Enantioselective electrocatalytic oxidation of racemic alcohols on a TEMPO-modified graphite felt electrode by use of chiral base (TEMPO = 2,2,6,6-tetramethylpiperidin-1-yloxyl)

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The *S*-isomers of four racemic *sec*-alcohols, which possess a chiral centre at the α-position to the hydroxy group, were oxidized to the corresponding ketones whereas the *R*-isomers remained unreacted on a TEMPO-modified graphite felt electrode in the presence of (−)-sparteine, where the enantiopurity of the remaining *R*-isomers was >99% and the current efficiency for the produced ketones was >90%.

In contrast to the vast amount of research on the entioselective reduction of ketones, the enantioselective oxidation of racemic alcohols has been largely ignored, with the exception of enzymatic oxidations.[1,2] Such a protocol could be applied to the resolution of racemic alcohols.[1,2] We report here a novel enantioselective oxidation of a number of racemic alcohols on a TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxyl)-modified graphite felt (GF) electrode in the presence of a chiral alkaloid, which provides a simple and clean process for optical resolution.

The TEMPO-modified electrode was prepared according to a procedure established by us.[3,4] Briefly, GF (National Electric Carbon Corp., WDF) was coated with a *ca.* 40 nm thick poly(acrylic acid) (PAA) (MW: 1 400 000) layer. The PAA layer was reacted with 4-amino-TEMPO (64%), followed by cross-linking with hexamethylenediamine (16%) and butylation with dibutyl sulfate to block the remaining carboxylate groups (20%).† The density of TEMPO on the electrode was 24 μmol cm^{-3}. The cyclic voltammograms (CVs) of 0.2 M (*R*)-(+)- and (*S*)-(−)-1-phenylethanol [(*R*)-**1** and (*S*)-**1**] on the TEMPO-modified electrode in the presence of 0.2 M (−)-sparteine are shown in Fig. 1. The anodic peak current for (*R*)-**1** was slightly larger than that for the blank, even if (−)-sparteine is present in the electrolyte solution. On the other hand, the anodic peak current for (*S*)-**1** was 2.2-fold larger than that for (*R*)-**1** and had no cathodic peak on reverse scan. This result means that (*S*)-**1** is easily oxidized electrocatalytically. The oxidation potential was shifted from 0.47 to 0.53 V (the oxidation potential of TEMPO-modified electrode itself). The use of (−)-strychnine instead of (−)-sparteine increased the peak current for (*R*)-**1** and slightly decreased the peak current for (*S*)-**1** in CVs. These results suggest that (−)-sparteine is characterized not only by higher electrocatalytic activity than for (−)-strychnine, but also by higher (*S*)-enantioselectivity for the racemate **1**. Such characteristics of chiral sparteine were confirmed by the time course of macroelectrolysis of a solution of racemic **1** in the presence of (−)-sparteine or (−)-strychnine (the electrolysis conditions are indicated below).

Preparative potential-controlled electrolysis was performed in MeCN solution, using an 'H' type divided cell separated by a cationic exchange membrane (Nafion 117). The anolyte contained 2 mmol of substrate, 1 mmol of tetralin as a chromatographic standard, 2 mmol of chiral base and 1 mmol of $NaClO_4$ as a supporting electrolyte in a total volume of 5 ml. The catholyte was 5 ml of MeCN solution containing 1 mmol of $NaClO_4$. Controlled potential electrolysis was carried out at +0.60 V (*vs.* Ag/AgCl) under a nitrogen atmosphere. The size of the modified anode was 1.0 × 1.0 × 0.5 cm. During electrolysis, the substrates and products were analysed by gas chromatography (GC) or high performance liquid chromatography (HPLC).‡ The anolyte was isolated after electrolysis.§ After 3 h of electrolysis in the presence of (−)-sparteine, (*S*)-**1** was completely oxidized to acetophenone whereas 92% of (*R*)-**1** remained unreacted. The current efficiency for the oxidation, the enantiomeric excess (ee) of the unreacted alcohol and the turnover number based on TEMPO were 95.1%, 99.6%‡,¶ and 87, respectively. In the presence of (−)-strychnine, (*S*)-**1** was fully oxidized and 72.2% of (*R*)-**1** remained unreacted after 4 h of electrolysis. The current efficiency for the oxidation, ee of the unreacted alcohol and the turnover number of TEMPO were 93%, 95% and 117, respectively. For comparison, the use of 2,6-lutidine showed non-enantioselectivity for (±)-**1** on the electrode (current efficiency 94.8%, ee 0% and turnover number 164), and a bare GF electrode yielded a poor enantioselective oxidation of (±)-**1** (3.5% ee) in spite of the presence of 2 mmol of (−)-sparteine and 0.2 mmol of 4-acetylamino-TEMPO in 5 cm^3 of MeCN. Racemic alcohols of *trans*-2-phenylcyclohexanol, octan-2-ol and cyclohex-2-en-1-ol were similarly electrolysed on the TEMPO-modified GF electrode in the presence of (−)-sparteine (Table 1). These racemic alcohols were also enantioselectively oxidized to the corresponding ketones and the unreacted alcohols proved to be composed of >99% of the

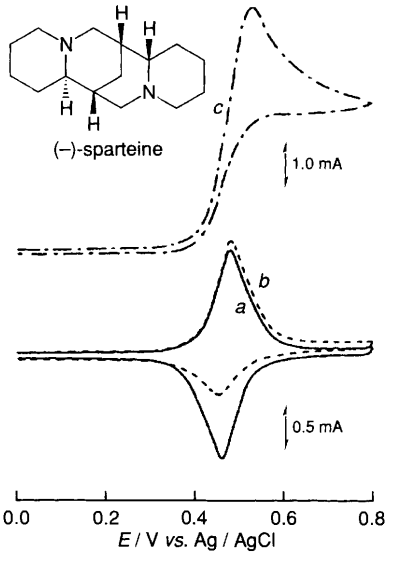
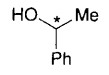
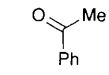
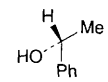
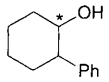
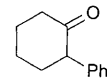
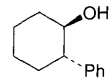
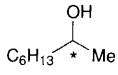
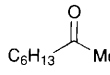
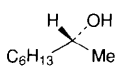
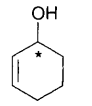
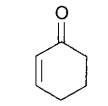
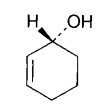
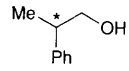
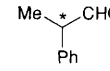


Fig. 1 Cyclic voltammograms on TEMPO-modified GF electrode (1.0 × 1.0 × 0.5 cm) in 0.2 M $NaClO_4$–MeCN (*a*) in the absence of both 1-phenylethanol and (−)-sparteine (blank experiment), (*b*) in the presence of 0.2 M (*R*)-**1** and 0.2 M (−)-sparteine and (*c*) in the presence of 0.2 M (*S*)-**1** and 0.2 M (−)-sparteine. Scan rate, 10 mV s^{-1}.

Table 1 Enantioselective oxidation of racemic alcohols on a TEMPO-modified GF electrode by use of (−)-sparteine

Racemic alcohol	Product	Main remained alcohol	Charge passed /C	Charge passed /F mol^{-1}	Oxidized alcohol (%)	Selectivity of product (%)	Current efficiency (%)	Turnover number	Unreacted alcohol (%)	$[\alpha]_D^{20}$	$R:S$	Ee (%)
			214.8	1.11	52.9[a]	92.4	95.1	87	46.2[a]	+44[c]	99.8:0.2	99.6
			226.0	1.17	53.8[a]	90.2	91.8	88	45.1[a]	−58[d]	99.7:0.3	99.4
			210.8	1.09	52.1[b]	93.0	95.4	85	46.5[b]	−9.5[e]	99.8:0.2	99.6
			197.6	1.02	50.3[b]	96.4	97.7	82	48.2[b]	+109[f]	99.9:0.1	99.8
			407.2	2.11	48.9[a]	97.8	92.7	160	0[a]	0	50.1:49.9	0.2

[a] Measured by HPLC (column: CHIRALCEL-OD, 0.46 cm × 25 cm, solvent: hexane–propan-2-ol = 95:5, flow speed: 0.5 ml min^{-1}). [b] Measured by GC (CP-Cyclodextrin-B-2,3,6-M-19, 0.25 mm × 25 m, temperature increased at 3 °C min^{-1} from 80 to 150 °C, injection temp. 200 °C, detection temp. 240 °C). [c] Compared with authentic sample (Fulka Chemica-Biochemica): $[\alpha]_D^{20}$ 45 ± 1 (*c* 5, MeOH); *R*:*S*. 99.5:0.5 (GC). [d] Compared with authentic sample (Falka Chemica-Biochemica): $[\alpha]_D^{20}$ −59 ± 1 (*c* 10, MeOH); (1*R*,2*S*):(1*S*,2*R*) > 99:1 (GC). [e] Lit.,[5] $[\alpha]_D^{25}$ −9.9 (neat). [f] Lit.,[6] $[\alpha]_D^{20}$ 112.0 (*c* 0.60, MeCl).

R-isomers. The current efficiency and selectivity for the ketones were also high. On the other hand, the complete electrooxidation of (±)-2-phenylpropanol, which has a chiral centre at the β-position to the hydroxy group, was non-enantioselective (Table 1). This means that a chiral R^1R^2CHOH moiety is necessary to attain an enantioselective oxidation via the present electrochemical method.

The TEMPO-modified electrode used for the preparative electrolysis was gradually inactivated during electrolysis. For example, the electrocatalytic current of the second run (an additional 2 mmol of substrate was added to the electrolyte after the first run of electrolysis) was slightly smaller than that of the first run. However, the electrocatalytic activity of the electrode was completely restored by immersion of the electrode in a solution of *m*-chloroperbenzoic acid (10 mM) in diethyl ether for one day. Furthermore, it was ascertained that (−)-sparteine does not react itself, by the fact that (−)-sparteine was recovered almost quantitatively from the electrolyte solution after electrolysis. This suggests that (−)-sparteine acts as a deprotonating agent for alcohols, and that the protons formed are reduced at the cathode to hydrogen gas, as the generation of gas at the cathode was observed.

Although the reaction mechanism is not clear, the following can be proposed: substrate, chiral base and TEMPO interact with each other strongly in a suitably sized domain which is formed by cross-linking of the hexamethylenediamine with the PAA layer, and electrons are transferred from the electrode to the substrate *via* the mediator. The deprotonation of the substrate by the chiral base then proceeds enantioselectively. The higher enantioselectivity induced by the use of (−)-sparteine rather than (−)-strychnine may be caused by a tighter interaction between the substrate and (−)-sparteine than in the (−)-strychnine case, as suggested by a CPK model study. This supports the theory that the enantioselective oxidation of racemic alcohols proceeds on the TEMPO-modified electrode only in the presence of a chiral base.

The unreacted *R*-alcohols were easily isolated from the electrolyte solution with more than 90% recovery by conventional methods. The separated carbonyl products can be transformed back to the racemic alcohols by chemical or electrochemical reduction. The present method, therefore, can provide a valuable electrochemical resolution process for racemic alcohols.

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Footnotes

† The values were determined by back titration with 0.2 M HCl.

‡ The HPLC and GC conditions are shown in the footnotes (*a*) and (*b*) of Table 1, respectively.

§ After the electrolysis was over, the MeCN was evaporated and the residue was dissolved in ethyl acetate (30 ml), washed with 0.1 M HCl and H_2O, dried with sodium sulfate and concentrated. Then, for example, the reaction mixture from 1-phenylethanol thus obtained was chromatographed on silica gel column (Wako Gel C-200, 3 cm × 50 cm) and eluted with hexane–ethyl acetate (9:1 v/v). The eluted solution was evaporated and the product distilled. The product was identified by conventional methods. The reaction mixtures of the other substrates were similarly treated.

¶ Compared with authentic sample (Fulka Chemica-Biochemica): $[\alpha]_D^{20}$ 45 ± 1 (*c* 5, MeOH); *R*:*S* >99.5:0.5 (GC).

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