6-Halo-2-pyridone as an Efficient Organocatalyst for Ester Aminolysis

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1. General Information

All reagents and solvents were purchased from either Tokyo Chemical Industry Co., Ltd., or FUJIFILM Wako Pure Chemical Corporation, Kanto Chemical Co., Ltd., Sigma-Aldrich Co. LLC, and were used without further purification. Unless otherwise noted, all reactions were conducted without any inert gas. Chromatography was carried out with Wakogel® C-200 silica gel (FUJIFILM Wako Pure Chemical Corporation, granule, 0.075-0.150 mm). NMR spectra were recorded at 400 MHz for 1H and 100 MHz for 13C on JEOL JNM-ECZ400R spectrometer. Chemical shifts are reported in part per million (ppm, δ) relative to residual solvent peaks of CDCl₃ (7.26 ppm for 1H NMR, 77.0 ppm for 13C NMR) and coupling constant (J values) are given in Hertz. IR spectra were recorded on a JASCO IR FT/IR 4100 spectrometer. High-resolution mass spectra (HRMS) were measured on a JEOL Accu TOF T-100 equipped with an ESI ionization unit. High performance liquid chromatography was carried out with PU-2089 plus HPLC pump (JASCO), LC-NetII/ADC (JASCO), UV-2075 plus UV/Vis detector (JASCO).
2. Detail of Catalyst Screening

Table S1. Catalyst screening.

| Catalyst | % Yield |
|----------|---------|
| 1        | 37%     |
| 2        | 25%     |
| 3        | 17%     |
| 4        | 30%     |
| 5        | 20%     |
| 6        | 20%     |
| 7a       | 30%     |
| 7b       | 30%     |
| 7c       | 30%     |
| 7d       | 22%     |
| 8        | 32%     |
| 9a       | 22%     |
| 9b       | 30%     |
| 9c       | 31%     |
| S1       | 20%     |
| S2       | 31%     |
| S3       | 36%     |
| S4       | 31%     |
| S5       | 16%     |
Table S2. Catalyst screening.

|       | R       | Yield |
|-------|---------|-------|
|       | NO$_2$ (10a) | 23%   |
|       | Cl (10b)   | 27%   |
|       | OMe (10c)  | 34%   |
|       | OH (S6)    | 20%   |
| CF$_3$ (11a) | 37%   |
|       | Cl (11b)   | 32%   |
|       | OMe (11c)  | 34%   |
|       | OH (S7)    | 18%   |
|       | NO$_2$ (12a) | 42%   |
|       | Cl (12b)   | 51%   |
|       | OMe (12c)  | 41%   |

R$\xrightarrow{\text{BnNH$_2$ (1.2 eq.)}}$ CDCl$_3$ (0.1 M) (20 mol%) rt, 5 h

|       | R       | Yield |
|-------|---------|-------|
|       | Cl (13a) | 81%   |
|       | Br (13b) | 78%   |
|       | I (13c)  | 86%   |
|       | F (13d)  | 31%   |
|       | CO$_2$Me (13e) | 50% |
|       | OMe (13f) | 52% |
|       | CH$_3$ (13g) | 34% |
|       | CO$_2$H (S8) | 16% |
|       | Cl (14a) | 58%   |
|       | NO$_2$ (14b) | 22% |
|       | CO$_2$H (S9) | 6% |

S10 S11 S12
Table S3. Study of solvent effect.

| Entry | Solvent         | Conversion$^a$ | Conversion$^a$ without catalyst |
|-------|-----------------|----------------|---------------------------------|
| 1     | CHCl$_3$        | 24%            | -                               |
| 2     | CH$_2$Cl$_2$    | 34%            | <1%                             |
| 3     | THF             | 18%            | -                               |
| 4     | Et$_2$O         | 29%            | 2%                              |
| 5     | DME             | 22%            | -                               |
| 6     | Benzene         | 46%            | -                               |
| 7     | Toluene         | 52%            | 2%                              |
| 8     | Chlorobenzene   | 48%            | -                               |
| 9     | Trifluoromethylbenzene | 48%         | 2%                              |
| 10    | Hexane          | 74%            | 3%                              |
| 11    | DMF             | 13%            | -                               |
| 12    | DMSO            | 30%            | -                               |
| 13    | MeCN            | 41%            | <1%                             |
| 14    | Pyridine        | 10%            | -                               |
| 15    | t-BuOH          | 18%            | -                               |

$^a$ Conversion was calculated based on $^1$H NMR spectroscopy.
3. Experimental Procedure and Characteristic Data

Catalyst $7c^1$, $7d^2$, $10c^3$, $11c^4$, $13e^5$, $13f^6$, $14a^7$, $14b^8$ and ester $21a^9,10$ were prepared by using known methods. Experimental procedures for preparing catalyst $12c$, $13c$ and esters $3$, $15$, $21b$, $24a$, $25$ are described below. Other catalysts and substrates were purchased from commercial suppliers.

**Preparation of 5-methoxy-2-pyridone (12c)**

\[
\begin{align*}
\text{MeO} & \quad \text{Br} \\
\text{N} & \quad \text{N} \\
\text{BnOH} & \quad 120^\circ \text{C} \\
\text{Na} & \quad 10\% \\
\text{H}_2 & \quad \text{Pd/C} \\
\text{AcOEt} & \quad 92\%
\end{align*}
\]

To a stirred BnOH (12 mL) was added Na (304 mg, 13.2 mmol) at 0°C under Ar atmosphere. The reaction mixture was warmed to 100°C, then 2-bromo-5-methoxypyridine (2.26 g, 12.0 mmol) was added to the mixture. After stirring the mixture at 120°C for 24 h, the reaction mixture was cool to rt, then the mixture was put on a silica gel and purified by column chromatography to give a 2-(benzyloxy)-5-methoxypyridine (251 mg, 10%). To a stirred solution of 2-(benzyloxy)-5-methoxypyridine (251 mg, 1.2 mmol) in AcOEt (6 mL) was added 10 wt% Pd/C (25 mg) under Ar atmosphere. Ar was replaced by H$_2$, then the mixture was stirred at room temperature for 30 min. The suspension was filtered through a pad of celite® and the filtrate was concentrated in vacuo. to provide a 5-methoxy-2-pyridone (12c) (135 mg, 92%). The characteristic data was consistent with reported value.$^{11}$

**Preparation of 6-iodo-2-pyridone (13c)$^{12}$**

\[
\begin{align*}
\text{Br} & \quad \text{OMe} \\
\text{N} & \quad \text{N} \\
\text{THF} & \quad \text{–78 °C} \\
\text{i}_2 & \quad \text{n-BuLi} \\
\text{TMSCl} & \quad \text{Nal} \\
\text{MeCN} & \quad \text{MeCN}
\end{align*}
\]

$1$ J. Zeng, Y. J. Tan, M. L. Leow, X.-W. Liu, *Org. Lett.* 2012, 14, 4386-4389.
$2$ O. M. Singh, S. J. Singh, S. N. Kim, S.-G. Lee, *Bull. Korean Chem. Soc.* 2007, 28, 115-117.
$3$ S. Hanessian, O. M. Saavedra, V. Mascitti, W. Marterer, R. Oehrlein, C.-P. Mak, *Tetrahedron* 2001, 16, 3267-3280.
$4$ S. McN. Sieburth, C.-H. Lin, D. Rucando, *J. Org. Chem.* 1999, 64, 950-953.
$5$ H.-B. Zhou, G.-S. Liu, Z.-J. Yao, *Org. Lett.* 2007, 9, 2003-2006.
$6$ C. Kaneko, K. Uchiyama, M. Sato, N. Katagiri, *Chem. Pharm. Bull.* 1986, 34, 3658-3671.
$7$ M. J. Bingham, M. J. Huggett, M. Huggett, Y. Kiyoi, S. E. Napier, O. Nimz, *PCT Int. Appl.*, 2007039563 A1.
$8$ A. T. Plowright, P. Barton, S. Bennett, A. M. Birch, S. Birtles, *et al.*, *Med. Chem. Commun.* 2013, 4, 151-158.
$9$ Y. Baek, T. A. Betley, *J. Am. Chem. Soc.* 2019, 141, 7797-7806.
$10$ T. O. Vieira, M. J. Green, H. Alper, *Org. Lett.* 2006, 8, 6143-6145.
$11$ V. S. Chan, S. W. Krabbe, C. Li, L. Sun, Y. Liu, A. J. Nett, *ChemCatChem*, 2019, 11, 5748-5753.
$12$ Y. Yuan, W. Dong, X. Gao, H. Gao, X. Xie, Z. Zhang, *J. Org. Chem.* 2018, 83, 2840-2846.
To a stirred solution of 2-bromo-6-methoxypyridine (0.86 mL, 7.1 mmol) in THF (11 mL) was added n-BuLi (1.56 M in hexane, 5 mL, 7.8 mmol) at −78°C under Ar atmosphere. The reaction mixture was stirred at same temperature for 1 h, then a solution of I₂ (2.16 g, 8.5 mmol) in THF (10 mL) was added. The reaction mixture was gently warm to room temperature. The reaction was quenched with a saturated aqueous NH₄Cl (40 mL) and extracted by AcOEt (30 mL x 3). Combined organic layers were washed with brine (40 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated in vacuo. To a stirred suspension of crude mixture and NaI (3.2 g, 21 mmol) in MeCN (36 mL) was added TMSCl (4.5 mL, 35.6 mmol) at room temperature under Ar atmosphere. After the reaction mixture was stirred at same temperature for 13 h, the reaction was quenched with a saturated aqueous NaS₂O₃ (40 mL) and extracted by CH₂Cl₂ (30 mL x 3). Combined organic layers were washed with brine (40 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated in vacuo. A Et₂O (5 mL) was added the residue and the insoluble material was filtered off and washed with Et₂O (5 mL x 2). The combined Et₂O solution was concentrated in vacuo. and the residue was purified by flash column chromatography on silica gel (Hexane : AcOEt = 10 : 1) to give a 6-iodo-2-pyridone (13c) (360 mg, 23%) as a colorless solid and 2-iodo-6-methoxypyridine (809 mg, 49%) as a colorless oil.

Characteristic data of 6-iodo-2-pyridone (13c)

1H NMR (400 MHz, CDCl₃): δ 6.63 (dd, J = 9.0, 0.8 Hz, 1H), 6.80 (dd, J = 7.0, 0.8 Hz, 1H), 7.15 (dd, J = 9.0, 7.0 Hz, 1H). 13C NMR (100 MHz, CDCl₃): δ 97.3, 117.6, 120.0, 141.6, 165.6. IR (neat, ATR) 2837, 2360, 2338, 1633, 1574, 1533, 1450, 1160, 977, 914, 789 cm⁻¹. HRMS (ESI-TOF) m/z [M + Na]^+ calcd for [C₅H₅INO₄]^+ 221.9416, found 221.9413.

Preparation of 4-phenylbutanoic acid p-nitrophenylester (3)

To a stirred solution of 4-nitrophenol (556 mg, 4.0 mmol) and 4-phenylbutanoic acid (657 mg, 4.0 mmol) in CH₂Cl₂ (40 mL) was added DCC (908 mg, 4.4 mmol) and DMAP (49 mg, 0.4 mmol) at 0 °C under Ar atmosphere. After stirring the mixture at room temperature for 13 h, the reaction was quenched with a saturated aqueous NH₄Cl (30 mL) and extracted by AcOEt (30 mL x 3). Combined organic layers were washed with brine (30 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane : AcOEt = 20 : 1) to give a 4-nitrophenyl ester 3 (1.10 g, 96%) as a colorless solid.

1H NMR (400 MHz, CDCl₃): δ 2.11 (tt, J = 7.4, 7.4 Hz, 2H), 2.62 (t, J = 7.4 Hz, 2H), 2.76 (t, J = 7.4 Hz, 2H), 7.19-7.28 (5H), 7.32 (m, 2H), 8.27 (m, 2H). 13C NMR (100 MHz, CDCl₃): δ 26.2, 35.5, 34.9, 122.4 (2C), 125.2 (2C), 126.2, 128.5 (4C), 140.8, 145.2, 155.4, 171.0. IR (neat, ATR) 2933, 1762, 1591, 1533, 1491, 1345,
1204, 1161, 1114, 920, 861, 746 cm\(^{-1}\). HRMS (ESI-TOF) m/z [M + Na]\(^+\) calcd for [C\(_{16}\)H\(_{15}\)NNaO\(_4\)]\(^+\) 308.0899, found 308.0890.

**Preparation of 4-phenylbutanoic acid phenylester (15)**

![Chemical Structure](image)

To a stirred solution of phenol (564 mg, 6.0 mmol) and 4-phenylbutanoic acid (985 mg, 6.0 mmol) in CH\(_2\)Cl\(_2\) (60 mL) was added DCC (1.36 g, 6.6 mmol) and DMAP (73.3 mg, 0.6 mmol) at 0 °C under Ar atmosphere. After stirring the mixture at room temperature for 13 h, the reaction was quenched with a saturated aqueous NH\(_4\)Cl (40 mL) and extracted by AcOEt (30 mL x 3). Combined organic layers were washed with brine (50 mL) and dried over anhydrous Na\(_2\)SO\(_4\). The mixture was filtered and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography on silica gel (Hexane : AcOEt = 20 : 1) to give a phenyl ester 15 (1.27 g, 88%) as a colorless solid. The characteristic data were consistent with reported value.\(^{13}\)

**Preparation of benzylester (21b)**

![Chemical Structure](image)

To a stirred solution of benzyl alcohol (0.62 mL, 6.0 mmol) and 4-phenylbutanoic acid (985 mg, 6.0 mmol) in CH\(_2\)Cl\(_2\) (60 mL) was added DCC (1.36 g, 6.6 mmol) and DMAP (73.3 mg, 0.6 mmol) at 0 °C under Ar atmosphere. After stirring the mixture at room temperature for 13 h, the reaction was quenched with a saturated aqueous NH\(_4\)Cl (40 mL) and extracted by AcOEt (30 mL x 3). Combined organic layers were washed with brine (50 mL) and dried over anhydrous Na\(_2\)SO\(_4\). The mixture was filtered and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography on silica gel (Hexane : AcOEt = 20 : 1) to give a phenyl ester 21b (1.27 g, 84%) as a colorless solid. The characteristic data were consistent with reported value.\(^{14}\)

**Preparation of Boc-Gly-OBn (24a)**

![Chemical Structure](image)

To a stirred solution of Boc-Gly-OH (1.75 g, 10.0 mmol) and NEt\(_3\) (1.7 mL, 12.0 mmol) in DMF (40

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\(^{13}\) M. S. Carle, G. K. Shimokura, G. K. Murphy, \textit{Eur. J. Org. Chem.}, 2016, 3930-3933.

\(^{14}\) W. Wang, H. Liu, S. Xu, Y. Gao, \textit{Syn. Commun.}, 2013, \textbf{43}, 2906-2912.
mL) was added benzyl bromide (2.4 mL, 20 mmol) at 0 °C under Ar atmosphere. After stirring the mixture at room temperature for 17 h, the reaction was quenched with a saturated aqueous NH₄Cl (30 mL) and extracted by Et₂O (20 mL x 3). Combined organic layers were washed with brine (30 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane : AcOEt = 9 : 1) to give a benzyl ester 24a (2.41 g, 91%) as a colorless oil. The characteristic data were consistent with reported value.¹⁵

**Preparation of Boc-L-Leu-OBn (25)**

![Chemical structure of Boc-L-Leu-OBn](image)

To a stirred solution of Boc-Leu-OH (2.31 g, 10.0 mmol) and NEt₃ (1.7 mL, 12.0 mmol) in DMF (40 mL) was added benzyl bromide (2.4 mL, 20 mmol) at 0 °C under Ar atmosphere. After stirring the mixture at room temperature for 17 h, the reaction was quenched with a saturated aqueous NH₄Cl (30 mL) and extracted by Et₂O (20 mL x 3). Combined organic layers were washed with brine (30 mL) and dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (Hexane : AcOEt = 15 : 1) to give a benzyl ester 25 (2.96 g, 92%) as a colorless oil. The characteristic data were consistent with reported value.¹⁶

**General Procedure for Ester Aminolysis catalyzed by 2-Pyridone**

A mixture of an ester (0.1 mmol), amine (0.12 mmol) and 6-chloro-2-pyridone 13a (20 mol%) in toluene (0.1 mL) was stirred. The reaction was monitored by TLC. After completion of the reaction, the mixture was put on silica gel and purified by column chromatography to give the corresponding amide. The catalyst 13a could be recovered quantitatively at the purification of silica gel column chromatography (hexane : AcOEt = 10 : 1).

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¹⁵ C. Wiles, P. Watts, S. J. Haswell, E. Pombo-Villar, *Tetrahedron* 2003, **59**, 10173-10179.

¹⁶ F. E. Dutton, B. H. Lee, S. S. Johnson, E. M. Coscarelli, P. H. Lee, *J. Med. Chem.* 2003, **46**, 2057-2073.
Characteristic data of amides 4, S13, S14, S15, 23, 27, 28, 29, 30 were consistent with reported values.

4-Phenylbutanoic acid prolinamide (S16)

Rotamer was detected in $^1$H and $^{13}$C NMR spectra. (1 : 0.2)

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.81-2.39 (9.6 H), 2.56 (m, 0.4 H), 2.67 (t, $J=7.4$ Hz, 2H), 3.40 (m, 1H), 3.50-3.59 (1.2 H), 3.64 (ddd, $J=5.9, 5.9, 5.9$ Hz, 0.2 H), 4.30 (dd, $J=8.4, 2.4$ Hz, 2H), 4.54 (dd, $J=8.6, 3.4$ Hz, 2H), 5.12 (s, 0.4 H), 5.12 (d, $J=12.4$ Hz, 1H), 5.20 (d, $J=12.4$ Hz, 1H), 7.10-7.40 (12.3 H). $^{13}$C NMR (100 MHz, CDCl$_3$): 22.5, 24.7, 26.0, 26.1, 29.1, 31.4, 33.4, 33.4, 35.0, 35.1, 46.3, 46.9, 58.7, 59.4, 66.7, 67.1, 125.8, 128.0 (2C), 128.1, 128.2 (2C), 128.3, 128.4, 128.5 (2C), 128.5 (2C), 128.6, 128.6, 135.2, 135.7, 141.7, 171.6, 172.0, 172.2. IR (neat, ATR) 2949, 2361, 1740, 1643, 1421, 1166, 1024, 743 cm$^{-1}$. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for [C$_{22}$H$_{25}$NNaO$_3$]$^+$ 374.1732, found 374.1728.

Boc-Gly-L-Leu-OEt (28)

17 T. Maki, K. Ishihara, H. Yamamoto, Org. Lett. 2005, 7, 5043-5046.
18 K. Ishihara, S. Ohara, H. Yamamoto, J. Org. Chem., 1996, 61, 4196-4197.
19 K. Arnold, B. Davies, D. Hérault, A. Whitting, Angew. Chem. Int. Ed. 2008, 47, 2673-2676.
20 T. E. La Cruz, S. D. Rychnovsky, Chem. Commun., 2004, 168-169.
21 T. Maki, K. Ishihara, H. Yamamoto, Org. Lett. 2006, 8, 1431-1434.
22 J. C. Barrow, K. E. Rittle, P. L. Ngo, H. G. Selnick, S. L. Graham, et al., ChemMedChem 2007, 2, 995-999.
23 D. N. Sawant, D. B. Bagal, S. Ogawa, K. Selvam, S. Saito, Org. Lett. 2018, 20, 4397-4400.
24 I. Held, E. Larionov, C. Bozler, F. Wagner, H. Zipse, Synthesis, 2009, 13, 2267-2277.
25 K. C. Nadimpally, K. Thalluri, N. B. Palakurthy, A. Saha, B. Mandal, Tetrahedron Lett. 2011, 52, 2579-2582.
CHIRAL-Cel OD-H, \( i\)-PrOH : Hexane = 4 : 96, UV 254 nm, flow rate 1.0 mL/min, L-isomer \( t_R \) = 6.78 min, D isomer \( t_R \) = 6.04 min. 92.1% ee.

**L-Proline benzylamide (29)**

\[ \text{CHIRAL-PAK IB N-5, } i\text{-PrOH (0.1% Ethanolamine)} : \text{Hexane (0.1% Ethanolamine)} = 1 : 4, \text{UV 254 nm, flow rate 1.0 mL/min, L-isomer } t_R = 6.917 \text{ min, D isomer } t_R = 7.38 \text{ min. } >99\% \text{ ee.} \]

**Boc-L-Leu-NHBn (30)**

\[ \text{CHIRAL-Cel OD-H, } i\text{-PrOH : Hexane = 3 : 97, UV 243 nm, flow rate 1.0 mL/min, L-isomer } t_R = 10.56 \text{ min, D isomer } t_R = 7.67 \text{ min.} \]
$^{1}H$ NMR (400 MHz, CDCl$_3$) spectra of 6-iodo-2-pyridone 13c
$^{1}H$ NMR (400 MHz, CDCl$_3$) spectra of $p$-nitrophenylester 3

![Chemical Structure of 3](image)
$^1$H NMR (400 MHz, CDCl$_3$) spectra of S16
Chiral HPLC analysis of Boc-Gly-L-Leu-OEt (28)

CHIRAL-Cel OD-H, i-PrOH : Hexane = 4 : 96, UV 254 nm, flow rate 1.0 mL/min, L-isomer $t_R = 6.78$ min, D isomer $t_R = 6.04$ min. 92.1% ee.

(L)-28

(D)-28

96.377%

3.623%
Chiral HPLC analysis of L-Proline benzylamide (29)

CHIRAL-PAK IB N-5, i-PrOH (0.1% Ethanolamine) : Hexane (0.1% Ethanolamine) = 1 : 4, UV 254 nm, flow rate 1.0 mL/min, L-isomer $t_R = 6.92$ min, D isomer $t_R = 7.38$ min. >99% ee.

Intensity [µV]

Retention Time [min]

(L)-29

99.639%

(D)-29

0.361%

(L)-29 + (D)-29

(L)-29

(D)-29

(D)-29

Peak information: aminolysi

| # | Peak name | CH | IR | Area | Area% | Area% | Area% | N/A | NTP | Disp | S | S
|---|----------|----|----|------|-------|-------|-------|-----|-----|-----|---|---
| 1 | Unknown  | 1  | 6.917 | 99157 | 9713 | 99.639 | N/A | 10536 | 1.871 | 1.137 |
| 2 | Unknown  | 1  | 7.383 | 36048 | 48 | 0.361 | N/A | 16404 | N/A | 0.992 |
Chiral HPLC analysis of Boc-L-Leu-NHBn (30)

CHIRAL-Cel OD-H, i-PrOH : Hexane = 3 : 97, UV 243 nm, flow rate 1.0 mL/min, L-isomer $t_R = 10.56$ min, D isomer $t_R = 7.67$ min.

(L)-30

(D)-30

0.533%

99.467%

racemate

(L)-30

(D)-30