the crude product. The product was purified by flash column chromatography (AP 300, 100g; eluent, 9:1 hexane–ethyl acetate) and then distillation (58 °C/0.01 mmHg) to give **1d** (0.120 g, 0.515 mmol, 7.0% yield) as a colorless liquid. ¹H NMR (600 MHz, CDCl₃) δ 1.30 (s, 6H, CH₃), 2.98 (s, 2H, C₆H₅CH₂), 4.51 (s, 1H, NH), 4.56 (s, 2H, CH₂O), 5.23 (d, 1H, *J* = 10.3 Hz, CH=CHH), 5.32 (d, 1H, *J* = 17.2 Hz, CH=CHH), 5.91–5.97 (m, 1H, CH=CH₂), 7.13 (dd, 2H, *J* = 1.38, 7.57 Hz, aromatic), 7.23 (dt, 1H, *J* = 1.38, 7.57 Hz, aromatic), 7.28 (d, 2H, *J* = 7.57 Hz, aromatic). ¹³C NMR (151 MHz, CDCl₃) δ 27.3, 45.3, 53.1, 64.9, 117.5, 126.3, 128.0, 130.5, 133.1, 137.8, 155.6. IR (PTFE film) 3344, 2926, 1707, 1504, 1453, 1267, 1207, 1081, 924.4, 801.4, 732.2, 701.0 cm⁻¹. Anal Calcd for C₁₄H₁₉NO₂: C, 72.07; H, 8.21; N, 6.00, found: C, 72.28; H, 8.50; N, 6.06.

N-Allyloxycarbonyl-(*S*)-proline *tert*-butyl ester (**1g**)

A 200-mL-three-necked flask connected to a supply of argon was equipped with a Teflon-coated magnetic stirring bar. The flask was charged with (*S*)-proline *tert*-butyl

ester hydrochloride (2.08 g, 10.0 mmol). Through an inlet capped by a septum rubber, dry dichloromethane (46 mL) and triethylamine (2.79 mL, 20.0 mmol) were introduced followed by slow addition of allyl chloroformate (1.45 g, 12.0 mmol) using a dropping funnel at 0 °C. After the rubber was replaced with a glass stopper coated by silicon grease, the mixture was stirred at 30 °C for 12 h. 1 M HCl_{aq} (45 mL) was added and the organic layer was washed successively with saturated aqueous sodium hydrogen carbonate (45 mL) and brine (45 mL). The pale yellow organic layer was dried over sodium sulfate. After removing the drying agent by filtration the filtrate was concentrated under reduced pressure to give the crude product. The product was purified by flash column chromatography (AP 300, 80g; eluent, 9:1 hexane–ethyl acetate) and then distillation (90 °C/0.01 mmHg) to give **1g** (1.51 g, 5.91 mmol, 59% yield) as a colorless liquid. ¹H NMR (600 MHz, CDCl₃) δ 1.44 (s, 9H, CH₃), 1.84–1.92 (m, 3H), 2.18–2.30 (m, 1H), 3.38–3.53 (m, 2H, NCH₂), 4.12–4.20 (m, 1H, NCHCOO), 4.45–4.59 (m, 2H, OCH₂), 5.11–5.19 (m, 1H, CH=CHH), 5.26–5.34 (m, 1H, CH=CHH), 5.86–5.99 (m, CH=CH₂). ¹³C NMR (151 MHz, acetone-*d*₆) δ 23.9, 31.5, 47.6, 60.3, 65.9, 81.3, 116.8, 134.3, 154.6, 172.7 (major). 24.8, 30.4, 47.0, 60.8, 65.9, 81.1, 117.0, 134.5, 155.0, 172.4 (minor). IR (PTFE film) 2978, 2883, 1709, 1406, 1347, 1219, 1155, 986.5, 924.2, 839.5, 768.6 cm⁻¹. Anal Calcd for C₁₃H₂₁NO₄: C, 61.16; H, 8.29; N, 5.49, found: C, 61.01; H, 8.41; N, 5.14.

(3) Deallyloxycarbonylation

Catalytic deprotection of allyl carbonate **1a**: A mixture of allyl 2-phenylethyl carbonate (**1a**) (10.8 g, 52.2 mmol) and methanol (95 mL), which was placed in a 150-mL Schlenk tube containing a Teflon-coated magnetic stirring bar under argon atmosphere, was degassed by three freeze–thaw cycles. To this solution, [CpRu(π -C₃H₅)(2-quinolinecarboxylato)]PF₆ (55.0 mg, 105 μ mol) was added. The inlet was sealed by a glass stopper coated in silicon grease. The yellow solution was stirred for 0.5 h at 30 °C. The reaction mixture was concentrated under reduced pressure (100 mmHg) to give a crude product in which the yield and purity were determined to be >99% by ¹H-NMR analysis ((600 MHz, CDCl₃) **1a**: δ 4.35 (t, 2H, J = 6.91 Hz, CH₂CH₂O), **2a**: δ 3.87 (q, 2H, J = 6.19 Hz, CH₂CH₂OH)). This product was distilled (55 °C/0.01 mmHg) to give **2a** (6.28 g) in 99% isolated yield. ¹H NMR spectra of crude product were attached at the end of this material.

Catalytic deprotection of **1a** for attaining a TON of 1,000,000: In 20-mL Schlenk tube equipped with a young's tap containing **1a** (5.20 g, 2.52 mmol) and methanol (5 mL) was degassed by three freeze–thaw cycles. To this, a methanol solution containing 1 mM [CpRu(π -C₃H₅)(2-quinolinecarboxylato)]PF₆ (2.5 μ L, 2.5 nmol) was added. The solution was stirred for 9 d at 70 °C under a slow argon flow and addition of methanol (0.4 mL/h). The yield was determined to be 99% by ¹H NMR analysis.

Deprotection of allyl carbamate: The general procedure was described in the manuscript. Listed below are the reaction scale, the yield and ^1H NMR signals of **1** and **2** for determination of the yield. ^1H NMR spectra of crude product were attached at the end of this material.

Allyl *N*-(2-phenylethyl)carbamate (**1b**): 0.300 mmol; >99%; ^1H NMR (600 MHz, acetone- d_6) **1b**: δ 2.81 (t, 2H, $J = 7.57$ Hz, $\text{C}_6\text{H}_5\text{CH}_2$), **2b**: δ 3.17 (t, 2H, $J = 7.57$ Hz, $\text{C}_6\text{H}_5\text{CH}_2$). ^1H NMR data was consistent with the commercially available authentic sample.

Allyl *N*-cyclohexylcarbamate (**1c**): 0.267 mmol; >99%; ^1H NMR (600 MHz, acetone- d_6) **1c**: δ 4.48 (d, 2H, $J = 5.51$ Hz, CH_2O), **2c**: δ 1.67 (d, 1H, $J = 13.08$ Hz, cyclohexyl). ^1H NMR data was consistent with the commercially available authentic sample.

Allyl *N*-2-(2-methyl-3-phenylpropyl)carbamate (**1d**): 0.188 mmol; >99%; ^1H NMR (600 MHz, CDCl_3) **1d**: δ 1.30 (s, 6H, CH_3), **2d**: δ 1.34 (s, 6H, CH_3). ^1H NMR data was consistent with the commercially available authentic sample.

Allyl *N*-phenylcarbamate (**1e**): 0.28 mmol; 88%; ^1H NMR (600 MHz, acetone- d_6) **1e**: δ 7.01 (t, 1H, $J = 7.57$ Hz, aromatic), **2e**: δ 7.60–7.68 (m, 3H, aromatic). ^1H NMR data was consistent with the commercially available authentic sample.

Allyl morpholine-4-carboxylate (**1f**): 0.280 mmol; 99%; ^1H NMR (600 MHz, acetone-

*d*₆) **1f**: δ 3.59 (t, 4H, J = 3.79 Hz, CH₂OCH₂), **2f**: δ 4.00 (t, 4H, J = 4.82 Hz, CH₂OCH₂). ¹H NMR data was consistent with the commercially available authentic sample.

N-Allyloxycarbonyl-(*S*)-proline *tert*-butyl ester (**1g**): 0.30 mmol; >99%; ¹H NMR (600 MHz, CD₃OD) **1g**: δ 1.42 (s, 9H, C(CH₃)₃, major) and 1.43 (s, 9H, C(CH₃)₃, minor), **2g**: δ 1.50 (s, 9H, C(CH₃)₃). ¹H NMR data was consistent with the commercially available authentic sample. The optical purity was determined to be >99% ee by HPLC analysis after removal of the *tert*-butyl group in CF₃COOH at 30 °C for 1 h to form proline (Figure S1). Conditions: column, CHIRALPAK WH; eluent, a 0.25 mM aqueous copper sulfate; flow rate, 1.5 mL/min; detection, 254-nm light. t_R of *S*, 4.1 min; t_R of *R*, 6.3 min.

(4) Synthesis of tripeptide

AOC-(*S*)-Pro-Gly-*Ot*-C₄H₉ (**11**)

A dry and argon-filled 20-mL-three-necked flask containing a Teflon-coated magnetic stirring bar was charged with glycine *tert*-butyl ester hydrochloride (172 mg, 1.00 mmol), dry dichloromethane (1.7 mL), (*S*)-*N*-AOC-proline⁷ (354 mg, 1.91 mmol), and PyBOP (620 mg, 1.20 mmol). To the resulting clear solution was added DIEA (0.52 mL, 387 mg, 3.00 mmol) at 0 °C. The inlet was sealed by a glass stopper coated

by silicon grease. The mixture was stirred at room temperature for 4 h, the solution was diluted with ethyl acetate (10 mL). This solution was washed successively with a 1 M HCl_{aq} (10 mL), sodium hydrogen carbonate (10 mL) and brine (10 mL). After drying over sodium sulfate, the solution was filtered and the volatiles removed by evaporation under reduced pressure. The residue was purified by flash column chromatography (AP 300, 10 g; eluent, 3:2 hexane–ethyl acetate) to give the dipeptide **11** (261 mg, 0.837 mmol, 98.5% yield) as a colorless oil. ¹H NMR (600 MHz, acetone-*d*₆) δ 1.43 (s, 9H, C(CH₃)₃), 1.83–2.24 (brn, 4H, CH₂), 3.40–3.47 (br, 1H, CHH), 3.48–3.56 (br, 1H, CHH), 3.75–3.87 (m, 2H, CHH and CH), 4.30 (dd, 1H, *J* = 6.89 Hz, CHH), 4.53 (br, 2H), 5.10 (d, 1H, *J* = 9.64 Hz, CH=CHH minor), 5.17 (d, 1H, *J* = 10.33 Hz, CH=CHH major), 5.26 (d, 1H, *J* = 17.2 Hz, CH=CHH minor), 5.32 (d, 1H, *J* = 17.2 Hz, CH=CHH major), 5.85–6.00 (m, 1H, CH=CH₂). ¹³C NMR (151 MHz, CDCl₃) δ 24.0, 24.9, 28.2, 32.0, 42.2, 42.4, 47.5, 48.0, 61.2, 61.5, 65.9, 66.2, 81.5, 100.8, 116.6, 117.1, 134.4, 155.0, 155.7, 170.0, 172.8, 173.2. IR (PTFE film) 3321, 3085, 2978, 1698, 1532, 1405, 1364, 1156, 1034, 984.4, 923.9, 848.2, 770.2 cm⁻¹. Anal. Calcd for C₁₅H₂₄N₂O₅: C, 57.68, H, 7.74, N, 8.97. Found: C, 57.49, H, 7.84, N, 8.73.

H-Pro-Gly-Ot-C₄H₉

A mixture of dipeptide (**11**) (15.6 mg, 0.050 mmol), methanol (5 mL), and trifluoromethanesulfonic acid (7.5 mg, 0.050 mmol) was placed in a 20-mL Schlenk

tube containing a Teflon-coated magnetic stirring bar under an atmosphere of argon and degassed by three freeze–thaw cycles. To this solution was added [CpRu(π -C₃H₅)(2-quinolinecarboxylato)]PF₆ (0.3 mg, 0.5 μ mol). The inlet was sealed by a young's tap. The yellow solution was stirred for 2 h at 30 °C. The yield was determined to be 99% yield by ¹H NMR after a part of reaction mixture was concentrated under reduced pressure (100 mmHg). ¹H NMR (600 MHz, CD₃OD) δ 1.47 (s, 9H, CH₃), 2.04–2.15 (m, 3H, CH₂CHH), 2.41–2.48 (m, 1H, CHH), 3.15–3.30 (m, 1H, NCHHCH₂), 3.39–3.44 (m, 1H, NCHHCH₂), 3.87 (d, 1H, *J* = 17.2 Hz, OOCCHHN), 3.98 (d, 1H, *J* = 17.2 Hz, OOCCHHN), 4.31 (t, 1H, *J* = 6.89 Hz, CH). After the resulting methanol solution was treated with NaHCO₃ (100 mg), DMF (1 mL) was added. The resulting mixture was concentrated to remove volatiles to afford the DMF solution of the product. ¹H NMR (600 MHz, CD₃OD–DMF-*d*₇ 9:1) δ 1.45 (s, 9H, CH₃), 1.70–1.86 (m, 3H, CH₂CHH), 2.09–2.16 (m, 1H, CHH), 2.91–2.99 (m, 2H, NCH₂CH₂), 3.71 (dd, 1H, *J* = 1.06 and 6.20 Hz, CH), 3.84 (s, 2H, OOCCH₂N). This was used for the next reaction without further purification.

AOC-Pro-Pro-Gly-Ot-C₄H₉

A dry and argon-filled 20-mL-two-necked flask containing a Teflon-coated magnetic stirring bar was charged with H-Pro-Gly-Ot-C₄H₉ (50 μ mol) in DMF, dry dichloromethane (1 mL), (*S*)-*N*-AOC-proline (12 mg, 60 μ mol), and PyBOP (42 mg, 80

μmol). To the resulting solution was added DIEA (26 μL , 150 μmol) and the inlet was sealed by a glass stopper coated by silicon grease. The mixture was stirred at room temperature for 10 h. The mixture was diluted with ethyl acetate (5 mL) and washed successively with a 1 M HCl aq (1 mL x 2), sodium hydrogen carbonate (1 mL x 2) and brine (3 mL). After drying over sodium sulfate, the solution was filtered and the volatiles removed by evaporation under reduced pressure. The residue was then purified by preparative TLC (90:10 ethyl acetate-methanol) to afford AOC-Pro-Pro-Gly-Ot-C₄H₉ as a colorless oil (20.0 mg, 48.9 μmol , 98% yield). ¹H NMR (600 MHz, CDCl₃) δ 1.44 (brs, 9H, C(CH₃)₃), 1.79–2.57 (m, 8H, CH₂), 3.49–3.99 (m, 6H, CH₂ and CH), 4.32–4.70 (m, 4H, CH₂), 5.15–5.22 (m, 1H, CH=CHH), 5.23–5.34 (m, 1H, CH=CHH), 5.82–5.97 (m, 1H, CH=CH₂), 7.24 (br, 1H, NH), 8.15 (br, 1H, NH). ¹³C NMR (151 MHz, CDCl₃) δ 22.1, 23.4, 24.2, 25.2, 26.9, 28.0, 29.3, 29.4, 30.4, 31.7, 41.9, 42.2, 46.6, 46.9(2), 46.9(6), 47.0, 47.2, 57.5, 58.2, 58.5, 59.6, 59.7, 60.9, 65.7, 65.9, 66.0, 81.4, 81.8, 81.9, 117.0, 117.2, 117.3, 132.7, 132.9, 133.0, 153.9, 154.8, 155.0, 168.3, 168.7, 171.2, 171.3(6), 171.3(9), 171.4, 172.4, 172.7. IR (PTFE film) 3316, 2975, 1689, 1533, 1409, 1363, 1152, 987.2, 922.7, 847.3, 767.8 cm⁻¹. HRMS m/z (MH⁺) obsd 410.2481, calcd 410.2291.

H-Pro-Pro-Gly-Ot-C₄H₉ (12)

A mixture of AOC-Pro-Pro-Gly-Ot-C₄H₉ (2.1 mg, 0.050 mmol), methanol-*d*₄ (0.5

mL), and trifluoromethanesulfonic acid (0.75 mg, 0.050 mmol) was placed in a 5-mL Schlenk tube under an atmosphere of argon and degassed by three freeze–thaw cycles. This solution was transferred to NMR tube equipped with Young’s tap containing [CpRu(π -C₃H₅)(2-quinolinecarboxylato)]PF₆ (0.3 mg, 0.5 μ mol). The inlet was sealed by a young’s tap. The yellow solution was stored for 2 h at 30 °C. The yield was determined to be 99% yield determined by ¹H NMR ((600 MHz, CD₃OD) **12**: δ 14.7 (br, 9H, C(CH₃)₃), 19.1–2.22 (m, 6H, CH₂), 2.26–2.46 (m, 1H, CHH), 2.46–2.58 (m, 1H, CHH), 3.28–3.34 (m, 1H, CHH), 3.38–3.46 (m, 1H, CHH), 3.55–3.63 (m, 1H, CHH), 3.65–3.70 (m, 1H, CHH), 3.72 (d, 1H, CHH), 3.93 (d, 1H, CHH), 4.46–4.57 (m, 2H, CH). allyl methyl ether: δ 3.92 (d, 2H, J = 5.96 Hz, CH₂CH), 5.17 (dd, 1H, J = 1.37, 10.5 Hz, CH=CHH), 5.27 (dd, 1H, J = 1.37, 17.2 Hz, CH=CHH), 5.85–5.93 (m, 1H, CH=CHH)). HRMS m/z (MH⁺) obsd 326.2091, calcd 326.2080.

H-Pro-Pro-Gly-OH (**9** ($n = 1$))

After the methanol-*d*₄ solution of **12** was concentrated under reduced pressure (100 mmHg), to this was added CF₃COOH (300 μ L). The mixture was stir for 2 h at 30 °C and all volatile was removed under reduced pressure (0.01 mmHg) to give the H-Pro-Pro-Gly-OH (**9** ($n = 1$)) in quantitative yield as a crude mixture. The physical property was consistent with the reported value.⁸

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Figure S1. HPLC Chart of proline. Conditions: column, CHIRALPAK WH; eluent, a 0.25 mM CuSO₄ solution; flow rate, 1.5 mL/min; detection, 254-nm light. **a:** The product obtained by the present catalytic deallylcarboxylation of protected (*S*)-proline (**1g**) followed by hydration of *tert*-butyl ester. **b:** Authentic racemic sample.

¹H NMR spectrum of
crude product **2d**

¹H NMR spectrum of reaction mixture:
product **2g** and allyl methyl ether

¹H NMR spectrum of reaction mixture:
product 12 and allyl methyl ether