Chiral azabicyclo-*N*-oxyls mediated enantioselective electrooxidation of *sec*-alcohols

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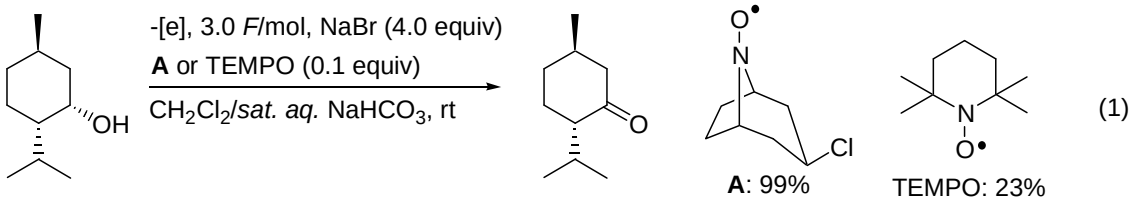
Abstract- Enantiomerically pure azabicyclo-*N*-oxyls were prepared from L-hydroxyproline. They mediated enantioselective electrooxidation of racemic *sec*-alcohols to afford optically active *sec*-alcohols with moderate to high *s* value (up to 21).

2,2,6,6-Tetramethylpiperidine-*N*-oxyl (TEMPO) has been utilized in chemical[1] and electrochemical oxidation[2] of alcohols as a mediator. Also, optically active *N*-oxyls structurally modified from TEMPO were effective for oxidative kinetic resolution of *sec*-alcohols by chemical and electrochemical methods.[3] We have recently reported preparation of several azabicyclo-*N*-oxyls and their mediatory role for electrooxidation of alcohols.[4] This oxidation was applicable to a transformation of sterically hindered *secondary* alcohols into the corresponding ketones in higher yields than those of TEMPO-mediated reactions (Eq. 1). We wish to report herein the preparation of enantiomerically pure azabicyclo-*N*-oxyls and their mediatory role for enantioselective electrooxidation of racemic *sec*-alcohols.[5]



(1)

The chiral azabicyclo skeleton was prepared from L-hydroxyproline as shown in Eq. 2. Namely, the electrooxidation of *N*-methoxycarbonyl-L-hydroxyproline ethyl ester (**1**) afforded methoxylated compound **2** in 94% yield, which was allylated with

Key words: chiral nitroxyl radical; enantioselective oxidation; optically active alcohol; electrooxidation

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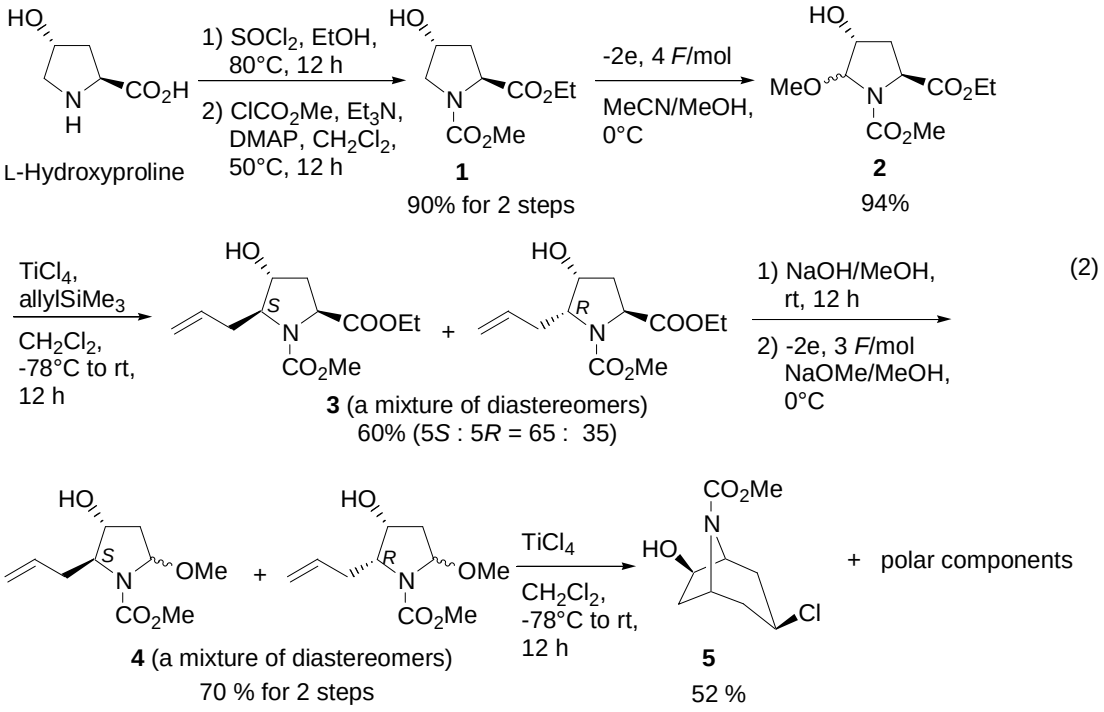
allyltrimethylsilane catalyzed by $TiCl_4$ to give allylated compound **3** as a diastereomer mixture. Alkaline hydrolysis of **3** followed by electrooxidation afforded methoxylated diastereomeric mixture **4** in 70% yield. $TiCl_4$-catalyzed cyclization[6] for (2*S*)-isomer of **4** afforded the corresponding azabicyclo compound **5** in enantiomerically pure form,[7] while (2*R*)-isomer of **4** did not give the corresponding cyclized product but polar components.



Enantiomerically pure azabicyclo-*N*-oxyls **7a** and **7b**-**k** attached with various *O*-protecting groups were synthesized by usual methods as shown in Eq. 3. The yields are summarized in Table 1. Acylation for hydroxyl group of **5** gave **6b**-**k**.[8] After *N*-methoxycarbonyl group of **5** and **6b**-**k** were removed with Me_3SiI, successive oxidation with *m*CPBA afforded *N*-oxyls **7a**-**k**.[9]

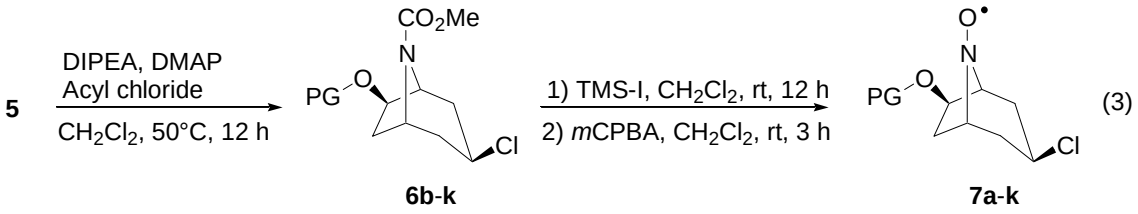


Table 1. Preparation of enantiomerically pure *N*-oxyls **7a**-**k**

Entry	PG	Yield of **6b-k** (%)		Yield of **7a-k** (%)	
1	H		—	**7a**	35
2	Acetyl	**6b**	88	**7b**	65
3	Pivaloyl	**6c**	49	**7c**	50
4	Benzoyl	**6d**	96	**7d**	59
5	3,5-Dimethylbenzoyl	**6e**	54	**7e**	47
6	2-Phenylbenzoyl	**6f**	70	**7f**	30
7	1-Naphthoyl	**6g**	67	**7g**	57
8	1-(2-Methylnaphthoyl)	**6h**	31	**7h**	37
9	2-Naphthoyl	**6i**	75	**7i**	70
10	Tosyl	**6j**	73	**7j**	48
11	Phenylcarbamoyl	**6k**	66	**7k**	57

Cyclic voltammogram for **7g** showed reversible wave pattern similar to that for azabicyclo-*N*-oxyl **A**.[4,10] This strongly suggests that enantiomerically pure azabicyclo-*N*-oxyls could also play the role of an oxidation mediator just like **A** (Fig. 1).

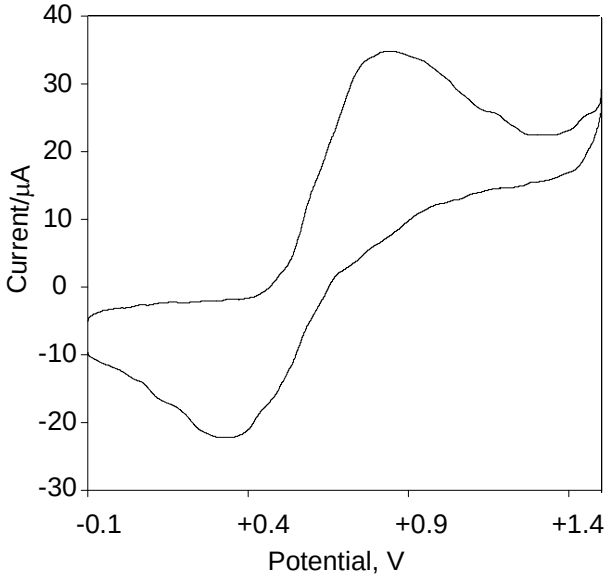
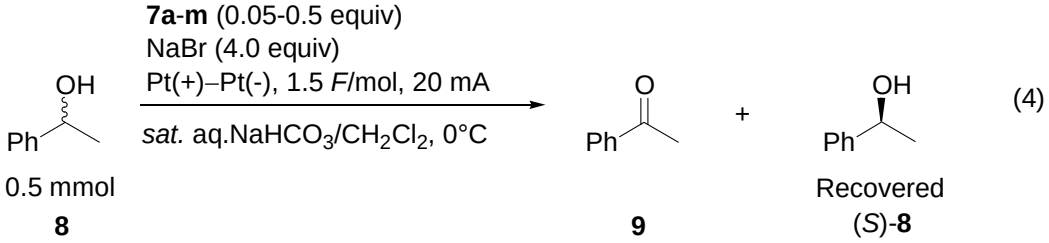


Figure 1. Cyclic voltammogram for **7g**.

The enantioselective electrooxidation of DL-1-phenylethanol (**8**) catalyzed with chiral azabicyclo-*N*-oxyls **7a**-**m** was carried out as follows (Eq. 4).[11] That is, the oxidation was conducted using platinum electrodes in an undivided beaker-type cell, containing a catalytic amount of **7a**-**m**, excess amount of sodium bromide, and a mixture of CH_2Cl_2 and saturated aqueous $NaHCO_3$ as solvent. After passing through 1.5 *F*/mol of electricity at constant current (20 mA, terminal voltage: ca 3V) at 0°C, acetophenone **9**

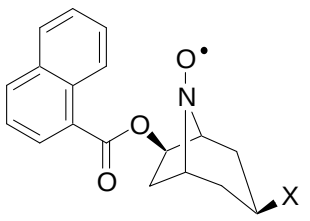
and (*S*)-**8** were obtained. The results are shown in Table 2. 0.1 equiv of *N*-oxyl **7a** did not work as a mediator for oxidation at all (entry 1).[13] In the case of using acetylated *N*-oxyl **7b**, pivaloylated **7c**, 3,5-dimethylbenzoylated **7e**, and 2-phenylbenzoylated **7f**, (*S*)-**8** was recovered with low *s* value (entries 2, 3, 5 and 6),[14] while use of benzoylated **7d** afforded (*S*)-**8** with moderate *s* value of 8 (entry 4). The most efficient *N*-oxyl **7g** which was protected with 1-naphthoyl group gave (*S*)-**8** with high *s* value of 21 (entry 7). Other *N*-oxyls **7h**-**m** were less effective than **7g** (entries 11-16).[15,16] Although 0.2 or 0.5 equiv of *N*-oxyl **7g** worked well as a chiral mediator for the enantioselective oxidation, 0.05 equiv of **7g** was somewhat ineffective for enantioselectivity (entries 8-10).



(4)

Table 2 Enantioselective oxidation of DL-phenylethanol (**8**) catalyzed by **7a**-**m**

Entry	*N*-oxyl **7a**-**m** (equiv)	Yield of **9** (%)	Yield of recovered (*S*)-**8** (%)	% ee of (*S*)-**8**	*s*
1	**7a** (0.1)	14	86	0	0
2	**7b** (0.1)	58	33	7	1
3	**7c** (0.1)	44	56	19	2
4	**7d** (0.1)	38	57	47	8
5	**7e** (0.1)	60	33	23	2
6	**7f** (0.1)	42	57	38	5
7	**7g** (0.1)	43	56	64	21
8	**7g** (0.05)	45	50	62	10
9	**7g** (0.2)	42	54	64	20
10	**7g** (0.5)	42	53	65	20
11	**7h** (0.1)	51	49	37	3
12	**7i** (0.1)	42	57	41	5
13	**7j** (0.1)	35	44	13	2
14	**7k** (0.1)	50	44	27	2
15	**7l** (0.1)	43	43	42	4
16	**7m** (0.1)	41	59	22	2



X = Br : **7l**
H : **7m**

Table 3 summarizes the enantioselective oxidation of some *sec*-alcohols **10**-**14** mediated by **7g**, which was passed through 1.5 *F*/mol of electricity at constant current (20 mA, terminal voltage: ca 3V) at 0°C (Eq. 5). (*S*)-1-(2-Methylphenyl)ethanol ((*S*)-**10**) and (*S*)-1-(2,4,6-trimethylphenyl)ethanol ((*S*)-**11**) were obtained in 47% yield with 72% ee for (*S*)-**10** (entry 1) and in 47% yield with 64% ee for (*S*)-**11** (entry 2). Although in the case of 1-(1-naphthalenyl)ethanol (**12**) and 1-indanol (**14**), (*S*)-**12** and (*S*)-**14** were obtained with low *s* value of 6 and 5, respectively (entries 3 and 5), 1-(2-naphthalenyl)ethanol (**13**) gave (*S*)-**13** with good *s* value of 11 (entry 4).

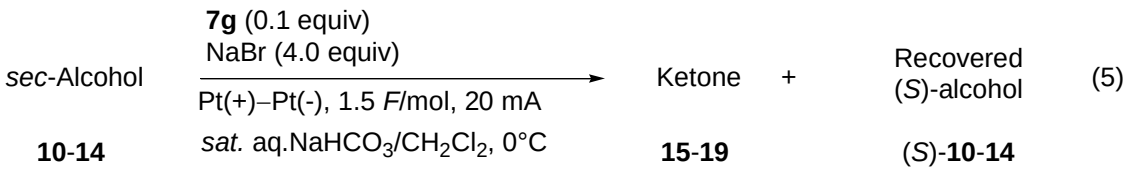
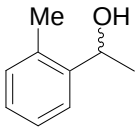
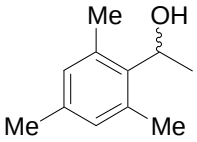
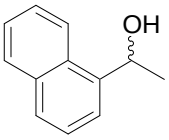
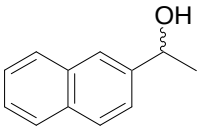
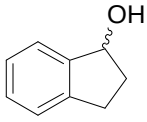
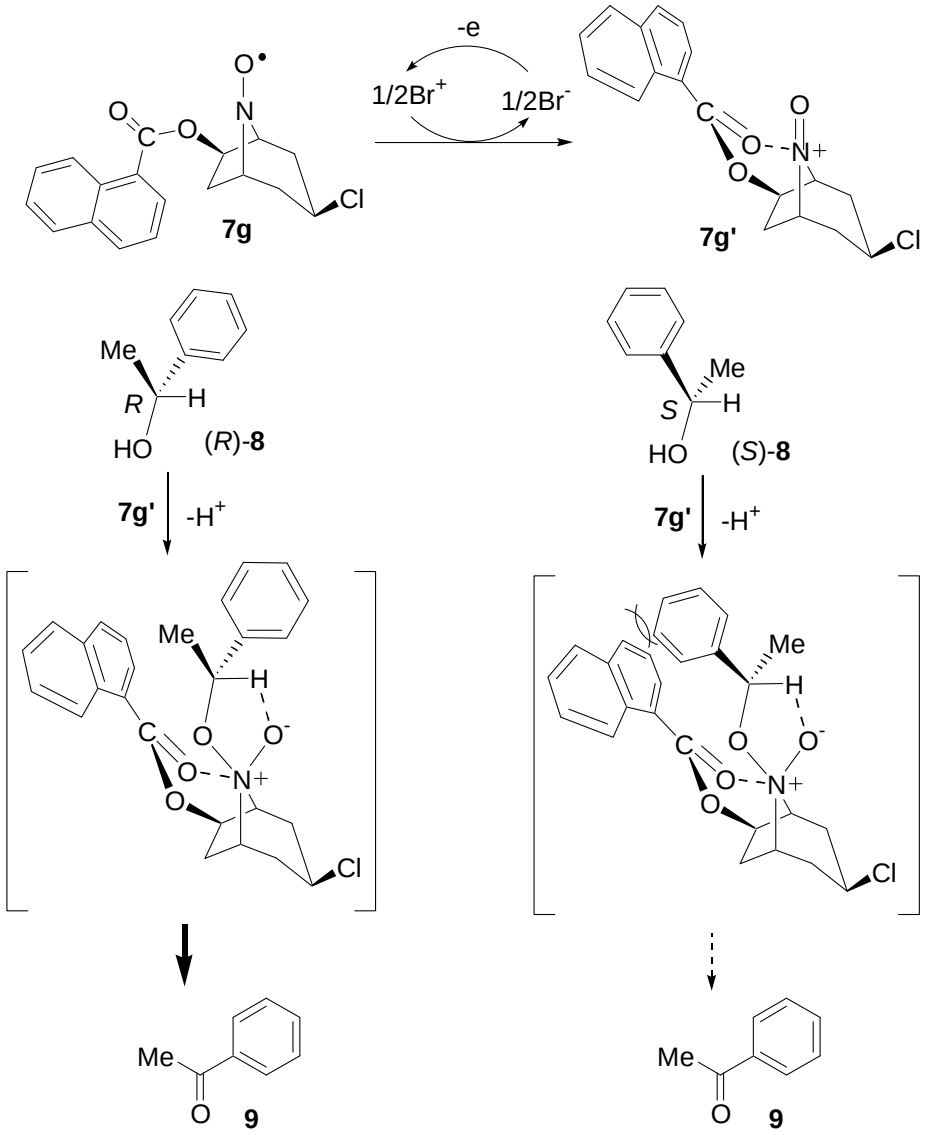


Table 3 Enantioselective oxidation of various *sec*-alcohols **10**-**14** catalyzed by **7g**

Entry		*sec*-Alcohol	Yield of ketone (%)		Yield of recovered (*S*)-alcohol (%)	% ee of (*S*)-**10**-**14**	*s*
1	**10**		**15**	43	47	72	18
2	**11**		**16**	49	47	64	8
3	**12**		**17**	40	60	39	6
4	**13**		**18**	52	45	76	11
5	**14**		**19**	52	47	53	5

Scheme 1 shows our proposed mechanism for kinetic resolution of DL-**8** mediated by chiral *N*-oxyl **7g**. The carbonyl group of *N*-oxoammonium ion **7g'**, which is generated

by the oxidation of **7g** with bromonium ion, might coordinate to the oxoammonium group. Since (*R*)-**8** can smoothly approach **7g'** to form the active intermediate, (*R*)-**8** might be easily oxidized to afford acetophenone (**9**). On the other hand, the formation of intermediate composed of (*S*)-**8** and **7g'** seems to be somewhat difficult.



Scheme 1. Plausible stereochemical course for kinetic resolution of DL-**8**.

In summary, we report preparation of enantiomerically pure azabicyclo-*N*-oxyls and their mediatory role for enantioselective electrooxidation of racemic *sec*-alcohols. *O*-Protecting group on azabicyclo-*N*-oxyls affected the enantioselectivity for the oxidation of *sec*-alcohols. Further modification of chiral *N*-oxyls is underway.

Acknowledgements

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References and notes

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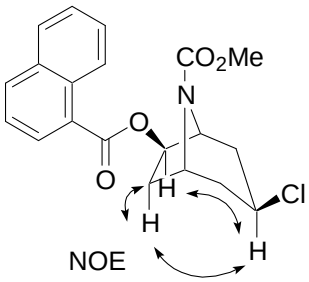
5. We found only one literature for enantioselective chemical oxidation mediated by C_2 symmetrical azabicyclo-*N*-oxyls with low enantioselectivities (*s* value: up to 2.5): Graetz, B.; Rychnovsky, S.; Leu, W.; Farmer, P.; Lin, R. *Tetrahedron: Asymmetry* **2005**, *16*, 3584-3598.
6. Physical data for **5**: Colorless oil. $[\alpha]^{24}_{D}$ = +5.6 (*c* 1.0, $CHCl_3$). IR (neat): 3480, 2955, 1705 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ 4.42 (br s, 1H), 4.25 (d, *J* = 6.4 Hz, 1H), 4.11 (br s, 1H), 4.11-3.98 (m, 1H), 3.74 (s, 3H), 2.80-2.50 (br s, 1H), 2.21-1.80 (m, 6H). [HR-FAB(+)]: *m/z* calcd for $C_9H_{15}ClNO_3$ $[M+H]^+$ 220.0740: found 220.0735.
7. The optical purity of **5** was determined after conversion to 1-naphthoylaed *N*-oxyl **7g** by chiral HPLC: Daicel Chiralcel OD-H column (4.6 mmϕ, 250 mm), *n*-hexane : isopropanol = 5 : 1, wavelength: 254 nm, flow rate: 1.0 mL/min, retention time: 12.3 min for (6*R*)-**7g**, 17.4 min for (6*S*)-**7g**.

8. The stereoconfiguration for **6g** was deduced by NOE correlation.



6g

9. Physical data for **7g**: Red amorphous. $[\alpha]_D^{27} = -13.3$ (*c* 1.0, $CHCl_3$). IR (neat): 2930, 1717 cm^{-1}. [HR-EI]: m/z calcd for $C_{18}H_{17}ClNO_3$ $[M]^+$ 330.0897: found 330.0899.
10. Cyclic voltammogram for **7g** was measured in 0.1 M Et_4NBF_4/MeCN solution using glassy-carbon as a working electrode, platinum as a counter electrode, and Ag/0.01 M $AgNO_3$ as a reference electrode. Concentration of **7g**: 1.0 mM. Scan rate: 30 mV/s. Cyclic voltammogram for other *O*-acyloxylated *N*-oxyls **7b-f,h-m** showed reversible wave pattern similar to that for **7g**, while that for hydroxylated *N*-oxyls **7a** was irreversible.
11. Representative procedure for the enantioselective electrooxidation of *sec*-alcohols: Anodic oxidation of DL-1-phenylethanol (DL-**8**) was carried out using platinum electrodes (1 cm x 2 cm) in an undivided beaker-type cell. DL-**8** (61 mg, 0.5 mmol), **7g** (16.5 mg, 0.05 mmol) and NaBr (206 mg, 2.0 mmol) were added into a mixture of CH_2Cl_2 (2.5 mL) and saturated aqueous $NaHCO_3$ (2.5 mL). After passing through 1.5 *F*/mol of electricity at constant current (20 mA) at 0°C, the mixture was poured in water and extracted with AcOEt (20 mL x 3). The combined organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane : AcOEt = 10 : 1) to afford acetophenone **9** (25.8 mg, 43% yield) and (*S*)-**8** (34.2 mg, 56% yield) as a colorless oil.[12]
12. The optical purity of (*S*)-**8** was determined by chiral HPLC: Daicel Chiralcel OB column (4.6 mmϕ, 250 mm), *n*-hexane : isopropanol = 15 : 1, wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 13.5 min for (*S*)-**8**, 17.5 min for (*R*)-**8**.
13. DL-**8** was oxidized in the absence of *N*-oxyl to afford **9** with 16% yield.
14. Kagan, H. B.; Fiaud, J. C. *Topics in Stereochemistry; Eliel, E. L., Ed.; Wiley & Sons: New York,* **1988,** *Vol. 18,* 249-330.
15. A precursor for *N*-oxyl **7l** was synthesized by $TiBr_4$-catalyzed cyclization of **4**.
16. A precursor for *N*-oxyl **7m** was synthesized by reductive dechlorination of **5**.