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Enantioselective Electrocatalytic Oxidation of Racemic *sec*-Alcohols Using a Chiral 1-Azaspiro[5.5]undecane-*N*-oxyl Radical

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Abstract : Nitroxyl radical (6*S*,7*R*,10*R*)-4-acetylamino-2,2,7-trimethyl-10-isopropyl-1-azaspiro[5.5]-undecane-*N*-oxyl reveals a reversible redox peak in cyclic voltammetry at + 0.62 V *vs.* Ag/AgCl. A preparative electrocatalytic oxidation of racemic *sec*-alcohols on the nitroxyl radical yielded mixtures of 51.4 – 63.9 % ketones and 36.1 – 48.6 % alcohols by 10 h of electrolysis. The current efficiency and turnover number of the reactions were 85.6 – 87.9 % and 20.6 – 25.6, respectively. The enantiopurity of the remaining (*R*)-isomers was 50 - 70 % and the *S* values as a selective factor was 4.1 – 4.6.

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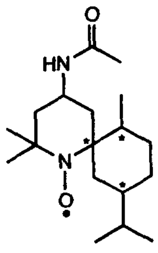
Optically active secondary alcohols are important chiral intermediates in synthesis of optically active substances. They have been prepared by chemical synthesis, biochemical method and optical resolution. Optical resolution of their racemates has been achieved by enantioselective acetylation[1] or oxidation[2] using an enzyme and by asymmetric epoxidation using a tartarate ester.[3] On the other hand, organic nitroxyl radicals such as 2,2,6,6-tetramethylpiperidinyl-*N*-oxyl are known to be an effective redox mediator for the oxidation of several functional groups in organic compounds.[4] The literature reports on the enantioselective oxidation of racemic secondary alcohols using chiral nitroxyl radicals,[5-7] but these works were mainly carried out by non-electrochemical methods. In order to construct a clean and simple reaction system, we have carried out electrocatalytic oxidation of racemic 1-phenylethanol using (±)-*trans,cis*-4-benzoyloxy-2,2,8a-trimethyldecahydroquinolinyl-*N*-oxyl as a chiral nitroxyl radical.[8] Unfortunately, this reaction exhibited no enantioselectivity: the chiral nitroxyl radical oxidized the (*R*)- and (*S*)-forms of 1-phenylethanol equally. We report here the enantioselective electrocatalytic oxidation of racemic *sec*-alcohols using a chiral 1-azaspiro[5.5]undecane-*N*-oxyl radical.



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Four isomers of optically active 4-acetylamino-2,2,7-trimethyl-10-isopropyl-1-azaspiro[5.5]undecane-*N*-oxyl radicals (1) were prepared by the reaction of acetonin with (+)-dihydrocarvone as the starting material.[6] In the electrochemical behavior in

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cyclic voltammetry of the nitroxyl radicals, (6*R*,7*S*,10*R*)- and (6*S*,7*R*,10*R*)-isomers gave reversible redox waves.[9] On the other hand, (6*R*,7*R*,10*R*)- and (6*S*,7*S*,10*R*)-isomers were gradually decomposed during the measurement of cyclic voltammogram (CV). Figure 1 shows the CV of (6*S*,7*R*,10*R*)-**1**, in which a reversible redox couple was observed. A similar electrochemical behavior has been reported by Bobbitt *et al.*[6] This redox couple corresponds to the one-electron oxidation of the oxoammonium ion. The radical (6*S*,7*R*,10*R*)-**1** was quite stable and no deactivation was observed in CV after repeated potential scanning. The redox potential was observed at + 0.62 V *vs.* Ag/AgCl and the peak split between the anodic and cathodic peak potentials was 70 mV. A linear relationship was observed between the anodic and cathodic current (i_{pa} and i_{pc}) and the square root of the potential scan rate ranging from 10 to 100 mV s^{-1}, and the diffusion coeffcient was estimated to be 1.3×10^{-5} cm^2 s^{-1}. These values are comparable to those for TEMPO derivatives,[4] suggesting a possible use of (6*S*,7*R*,10*R*)-**1** as catalyst in the electrocatalytic oxidation.

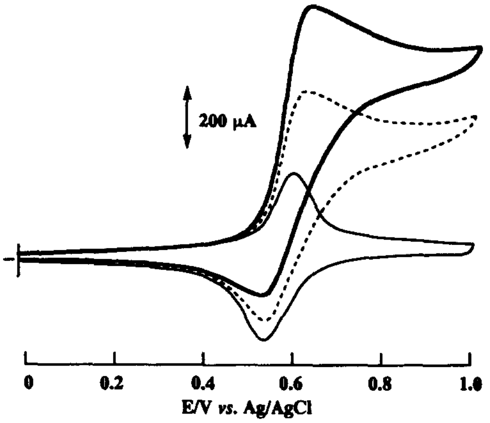


Figure 1 Cyclic voltammograms of 10 mM (6*S*,7*R*,10*R*)-**1** in 0.1 M NaClO$_4$ / CH$_3$CN at the scan rate of 50 mV/s. ——— : in the presence of 100 mM (*S*)-(+)-1-phenylethanol and 100 mM 2,6-lutidine, - - - - : in the presence of 100 mM (*R*)-(-)-1-phenylethanol and 200 mM 2,6-lutidine, ——— : blank.

The enantioselective oxidation of a chiral secondary alcohol on (6*S*,7*R*,10*R*)-**1** was carried out using (*R*)-(+)- and (*S*)-(-)-1-phenylethanol as substrates. The CVs of 100 mM (*R*)-(+)- and (*S*)-(-)-1-phenylethanol in the presence of 100 mM 2,6-lutidine as deprotonating agent are shown in Figure 1. The anodic peak current for (*S*)-(-)-1-phenylethanol was highly enhanced in comparison with the blank voltammogram ((6*S*,7*R*,10*R*)-**1** itself) and a small cathodic peak was observed on the reverse scan, showing that (*S*)-(-)-1-phenylethanol was efficiently oxidized electrocatalytically. In contrast to the CV for (*S*)-(-)-1-phenylethanol, the anodic peak current for *R*-(+)-isomer increased only slightly. These results clearly show that the electrocatalytic oxidation of (*S*)-(-)-1-phenylethanol on (6*S*,7*R*,10*R*)-**1** occurred more easily than that of (*R*)-(+)-1-phenylethanol.

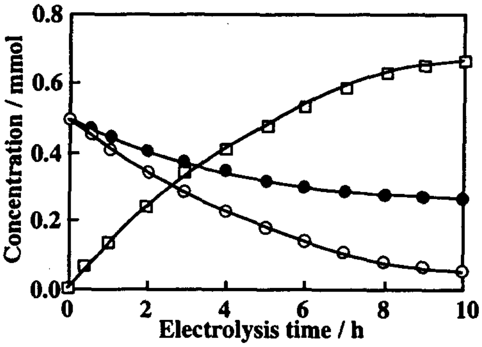
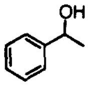
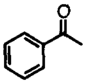
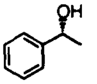
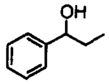
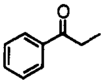
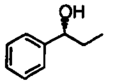
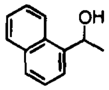
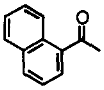
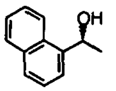
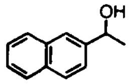
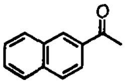
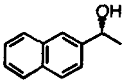


Figure 2 Macroelectrolysis of racemic 1-phenyletnanol by (6*S*,7*R*,10*R*)-**1** in the presence of 2,6-lutidine. ●: (*R*)-(+)-1-phenylethanol, ○: (*S*)-(-)-1-phenylethanol and □: acetophenone.

Preparative potential-controlled electrolysis was performed on a graphite felt electrode (Nippon Kynol Inc., 5 x 5 x 5 mm) in CH$_3$CN solution, using an 'H' type divided cell separated by a cationic exchange membrane (Nafion 117). The anolyte contained 0.05 mmol of (6*S*,7*R*,10*R*)-**1**, 1 mmol of substrate, 0.5 mmol of tetralin as a chromatographic standard, 2 mmol of 2,6-lutidine and 0.5 mmol of NaClO$_4$ in a total volume of 5 ml. The catholyte was 5 ml of

Table 1. Electrocatalytic Oxidation of Racemic *sec*-Alcohols by (6*S*,7*R*,10*R*)-1

Substrate	Product	Recovered alcohol	Config.	Charge passed C	Current efficiency %	%ee	Conversion %	*S*	Turnover number
			*R*	144.1	85.6	70	63.9	4.6	25.6
			*R*	116.7	87.3	52	52.8	4.1	21.1
			*R*	112.8	87.9	50	51.4	4.5	20.6
			*R*	135.1	86.1	60	60.3	4.1	24.1

CH_3CN solution containing 0.5 mmol of $NaClO_4$. Controlled potential electrolysis was carried out at + 0.8 V*vs*. Ag/AgCl under an argon atmosphere. During electrolysis, aliquots of anolyte were analyzed occasionally by HPLC.[10] The consumption of racemic 1-phenylethanol and formation of acetophenone are plotted against electrolysis time in Figure 2. After 10 h of electrolysis, the (*R*)- and (*S*)-forms of 1-phenylethanol were oxidized to acetophenone in 38.6 % and 89.2 % yield, respectively. The current efficiency and turnover number (given by ratio of mole of product x 2 / mole of (6*S*,7*R*,10*R*)-1) were 85.6 % and 25.6, respectively, at 10 h of electrolysis. The remaining (*R*)-(+)- and (*S*)-(-)-1-phenylethanol were 61.4 % and 10.8 %, respectively. Thus, the enantiomeric excess (*ee*) of the unreacted alcohol was 70 %. The efficiency of the resolution is characterized by S (= k_S/k_R), the selectivity factor.[11] The S value of this reaction was 4.6. Bobbitt and co-workers have reported the enantioselective oxidation of racemic 1-phenylethanol using an oxoammonium salt generated from (6*S*,7*R*,10*R*)-1 by disproportionation, in which *ee* of the remaining alcohol, turnover number and the S value were 20 %, 0.3 and 3.3, respectively.[6] Therefore, the electrolytic method is useful for the kinetic resolution of racemic 1-phenylethanol using (6*S*,7*R*,10*R*)-1.

Racemic 1-phenyl-1-propanol, 1-(1-naphthyl)ethanol and 1-(2-naphthyl)ethanol were similarly electrolyzed on (6*S*,7*R*,10*R*)-1 in the presence of 2,6-lutidine (Table 1). In the electrocatalytic oxidation of these racemic *sec*-alcohols, the (*S*)-isomers were oxidized in preference to the (*R*)-isomers. After 10 h of electrolysis, the racemic *sec*-alcohols were oxidized to the corresponding ketones in 85.6 – 87.9 % current efficiency, 51.4 – 63.9 % yield and 100 % selectivity. The turnover numbers based on (6*S*,7*R*,10*R*)-1 are higher than 20. The enantiopurity of the remaining (*R*)-isomers and the S values as a selective factor were 50 - 70 % and 4.1 – 4.6, respectively.

We have reported the first electrochemical method for the efficient, enantioselective oxidation of racemic *sec*-alcohols using a chiral nitroxyl radical: (6*S*,7*R*,10*R*)-4-acetylamino-2,2,7-trimethyl-10-isopropyl-1-azaspiro[5.5]undecane-*N*-oxyl. The electrocatalytic oxidation of the (*S*)-form of racemic *sec*-alcohols on this radical predominates over that of the (*R*)-form. We are now studying the (6*R*,7*S*,10*R*)-isomer of this nitroxyl radical for the enantioselective electrocatalytic oxidation of chiral alcohols.

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References and Notes

1. Wong, C.-H.; Whitesides, G. M. *Enzyme in Synthetic Organic Chemistry*; Pergamon, Oxford, 1994.
2. Danieli, B.; Lesma, G.; Passarella, D.; Riva, S. in *Advances in the Use of Synthons in Organic Chemistry* ; Donodoni, S.; Ed.; JAI Press, Greenwich, 1993, Vol. 1, pp 143.
3. Brunner, H. *Synthesis*, **1988**, 645.
4. Bobbitt, J. M.; Flores, M. C. L. *Heterocycles*, **1988**, *27*, 509.
5. Berti, C.; Perkins, M. J. *Angew. Chem. Int. Ed. Engl.*, **1979**, *18*, 864.
6. Ma, Z.; Huang, G.; Bobbitt, J. M. *J. Org. Chem.*, **1993**, *58*, 4837.
7. Rychnovsky, S. D.; McLernon, T. L.; Rajapakse, H. *J. Org. Chem.*, **1996**, *61*, 1194.
8. Kurashima, F.; Kashiwagi, Y.; Kikuchi, C.; Anzai, J.; Osa, T. *Heterocycles*, **1999**, *50*, 79.
9. Cyclic voltammetry was carried out in a CH_3CN solution containing 0.1 M $NaClO_4$ as supporting electrolyte. The glassy carbon disk electrode (3 mm diameter) was employed as a working electrode, and a platinum wire was used as a counter electrode. The anode potentials were referred to Ag/AgCl (0.1 M $NaClO_4$ in CH_3CN). Cyclic potential sweeps were generated by Hokuto Denko Model HAB-151 potentiostat/galvanostat. Cyclic voltammograms were recorded on a Graphtec Model WX1200 X-Y recorder. All electrochemical measurements were carried out at room temperature (*ca.* 20°C).
10. The HPLC analysis was carried out using Daisel CHIRALCEL®OD column (0.46 cm ϕ x 25 cm). The column temperature was kept constant at 40 °C. The analyte were eluted by a mixture of 2-propanol and *n*-hexane (2:33 by volumn) at 0.7 ml min^{-1} flow rate, and detected by UV absorption at 254 nm.
11. $S = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$ where ee is the fractional enantiomeric excess and C is the conversion. For an excellent discussion of kinetic resolutions see: Kagan, H. B.; Fiaund, J. C. *Top. Stereochem.*, **1988**, *18*, 249.