Oxidative C-C bond cleavage of *N*-alkoxycarbonylated cyclic amines by sodium nitrite in trifluoroacetic acid

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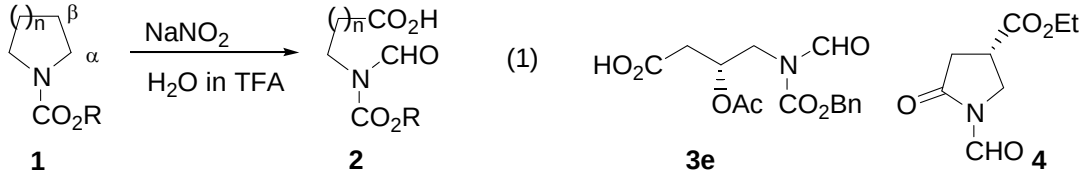
Abstract— Oxidative carbon-carbon bond cleavage of *N*-alkoxycarbonylated cyclic amines was accomplished by $NaNO_2$ in TFA to afford ω-amino carboxylic acid in high yield. Optically active 3-hydroxypiperidine derivatives and 3-pipecolinate, were converted to enantiomerically pure (*R*)-4-amino-3-hydroxybutanoic acid (GABOB) and (*S*)-2-pyrrolidone-4-carboxylate, respectively.

It is well known that trifluoroacetic acid (TFA) acts as an efficient medium for oxidation of hydrocarbons.[1] Recently, we found that efficient oxidation of adamantanes to 1-adamantanols was catalyzed by sodium nitrite ($NaNO_2$) under oxygen atmosphere in TFA.[2] In addition, 2 equiv of $NaNO_2$ in TFA[3] oxidized acyclic and cyclic secondary alcohols to the corresponding ketones and α,ω-dicarboxylic acid, respectively.[4] In the latter case, oxidative cleavage of cyclic secondary alcohols occurred between the α-carbon and the β-carbon. We report herein that this oxidizing agent works well as demonstrated by a unique reaction of *N*-alkoxycarbonylated cyclic amines **1** which reacted with $NaNO_2$ to afford the ring-opened products **2**[5] and its application to preparation of optically active compounds **3e** and **4** (Eq. 1).



1 **2** **3e** **4**

A typical example for the oxidative carbon-carbon (C-C) bond cleavage is shown in Eq. 2. The oxidation of **1a** (1 mmol) was carried out in TFA (5 mL) containing $NaNO_2$ (2 mmol) and H_2O (10 mmol) under aerobic condition. The oxidation smoothly proceeded

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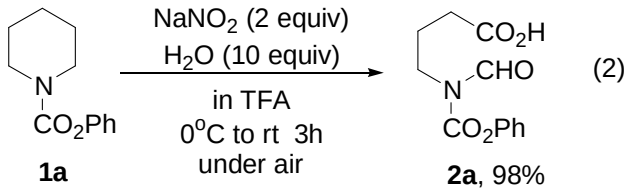
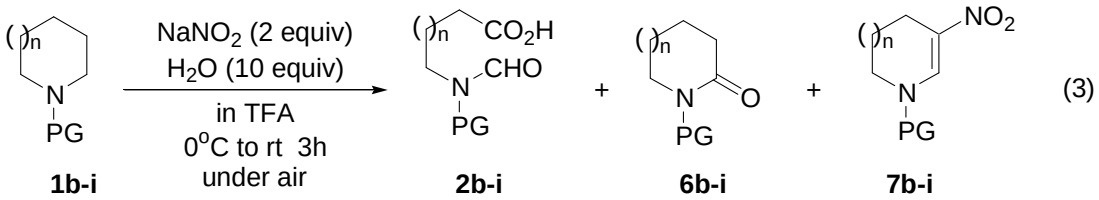
at 0°C to rt for 3 h to afford an oxidative ring-opened product **2a** in 94% yield.[6]



(2)

The oxidative cleavages of *N*-protected pyrrolidines **1b-d** and piperidines **1e-i** with $NaNO_2$ in TFA were examined to clarify generality of substrates (Eq. 3). The results are summarized in Table 1.



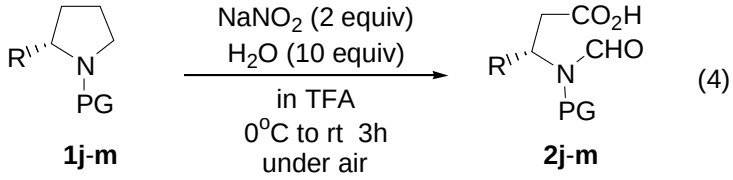
(3)

Table 1. Oxidative cleavage of *N*-protected cyclic amines **1b-i** with $NaNO_2$ in TFA

Entry	Substrate			Yield (%)			
	n	PG		**2**	**6**	**7**	**1**
1	0	CO_2Me	**1b**	74	9	0	0
2	0	CO_2Ph	**1c**	83	11	0	0
3	0	$CO_2CH_2CF_3$	**1d**	88	11	0	0
4	1	CO_2Me	**1e**	79	0	15	0
5	1	$CO_2CH_2CF_3$	**1f**	99	0	0	0
6	1	CHO	**1g**	0	0	0	>99
7	1	COMe	**1h**	0	0	0	>99
8	1	COPh	**1i**	0	0	0	>99

N-Alkoxycarbonylated pyrrolidines **1b-d** were transformed into the corresponding ring-opened products **2b-d** in good to high yields along with a small amount of pyrrolidine-2-ones **6b-d** (Entries 1-3). The oxidation of ***N***-methoxycarbonylpiperidine **1e** afforded ω-amino acid in good yield and 3-nitroenamine **7e** as a by-product (Entry 4), while electron-withdrawing groups[7] such as phenoxyl and trifluoroethoxyl groups were more efficient than methoxycarbonyl group (Eq. 2 and Entry 5). Interestingly, *N*-formylated and acylated piperidines **1g-i** were not oxidized at all under the reaction conditions (Entries 6-8). This may be due to the formation of protonated species for **1g-i** in TFA,[8] which are hardly oxidizable.

Next, the oxidative cleavages of substituted pyrrolidines **1j-m** were examined (Eq. 4). The results are summarized in Table 2.



(4)

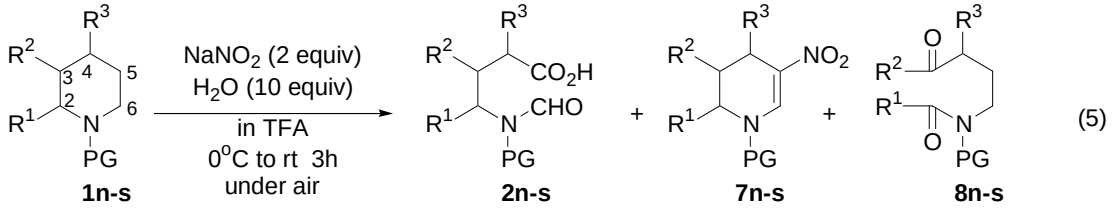
Table 2. Oxidative cleavage of α-substituted pyrrolidines **1j-m** with $NaNO_2$ in TFA

Entry	Substrate				Yield (%)	
	PG	R		Oxidation potential (v)[a]	**2**	**1**
1	CO_2Me	CH_2OAc	**1j**	2.24	96	0
2	$CO_2CH_2CF_3$	CH_2OAc	**1k**	2.50	41	59
3	CO_2Me	CO_2Me	**1l**	2.39	52	47
4	$CO_2CH_2CF_3$	CO_2Me	**1m**	2.82	<1	>99

[a] vs $Ag/AgNO_3$

The yields of the cleaved products **2j-m** may have interrelation with the oxidation potentials of **1j-m**. That is, easily oxidizable prolinol derivative **1j** was converted into the corresponding cleaved product **2j** in excellent yield (Entry 1), while compounds **1k**,**l**, which have relatively high oxidation potential, afforded **2k**,**l** in moderate yields (Entries 2 and 3). However, proline derivative **1m** with high oxidation potential was not oxidized at all (Entry 4).

We then subjected 2, or 3, or 4-methylated piperidines **1n-s** to same reaction conditions (Eq. 5). The results are summarized in Table 3.



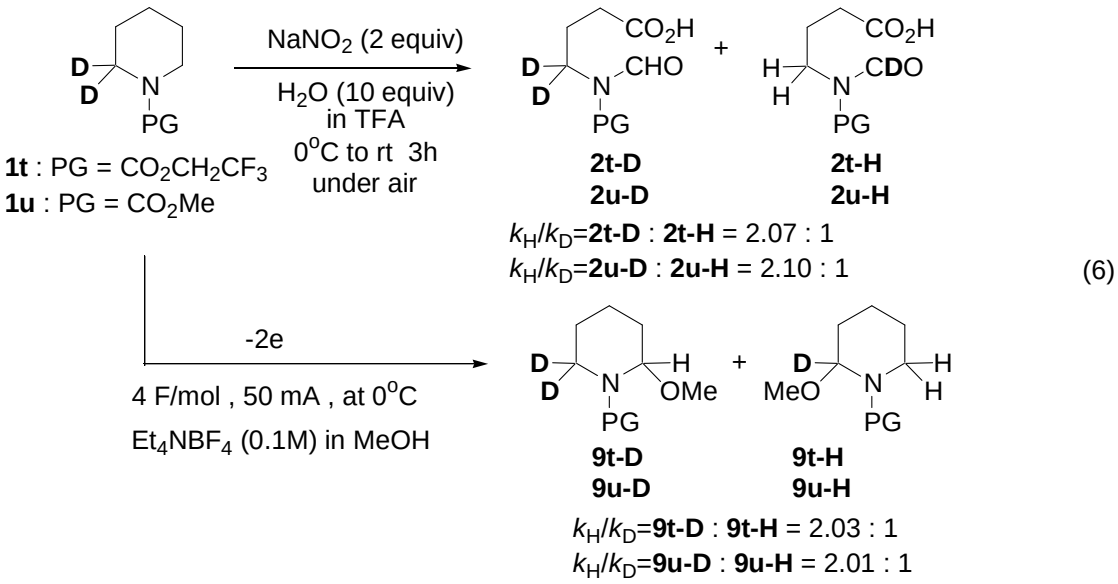
(5)

Table 3. Oxidative cleavage of *N*-protected piperidines **1n-s** with $NaNO_2$ in TFA

Entry	Substrate					Yield (%)		
	PG	R^1	R^2	R^3		**2**	**7**	**8**
1	CO_2Me	Me	H	H	**1n**	47	52	0
2	$CO_2CH_2CF_3$	Me	H	H	**1o**	79	20	0
3	CO_2Me	H	Me	H	**1p**	42	trace	11
4	$CO_2CH_2CF_3$	H	Me	H	**1q**	74	0	10
5	CO_2Me	H	H	Me	**1r**	43	45	0
6	$CO_2CH_2CF_3$	H	H	Me	**1s**	76	15	0

Trifluoroethoxycarbonyl served as a better protecting group than methoxycarbonyl in all cases (Entries 1-6). In the cases where 2-methylpiperidines **1n** and **1o** were oxidized, C-C bond cleavage occurred exclusively between the 5th and 6th position to afford **2n** and **2o** (Entries 1 and 2), while for 3-methylpiperidines **1p** and **1q**, cleavage occurred between the 5th and 6th position to afford **2p** and **2q** or at the 2nd and 3rd position to afford **8p** and **8q**, respectively (Entries 3 and 4).

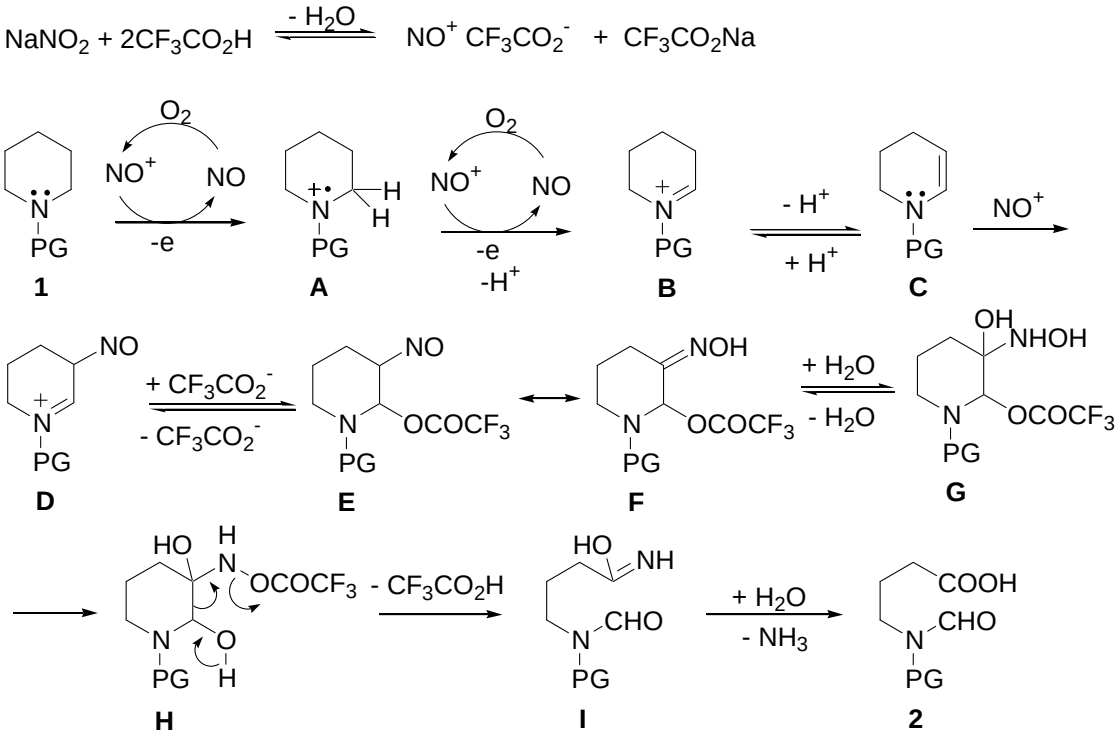
To obtain insight into the mechanism for our reaction, the kinetic isotope effect was measured using 2,2-dideuteriopiperidines **1t**,**u** (Eq. 6). The k_H/k_D values for the oxidation of **1t**,**u** was found to be almost similar with those of electrochemical oxidation.[9] These results strongly suggest that our oxidation proceed via single electron transfer.



(6)

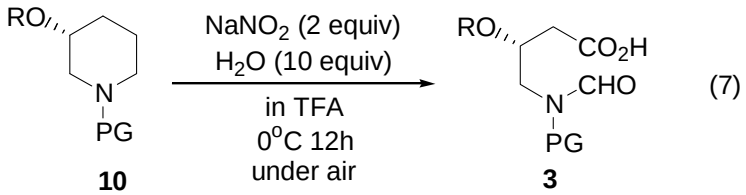
Plausible reaction mechanism is shown in Scheme 1. NO^+ generated from $NaNO_2$ and TFA plays an important role as an oxidant for **1** and intermediate **A** as well as a

nitrosation agent for enamine **C**. NO might be oxidized to NO^+ by molecular O_2,[10] while nitroso compound **E** is changed into oxime **F**, whose hydrated form **G** smoothly afford ring opened intermediate **I**. Finally, hydrolysis of **I** gives ω-*N*-formylamino carboxylic acid **2**.



Scheme 1. Plausible reaction mechanism.

Enantiomerically pure **3e** as a precursor for GABOB is of essence. Therefore, we examined the suitability of different protecting groups for both *N* and *O* towards exclusive oxidative cleavage between the 5th and 6th position of 3-hydroxypiperidine derivatives **10** (Eq. 7). The results are summarized in Table 4.



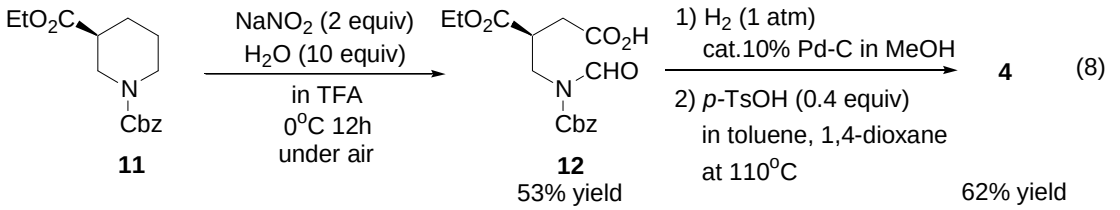
(7)

Table 4. Oxidative cleavage of *N*,*O*-protected 3-hydroxypiperidines **10**

Entry	Substrate			Yield (%) of **3**
	PG	R		
1	CO_2Ph	Ac	**10a**	trace
2	CO_2Ph	Bz	**10b**	trace
3	CO_2Me	Ac	**10c**	68
4	CO_2Me	Bz	**10d**	59
5	Cbz	Ac	**10e**	66
6	Cbz	Bz	**10f**	11
7	Cbz	COEt	**10g**	63
8	Cbz	Piv	**10h**	>99

Use of phenoxycarbonyl as *N*-protecting group led to only trace amount of the desired cleaved product **3a**,**b** (Entries 1 and 2). Change of the protecting group to methoxycarbonyl led to improvement in yields to 68% for **3c** and 59% for **3d** (Entries 3 and 4). The ease of deprotection made us decide to try benzyloxycarbonyl as *N*-protecting group, which gave comparable result to methoxycarbonyl (Entries 3 and 5). To further improve the yield, we tried various *O*-protecting groups (Entries 5-8), and enantiomerically pure **3e**[5d,11] was obtained from **10e** in good yield (Entry 5). Pivaloyl[12] emerged as the best protecting group to afford **3h**[13] in quantitative yield.

Also, oxidative carbon-carbon cleavage of 3-pipecolinate **11**[14] proceeded smoothly to afford **12**, which was transformed into enantiomerically pure **4**[15,16] (Eq. 8).



(8)

In summary, oxidative C-C bond cleavage of *N*-alkoxycarbonylated cyclic amines was accomplished by $NaNO_2$ in TFA to afford ω-amino carboxylic acid in high yield. Optically active 3-hydroxypiperidine derivative and 3-pipecolinate were converted to enantiomerically pure precursor for (*R*)-4-amino-3-hydroxybutanoic acid (GABOB) and (*S*)-2-pyrrolidone-4-carboxylate, respectively. The mechanistic study and further synthetic application are underway.

References and notes

1. Some examples: (a) Deno, N. C.; Messer, L. A. *J. Chem. Soc. Chem. Commun.* **1976**, 1051. (b) Stewart, R.; Spitzer, U. D. *Can. J. Chem.* **1978**, *56*, 1273-1279. (c) Nomura, K.; Uemura, S. *J. Chem. Soc. Chem. Commun.* **1994**, 129-130. (d)

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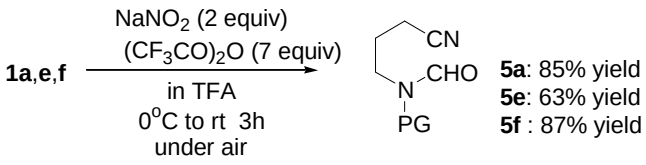
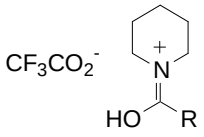
4. Matsumura, Y.; Yamamoto, Y.; Moriyama, N.; Furukubo, S.; Iwasaki, F.; Onomura, O. *Tetrahedron Lett*. **2004**, *45*, 8221-8224.
5. Ru porphyrin/2,6-dichloropyridine *N*-oxide system catalyzed oxidative ring cleavage of *N*-acylated cyclic amines has been reported: (a) Ito, R.; Umezawa, N.; Higuchi, T. *J. Am. Chem. Soc.* **2005**, *127*, 834-835. (b) Ru catalyzed oxidative ring cleavage of *N*-alkoxycarbonyl α,β-unsaturated cyclic amines, see: (c) Torii, S.; Inokuchi, T.; Kondo, K. *J. Org. Chem.* **1985**, *50*, 4980-4982. (d) Sakagami, H.; Kamikubo, T.; Ogasawara, O. *Synlett* **1997**, 221-222. Ozonolysis of them, see: (e) Gnad, F.; Poleschak, M.; Reiser, O. *Tetrahedron Lett*. **2004**, *45*, 4277-4280. Degradative autooxidation of *N*-acyl-3-piperidinones, see: (f) Schirmann, P. J.; Matthews, R. S.; Dittmer, D. C. *J. Org. Chem.* **1983**, *48*, 4426-4427.
6. Under anhydrous condition, oxidation of **1a**,**e**,**f** smoothly proceeded to give ω-amino nitriles **5a**,**e**,**f** in good to high yields. The reaction of ω-amino nitriles **5a**,**e**,**f** with $NaNO_2$ (2 equiv) and H_2O (10 equiv) in TFA did not proceed at all.



7. Oxidation potentials (vs $Ag/AgNO_3$): 2.16 V for **1a**, 2.10 V for **1e**, 2.33V for **1f**.
8. 

9. Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264-4268.
10. The oxidation of **1a** under nitrogen atmosphere gave **2a** in 25% yield along with recovered **1a** in 69% yield.
11. **Enantiomerically pure (*R*)-3-acetoxy-4-[(*N*-benzyloxycarbonyl-*N*-formyl)amino]butanoic acid (3e)**: Colorless oil; IR(neat) 3567 (br), 2963, 1730, 1698, 1333, 1237 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.64 (d, *J* = 6.9 Hz, 2H), 3.89 (dd, *J* = 3.6, 14.4

Hz, 1H), 4.02 (dd, *J* = 6.6, 11.4 Hz, 1H), 5.32 (s, 2H), 5.45 (m, 1H), 7.40 (m, 5H), 9.24 (s, 1H); ^{1}H-NMR (300MHz, DMSO-d_6) δ 1.80 (s, 3H), 2.60 (d, *J* = 8.8 Hz, 2H), 3.71 (dd, *J* = 10.6 Hz, 1H), 3.86 (dd, *J* = 5.7, 10.8 Hz, 1H), 5.00 (m, 1H), 5.30 (m, 2H), 7.34 – 7.45 (m, 5H), 9.13 (s, 1H), 12.31 (br s, 1H); ^{13}C-NMR (75MHz, $CDCl_3$) δ 20.3, 36.2, 42.4, 67.7, 69.0, 128.2, 128.4, 128.6, 134.1, 153.4, 163.0, 170.7, 173.2; $[\alpha]^{20}_{D}$ = +9.3 (*c* 1.0, $CHCl_3$); MS [HR-EI]: *m/z* calcd for $C_{15}H_{17}NO_7$ $[M]^+$ 323.1005: found 323.0993; Optical purity was determined by HPLC analysis employing a Daicel Chiralcel OJ-H column (4.6 mmø, 250 mm). *n*-Hexane : Ethanol = 5 : 1, 0.1% TFA, wavelength: 220 nm, flow rate: 1.0 mL/ min, retention time: 27.3 min (*R*), 30.9 min (*S*).

12. Oxidation potential (vs Ag/$AgNO_3$): 2.17 V for **10h**.
13. **Enantiomerically pure (*R*)-3-pivaloyloxy-4-[(*N*-benzyloxycarbonyl-*N*-formyl)amino]butanoic acid (3h)**: **C**olorless oil; IR(neat) 3200 (br), 2975, 1732, 1701, 1339, 1152, 1042 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.11 (s, 9H), 2.65 (d, *J* = 6.9 Hz, 2H), 3.79 (dd, *J* = 3.6, 14.4 Hz, 1H), 4.07 (dd, *J* = 7.8, 14.1 Hz, 1H), 5.32 (s, 2H), 5.44 (m, 1H), 7.39 (m, 5H), 9.21 (s, 1H); ^{1}H-NMR (300MHz, DMSO-d_6) δ 1.00 (s, 9H), 2.64 (d, *J* = 9.5 Hz, 2H), 3.66 (d, *J* = 10.6Hz, 1H), 3.92 (m, 1H), 5.29 (m, 3H), 7.36 - 7.43 (m, 5H), 9.12 (s, 1H), 12.39 (br s, 1H); ^{13}C-NMR (100MHz, $CDCl_3$) δ 26.9, 36.8, 38.6, 42.9, 67.3, 69.3, 128.5, 128.8, 128.9, 134.4, 153.6, 162.6, 175.2, 177.7; $[\alpha]^{20}_{D}$ = +3.0 (*c* 1.0, $CHCl_3$); MS [HR-EI]: *m/z* calcd for $C_{18}H_{23}NO_7$ $[M]^+$ 365.1474: found 365.1474; Optical purity was determined by HPLC analysis employing a Daicel Chiralcel OJ-H column (4.6 mmø, 250 mm), *n*-Hexane : Ethanol = 5 : 1, 0.1% TFA, wavelength: 220 nm, flow rate: 1.0 mL/ min, retention time: 10.1 min (*R*), 10.9 min (*S*).
14. Oxidation potential (vs Ag/$AgNO_3$): 2.21 V for **11**.
15. **Enantiomerically pure ethyl (*S*)-*N*-formyl-2-pyrrolidinone-4-carboxylate (4):** Colorless oil; IR(neat) 1887, 1767, 1717, 1476, 1399 cm^{-1}; ^{1}H-NMR (300MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.2 Hz, 3H), 2.84 (dd, *J* = 9.6, 18.6 Hz, 1H), 2.97 (dd, *J* = 7.2, 18.3 Hz, 1H), 3.30 (m, 1H), 3.94 (m, 2H), 4.23 (q, *J* = 7.2 Hz, 2H), 9.09 (s, 1H); ^{13}C-NMR (100MHz, $CDCl_3$) δ 14.1, 34.9, 35.7, 44.3, 61.9, 159.8, 171.6, 174.2; $[\alpha]^{20}_{D}$ = +23.6 (*c* 1.0, $CHCl_3$); MS [HR-EI]: *m/z* calcd for $C_8H_{11}NO_4$ $[M]^+$ 185.0688: found 185.0667; Optical purity was determined by HPLC analysis employing a Daicel Chiralcel OD-H column (4.6 mmø x 250 mm). *n*-Hexane : Ethanol = 15 : 1, wavelength: 220 nm, flow rate: 1.0 mL/ min, retention time: 27.4 min (*S*), 29.3 min (*R*).

16. Chemoenzymatic approach: Felluga, F.; Pitacco, G.; Prodan, M.; Pricl, S.; Visintin, M.; Valentin, E. *Tetrahedron: Asymmetry* **2001**, *12*, 3241-3249.