HETEROCYCLES, Vol. 101, No. 2, 2020, pp. 486 - 495. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 26th June, 2019, Accepted, 24th July, 2019, Published online, 13th August, 2019
DOI: 10.3987/COM-19-S(F)31

OXIDATIVE C-C BOND CLEAVAGE OF N-PROTECTED CYCLIC AMINES BY HNO_3-TFA SYSTEM

Kosuke Yamamoto, Hiroyuki Toguchi, Toshihiro Harada, Masami Kuriyama, and Osamu Onomura*

Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan. E-mail: onomura@nagasaki-u.ac.jp

Abstract – Oxidative C-C bond cleavage of N-protected cyclic amines was achieved by using 70% HNO_3 in trifluoroacetic acid (TFA) to afford ω-amino acid derivatives in high yields. The C-C bond cleavage reaction smoothly proceeded under aerobic condition with a simple procedure. The use of 70% HNO_3 as an oxidant source enabled to conduct the reaction at a higher substrate concentration than that of the previous condition using $NaNO_2$ in TFA. In addition, some ω-amino acids were obtained with improved reaction efficiency under the present reaction conditions.

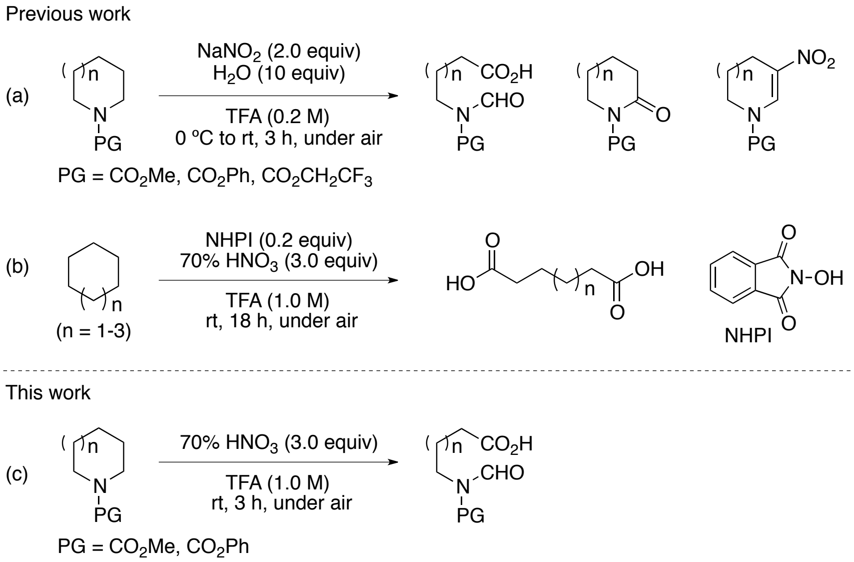
INTRODUCTION

Trifluoroacetic acid (TFA) is known as the simplest perfluoroacetic acid with strong acidity ($pK_a = 0.23$ at 25 °C in H_2O), and medium boiling point (72.4 °C), and has been used in a variety of organic transformations as solvent, reagent, and acid catalyst.[1] We previously demonstrated that TFA was an efficient reaction medium for the oxidation reaction.[2-4] For example, oxidation of adamantanes by the combination of $NaNO_2/O_2$/TFA system afforded adamantanol derivatives.[2] The $NaNO_2$/TFA system was also utilized in the oxidative C-C bond cleavage of cycloalkanols, providing dicarboxylic acids in high efficiency.[3]

Non-proteinogenic amino acids (NPAAs) have been attracted great attention in the field of medicinal and synthetic chemistry.[5] Because of an easy availability of a variety of cyclic amines, oxidative C-C bond cleavage of cyclic amines would be one of the promising approaches for the preparation of NPAAs.[6-10] In this context, our group has reported the oxidative C-C bond cleavage of a variety of *N*-alkoxycarbonylpiperidines and pyrrolidines by using $NaNO_2$ in TFA (Scheme 1a).[11] The C-C bond cleavage selectively

---

Dedicated with respect to Professor Kaoru Fuji on the occasion of his 80th birthday occurred between α-position and β-position of a nitrogen atom, affording N-protected β and γ-amino acids in high yields. However, the $NaNO_2$/TFA system required the substrate concentration of 0.2 M with additional H_2O to dissolve nitrite salt, and the use of nitrite salt limited an attempt to perform the reaction at higher concentration which might be more favorable for the large scale production. In addition, some *N*-methoxycarbonyl (Moc)-piperidine derivatives gave the corresponding amino acids in relatively low yields. Recently, we reported the combination of 70% HNO_3 and catalytic amount of *N*-hydroxyphthalimide (NHPI)[12] in TFA efficiently promoted the oxidative C-C bond cleavage of cycloalkanes to afford the corresponding dicarboxylic acids in high yields (Scheme 1b).[4a] The use of 70% HNO_3 instead of $NaNO_2$ enabled to conduct the reaction at a higher concentration. In this paper, we reported the oxidative cleavage of N-alkoxycarbonylated cyclic amines with 70% HNO_3 in TFA. The oxidative C-C bond cleavage of N-heterocycles proceeded even in the absence of NHPI catalyst, affording the corresponding ω-amino acids in good to high yields.

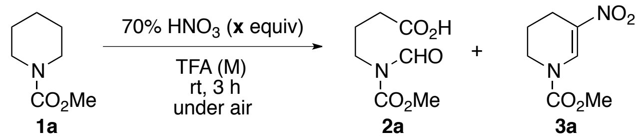


Scheme 1. Oxidative C-C bond cleavage reactions in TFA

RESULTS AND DISCUSSION

We began this study by exploring the oxidative C-C bond cleavage reaction by HNO_3 using *N*-Moc-piperidine as a model substrate. The optimization results are shown in Table 1. When *N*-Moc-piperidine (1 mmol) was treated with 3.0 equiv of 70% HNO_3 in trifluoroacetic acid (TFA) (5 mL, 0.2 M) in the presence of 0.2 equiv of *N*-hydroxyphthalimide (NHPI) under air atmosphere at room temperature, the desired ω-amino acid **2a** was obtained in 73% yield along with a small amount of 3-nitroenamine **3a** as a byproduct (Table 1, entry 1). *N*-Moc-piperidine was also effectively transformed to ω-amino acid **2a** in an identical yield even in the absence of NHPI catalyst (entry 2). Decreasing the amount of HNO_3 (2.0 or 1.0 equiv) resulted in decreased yields of **2a** (entries 3 and 4). Next, the effect of the reaction concentration was examined. Pleasingly, the amount of TFA did not affect the reaction efficiency even at a higher concentration, providing **2a** in 81% yield at the concentration of 1.0 M in TFA (entries 5-7). It is noteworthy that the concentration of the present reaction was 5 times higher than $NaNO_2$/TFA system.[11] In addition, the selectivity toward **2a** was improved compared with that observed in the previous conditions.[13] The effect of the concentration of HNO_3 was then examined at 1.0 M in TFA. Both concentrated HNO_3 and 60% HNO_3 were suitable oxidant for this transformation, affording **2a** in 83 and 79% yields, respectively (entries 8 and 9). The reaction under an Ar atmosphere did not affect the reaction efficiency, affording **2a** in 80% yield (entry 10). On the basis of these results, we selected the combination of 3.0 equiv of 70% HNO_3 and the concentration of 1.0 M in TFA as optimal reaction conditions for this transformation.[14]

Table 1. Optimization of oxidative cleavage reaction

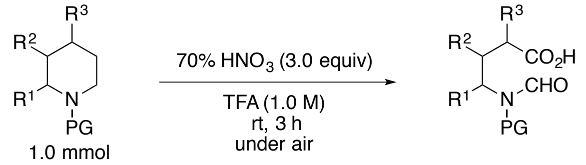


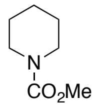
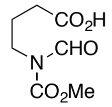
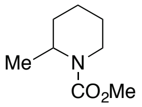
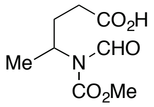
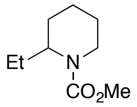
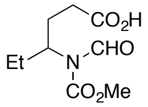
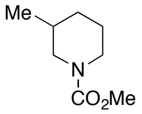
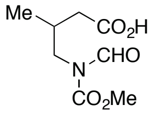
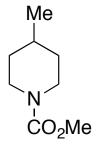
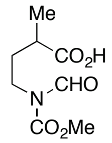
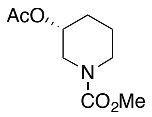
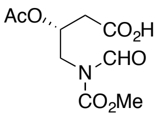
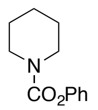
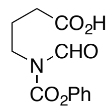
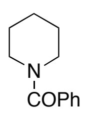
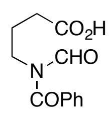
entry	x	conc. (M)	yield (%) 2a	yield (%) 3a
1[a]	3.0	0.2	73	3
2	3.0	0.2	73	4
3	2.0	0.2	39	n.d.
4	1.0	0.2	22	n.d.
5	3.0	0.25	79	0
6	3.0	0.5	75	trace
7	3.0	1.0	81	0
8[b]	3.0	1.0	83	0
9[c]	3.0	1.0	79	0
10[d]	3.0	1.0	80	0

[a] The reaction was carried out with 0.2 equiv of *N*-hydroxyphthalimide.
[b] 99% HNO_3 was used. [c] 60% HNO_3 was used. [d] Under an Ar atmosphere.
n.d. = not determined.

With the optimized conditions in hand, some substituted piperidines were subjected to the present oxidative cleavage reaction. The results are summarized in Table 2. *N*-Moc-piperidines with methyl or ethyl group at the 2-position were successfully transformed into the corresponding ω-amino acids **2b** and **2c** in 76 and 78% yields, respectively (Table 2, entries 2 and 3). Although *N*-Moc-3-methylpiperidine was consumed completely under the reaction conditions, the product **2d** was obtained in a moderate yield together with some unidentified byproducts (entry 4).[15] A methyl group at the 4-position of piperidine ring was tolerated in the present reaction to afford **2e** in a high yield (entry 5). Interestingly, previously reported $NaNO_2$/TFA system provided compounds **2b** and **2e** in moderate yields together with a large amount of 3-nitroenamines.[11] Optically active *N*-Moc-piperidine bearing acetoxy group at the 3-position was converted to enantiomerically pure **2f** in 73% yield (entry 6). Piperidines with other protecting groups were also tested in the present reaction. *N*-Phenoxycarbonyl protecting group are applicable for the present reaction conditions, affording **2g** in 76% yield (entry 7). Substrate with *N*-benzoyl group was not suitable for this oxidative cleavage reaction probably due to the formation of protonated species (entry 8).[11,16]

Table 2. Oxidative cleavage of piperidine derivatives

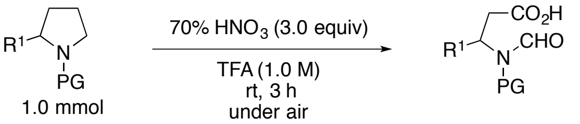


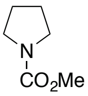
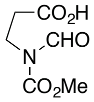
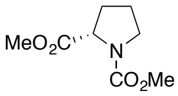
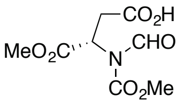
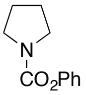
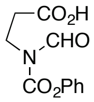
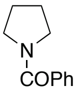
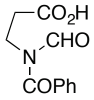
entry	substrate		product yield[a]	
1		**1a**		**2a**, 81% [79%]
2		**1b**		**2b**, 76% [47%]
3		**1c**		**2c**, 78% [n.a.]
4		**1d**		**2d**, 47% [42%]
5		**1e**		**2e**, 88% [43%]
6		**1f**		**2f**, 73% [68%]
7		**1g**		**2g**, 76% [98%]
8		**1h**		**2h**, n.d. [n.d.]

[a] Isolated yield after column chromatography. Yields given in ref. 11 are shown in brackets. n.a. = not available. n.d. = not detected.

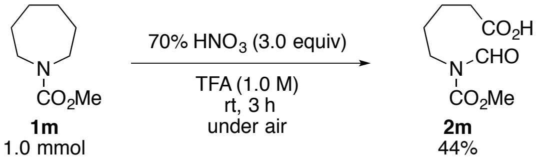
Next, oxidative cleavage of N-protected pyrrolidine was examined under the optimized conditions (Table 3). *N*-Moc-pyrrolidine **1i** was also a good substrate for this reaction to afford **2i** in a high yield, whereas *N*-Moc-L-proline derivative **1j** gave **2j** in a moderate yield (Table 3, entries 1 and 2). Pyrrolidine with *N*-phenoxycarbonyl group was successfully transformed to the desired amino acid **2k** when the reaction was conducted with 0.2 equiv of NHPI (entry 3). The oxidative cleavage of *N*-benzoylpyrrolidine **1l** did not proceed under the present reaction conditions (entry 4). The present reaction was also applicable to the oxidative cleavage of 7-membered N-heterocycle. As shown in Scheme 2, *N*-Moc-hexamethyleneimine **1m** gave the corresponding ω-amino acid **2m** in a moderate yield. In order to show the scalability of the present reaction, the oxidative cleavage of **1a** was performed on a 8.0 mmol scale, and the desired product **2a** was obtained in 76% yield (Scheme 3).

Table 3. Oxidative cleavage of pyrrolidine derivatives

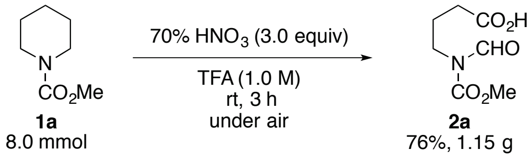


entry	substrate		product yield[a]	
1		**1i**		**2i**, 71% [74%]
2		**1j**		**2j**, 54% [52%]
3		**1k**		**2k**, 68%[b] [83%]
4		**1l**		**2l**, n.d. [n.d.]

[a] Isolated yield after column chromatography. Yields given in ref. 11 are shown in brackets.
[b] 0.2 equiv of NHPI. n.d. = not detected.



Scheme 2. Oxidative cleavage of 7-membered N-heterocycle



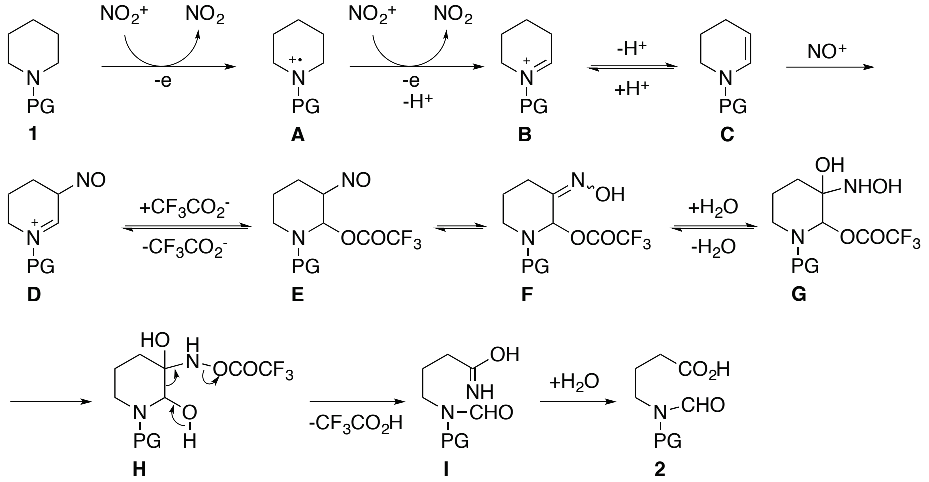
Scheme 3. Gram-scale experiment

On the basis of the previous literature,[11] tentative reaction mechanism of the oxidative cleavage reaction with 70% HNO_3 in TFA are proposed as shown in Scheme 4. Oxidation of compound **1** is initiated by nitronium ion (NO_2^+) which is generated from HNO_3 and TFA, affording iminium ion species **B** and enamine **C**.[17] Enamine **C** is trapped by in situ generated nitrosonium cation (NO^+) to give nitroso compound **D**. Nucleophilic addition of trifluoroacetoxy ion to **D** followed by oxime tautomerization, hydrolysis, and migration of a trifluoroacetyl group resulted in the formation of compound **H**. Elimination of trifluoroacetoxy ion and simultaneous C-C bond cleavage provide ring opened compound **I**. Finally, hydrolysis of compound **I** affords the corresponding ω-amino acid **2**.

$$HNO_3 + CF_3CO_2H \rightleftharpoons NO_2^+ + CF_3CO_2^- + H_2O$$

$$2NO_2 \rightleftharpoons N_2O_4 \rightleftharpoons NO_2^+ + HNO_2$$

$$HNO_2 + CF_3CO_2H \rightleftharpoons NO^+ + CF_3CO_2^- + H_2O$$



Scheme 4. Plausible mechanism

In conclusion, we have developed the oxidative C-C bond cleavage reaction of N-heterocycles using 70% HNO_3 in TFA for the synthesis of ω-amino acid derivatives. The present oxidative cleavage reaction smoothly proceeded under aerobic condition without any special experimental techniques. The use of 70% HNO_3 as oxidant source enabled to modify the reaction concentration, which improved the reaction efficiency and reduced the used amount of TFA. Further mechanistic study and application to other N-heterocycles are currently underway in our laboratory.

EXPERIMENTAL

General Information. Unless otherwise noted, all reactions were performed in a heavy-walled glass tube (Ace Glass, Inc., approximate total capacity 35 mL) equipped with a magnetic stir bar at room temperature under air. Infrared (IR) spectra were recorded on a Shimadzu FT-IR8100A or IRAfinity-1 spectrophotometer. Data are expressed as wavenumber of absorption (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a VARIAN Gemini-300 spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR). Chemical shift values are expressed in parts per million (ppm) relative to internal TMS (δ 0.00 ppm) for ^{1}H NMR and $CDCl_3$ (δ 77.0 ppm) for ^{13}C NMR. Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br, broad. High-resolution mass spectra (HRMS) were recorded on JEOL JMS-700N by electron impact ionization (EI) or fast atom bombardment (FAB) mass spectrometry. All chemicals were used as received without further purifications.

General procedure for the oxidative C-C bond cleavage of N-alkoxycarbonylated cyclic amines

To a solution of cyclic amine **1** (1.0 mmol) in trifluoroacetic acid (1.0 mL) was added 70% HNO_3 (270 mg, 3.0 mmol, 3.0 eq) under air atmosphere at room temperature. After stirring for 3 h at the same temperature, all volatiles were removed under reduced pressure to give the crude product. Purification by silica gel column chromatography afforded the cleaved product **2**.

Gram-scale experiment

Following the general procedure, gram-scale experiment was performed using **1a** (8.0 mmol, 1.14 g), trifluoroacetic acid (8.0 mL), and 70% HNO_3 (2.16 g, 24 mmol, 3.0 eq) in 300 mL round bottom flask, affording **2a** (1.15 g, 76%) after purification by silica gel column chromatography.

4-(*N*-(Methoxycarbonyl)formamido)butanoic acid (2a). Light yellow oil. IR (neat): 3200, 2950, 2361, 1761, 1713, 1441, 1417, 1348, 1279, 1161, 1126, 966, 769 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.22 (s, 1H), 3.91 (s, 3H), 3.73 (t, J = 7.0 Hz, 2H), 2.39 (t, J = 7.3 Hz, 2H), 1.90 (quin, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 162.9, 154.3, 53.9, 39.7, 30.9, 23.0. HRMS (EI) *m*/*z*: calcd for $C_7H_{11}NO_5$ ([M]$^+$) 189.0637, found 189.0645.

4-(*N*-(Methoxycarbonyl)formamido)pentanoic acid (2b). Light yellow oil. IR (neat): 3100, 2964, 1747, 1700, 1540, 1450, 1350, 1219, 954, 868, 777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.22 (s, 1H), 4.61-4.54 (m, 1H), 3.86 (s, 3H), 2.34-2.20 (m, 3H), 2.00-1.91 (m, 1H), 1.37 (d, J = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.6, 163.4, 154.1, 53.6, 48.0, 31.0, 28.0, 18.1. HRMS (EI) *m*/*z*: calcd for $C_8H_{13}NO_5$ ([M]$^+$) 203.0793, found 203.0798.

4-(*N*-(Methoxycarbonyl)formamido)hexanoic acid (2c). Light yellow oil. IR (neat): 3120, 2974, 2962, 2937, 1757, 1680, 1440, 1384, 1327, 1278, 1217, 948, 935, 783 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.29 (s, 1H), 4.41-4.31 (m, 1H), 3.88 (s, 3H), 2.34-2.21 (m, 3H), 2.00-1.87 (m, 2H), 1.76-1.64 (m, 1H), 0.84 (t, J = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6, 163.9, 154.5, 60.4, 53.8, 31.0, 26.7, 25.1, 10.8. HRMS (FAB) *m*/*z*: calcd for $C_9H_{16}NO_5$ ([M+H]$^+$) 218.1028, found 218.1031.

4-(*N*-(Methoxycarbonyl)formamido)-3-methylbutanoic acid (2d). Light yellow oil. IR (neat): 3150, 2964, 1747, 1700, 1539, 1448, 1838, 1190, 1080, 972, 777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.25 (s, 1H), 3.90 (s, 3H), 3.67-3.53 (m, 2H), 2.39-2.33 (m, 2H), 2.18-2.14 (m, 1H), 0.99 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.1, 163.3, 154.5, 54.0, 45.6, 38.6, 29.2, 17.4. HRMS (EI) *m*/*z*: calcd for $C_8H_{13}NO_5$ ($[M]^+$) 203.0793, found 203.0810.

4-(*N*-(Methoxycarbonyl)formamido)-2-methylbutanoic acid (2e). Light yellow oil. IR (neat): 3000, 2980, 1707, 1686, 1448, 1344, 1199, 1147, 953, 777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.21 (s, 1H), 3.91 (s, 3H), 3.73 (t, *J* = 7.3 Hz, 2H), 2.49 (sextet, *J* = 7.0 Hz, 1H), 1.99 (dq, *J* = 14.6, 7.5 Hz, 1H), 1.66 (dq, *J* = 14.1, 6.9 Hz, 1H), 1.25 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.7, 162.8, 154.3, 53.9, 38.6, 36.8, 31.3, 16.9. HRMS (EI) *m*/*z*: calcd for $C_8H_{13}NO_5$ ($[M]^+$) 203.0793, found 203.0815.

(*R*)-3-Acetoxy-4-(*N*-(methoxycarbonyl)formamido)butanoic acid (2f). Light yellow oil. $[\alpha]_D^{29}$ = +19.5 (*c* 1.0, $CHCl_3$, >99% ee). IR (neat): 3200, 2963, 1736, 1688, 1445, 1331, 1292, 1136, 1178, 1041, 962, 775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.38 (s, 1H), 5.44 (qd, *J* = 6.5, 3.5 Hz, 1H), 4.01 (dd, *J* = 14.7, 6.5 Hz, 1H), 3.93 (s, 3H), 3.87 (dd, *J* = 14.1, 3.5 Hz, 1H), 2.66 (d, *J* = 6.5 Hz, 2H), 2.01 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.8, 170.4, 163.0, 154.9, 67.7, 54.2, 42.5, 36.4, 20.6. HRMS (FAB) *m*/*z*: calcd for $C_9H_{13}NO_7$ ($[M+H]^+$) 248.0770, found 247.0771. HPLC: DAICEL CHIRALCEL OD-H column, hexane/EtOH = 10:1, 0.1% TFA, wavelength 254 nm, flow rate 1 mL/min, t_R = 12.9 min (*S*), 14.1 min (*R*).

4-(*N*-(Phenoxycarbonyl)formamido)butanoic acid (2g). Light yellow oil. IR (neat): 3080, 2950, 2349, 1755, 1709, 1537, 1336, 1199, 1169, 760 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.38 (s, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 3.86 (t, *J* = 7.0 Hz, 2H), 2.46 (t, *J* = 7.3 Hz, 2H), 2.01 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.5, 162.9, 152.5, 149.8, 129.6, 126.5, 121.1, 40.3, 31.0, 23.0. HRMS (EI) *m*/*z*: calcd for $C_{12}H_{13}NO_5$ ($[M]^+$) 251.0793, found 251.0788.

3-(*N*-(Methoxycarbonyl)formamido)propanoic acid (2i). Light yellow oil. IR (neat): 3150, 2950, 1720, 1686, 1533, 1448, 1342, 1078, 777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.20 (s, 1H), 3.97 (t, *J* = 7.6 Hz, 2H), 3.92 (s, 3H), 2.64 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7, 162.6, 154.0, 54.1, 36.2, 32.4. HRMS (EI) *m*/*z*: calcd for $C_6H_9NO_5$ ($[M]^+$) 175.0481, found 175.0456.

(*S*)-4-Methoxy-3-(*N*-(methoxycarbonyl)formamido)-4-oxobutanoic acid (2j). Light yellow oil. $[\alpha]_D^{29}$ = –67.3 (*c* 1.0, $CHCl_3$, >99% ee). IR (neat): 3300, 2961, 1749, 1700, 1454, 1396, 1352, 1205, 1176, 1018, 958, 775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.19 (s, 1H), 5.54 (t, *J* = 7.0 Hz, 1H), 3.94 (s, 3H), 3.75 (s, 3H), 3.37 (dd, *J* = 17.0, 7.0 Hz, 1H), 2.83 (dd, *J* = 17.0, 7.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 168.7, 162.0, 153.2, 54.5, 53.0, 49.6, 34.0. HRMS (EI) *m*/*z*: calcd for $C_8H_{11}NO_7$ ($[M]^+$) 233.0535, found 233.0554. HPLC: DAICEL CHIRALPAK AY-H column, hexane/EtOH = 10:1, 0.1 % TFA, wavelength 254 nm, flow rate 1 mL/min, t_R = 12.2 and 22.0 min (*S*), 14.3 and 27.4 min (*R*).

3-(*N*-(Phenoxycarbonyl)formamido)propanoic acid (2k). Light yellow oil. IR (neat): 3050, 1757, 1690, 1591, 1493, 1444, 1342, 1199, 1020, 760 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.35 (s, 1H), 7.43 (t, *J* =

7.6 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 7.17 (d, J = 7.6 Hz, 2H), 4.09 (t, J = 7.0 Hz, 2H), 2.73 (t, J = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.5, 162.6, 152.2, 149.7, 129.6, 126.6, 121.1, 36.7, 32.3. HRMS (EI) *m*/*z*: calcd for $C_{11}H_{11}NO_5$ ($[M]^+$) 237.0637, found 237.0619.

5-(*N*-(Methoxycarbonyl)formamido)pentanoic acid (2m). Colorless oil. IR (neat): 2959, 1736, 1682, 1445, 1339, 1290, 1194, 1165, 959, 775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.22 (s, 1H), 3.91 (s, 3H), 3.68-3.64 (m, 2H), 2.42-2.37 (m, 2H), 1.69-1.57 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.3, 162.9, 154.4, 53.9, 40.2, 33.3, 27.4, 21.5. HRMS (FAB) *m*/*z*: calcd for $C_8H_{14}NO_5$ ($[M+H]^+$) 204.0872, found 204.0872.

ACKNOWLEDGEMENTS

This work was supported by a MEXT Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" (No. 26105746) and a JSPS Grant-in-Aid for Scientific Research (C) (19K05459).

REFERENCES AND NOTES

1. S. E. López and J. Salazar, *J. Fluorine Chem.*, 2013, **156**, 73.
2. O. Onomura, Y. Yamamoto, N. Moriyama, F. Iwasaki, and Y. Matsumura, *Synlett*, 2006, 2415.
3. Y. Matsumura, Y. Yamamoto, N. Moriyama, S. Furukubo, F. Iwasaki, and O. Onomura, *Tetrahedron Lett.*, 2004, **45**, 8221.
4. (a) Y. Matsumoto, M. Kuriyama, K. Yamamoto, K. Nishida, and O. Onomura, *Org. Process Res. Dev.*, 2018, **22**, 1312; (b) O. Onomura, Y. Demizu, and F. Iwasaki, Jpn. Kokai Tokkyo Koho JP 5052362 B2, 2012.
5. (a) D. Seebach, A. K. Beck, and D. J. Bierbaum, *Chem. Biodivers.*, 2004, **1**, 1111; (b) M. Ordóñez, C. Cativiela, and I. Romero-Estudillo, *Tetrahedron: Asymmetry*, 2016, **27**, 999; (c) L. Kiss and F. Fülöp, *Chem. Rev.*, 2014, **114**, 1116; (d) M. Ordóñez and C. Cativiela, *Tetrahedron: Asymmetry*, 2007, **18**, 3; (e) *Enantioselective Synthesis of β-Amino Acids*, 2nd edn., ed. by E. Juaristi and V. A. Soloshonok, John Wiley & Sons, Inc., 2005.
6. Ru-Porphyrin/pyridine *N*-oxide system catalyzed oxidative ring cleavage of *N*-acyl cyclic amines: R. Ito, N. Umezawa, and T. Higuchi, *J. Am. Chem. Soc.*, 2005, **127**, 834.
7. Ozonolysis of N-protected cyclic enamines: (a) K. Bodmann, T. Bug, S. Steinbeisser, R. Kreuder, and O. Reiser, *Tetrahedron Lett.*, 2006, **47**, 2061; (b) F. Gnad, M. Poleschak, and O. Reiser, *Tetrahedron Lett.*, 2004, **45**, 4277.
8. $RuO_2/NaClO_4$ oxidation of *N*-alkoxycarbonyl cyclic enamines: (a) M. Kaname, S. Yoshifuji, and H. Sashida, *Chem. Pharm. Bull.*, 2008, **56**, 1310; (b) H. Sakagami, T. Kamikubo, and K. Ogasawara,

Synlett, 1997, 221; (c) S. Torii, T. Inokuchi, and K. Kondo, *J. Org. Chem.*, 1985, **50**, 4980.

9. Degradative autoxidation of *N*-acyl-3-piperidinones: P. J. Schirmann, R. S. Matthews, and D. C. Dittmer, *J. Org. Chem.*, 1983, **48**, 4426.
10. Silver-mediated deconstructive halogenation of *N*-acyl cyclic amines: (a) J. B. Roque, Y. Kuroda, L. T. Göttemann, and R. Sarpong, *Nature*, 2018, **564**, 244; (b) J. B. Roque, Y. Kuroda, L. T. Göttemann, and R. Sarpong, *Science*, 2018, **361**, 171.
11. O. Onomura, A. Moriyama, K. Fukae, Y. Yamamoto, T. Maki, Y. Matsumura, and Y. Demizu, *Tetrahedron Lett.*, 2008, **49**, 6728.
12. Recent examples for the NHPI-catalyzed reaction: (a) A. V. Arzumanyan, I. K. Goncharova, R. A. Novikov, S. A. Milenin, K. L. Boldyrev, P. N. Solyev, Y. V. Tkachev, A. D. Volodin, A. F. Smol'yakov, A. A. Korlyukov, and A. M. Muzafarov, *Green Chem.*, 2018, **20**, 1467; (b) P. A. Gunchenko, J. Li, B. Liu, H. Chen, A. E. Pashenko, V. V. Bakhonsky, T. S. Zhuk, and A. A. Fokin, *Mol. Catal.*, 2018, **447**, 72; (c) M. R. Patil, N. P. Dedhia, A. R. Kapdi, and A. V. Kumar, *J. Org. Chem.*, 2018, **83**, 4477; (d) S. H. Combe, A. Hosseini, L. Song, H. Hausmann, and P. R. Schreiner, *Org. Lett.*, 2017, **19**, 6156; (e) M. Petroselli, L. Melone, M. Cametti, and C. Punta, *Chem. Eur. J.*, 2017, **23**, 10616; (f) E. Gaster, S. Kozuch, and D. Pappo, *Angew. Chem. Int. Ed.*, 2017, **56**, 5912; (g) D. P. Hruszkewycz, K. C. Miles, O. R. Thiel, and S. S. Stahl, *Chem. Sci.*, 2017, **8**, 1282; (h) A. K. Yadav and L. D. S. Yadav, *Chem. Commun.*, 2016, **52**, 10621; (i) Y. L. Tnay and S. Chiba, *Chem. Asian J.*, 2015, **10**, 873; Recent review on NHPI-catalyzed oxidation, see: (j) L. Melone and C. Punta, *Beilstein J. Org. Chem.*, 2013, **9**, 1296.
13. The yields of 79% for **2a** and 15% for **3a** were reported in the oxidative cleavage of **1a** by $NaNO_2$/TFA, see ref. 11 for details.
14. The use of acetic acid instead of TFA gave trace amount of **2a**, and unreacted **1a** was observed in the crude ^{1}H NMR spectra in 92% yield.
15. As for all other entries, complete consumption of starting materials was observed.
16. The oxidative cleavage of *N*-acetylpiperidine also did not proceed under the present reaction conditions.
17. The generation of a brown-colored gas was observed in the early period of the reaction, which indicated that NO_2 gas would be generated in the reaction.