# Enantioselective electrocatalytic oxidation of racemic amines using a chiral 1-azaspiro[5.5]undecane *N*-oxyl radical

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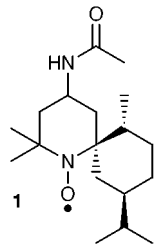
**A preparative electrocatalytic oxidation of racemic amines, which contain a chiral centre α to the amino group, on (6*S*, 7*R*, 10*R*)-4-acetylamino-2,2,7-trimethyl-10-isopropyl-1-azaspiro[5.5]undecane *N*-oxyl yielded mixtures of carbonyl compounds (54.3–66.1%) and amines (33.9–45.7%) after 5 h of electrolysis, in which the current efficiency, turnover number, enantiopurity of the remaining (*R*)-isomers and *S* values were 90.7–94.8%, 21.7–26.5, 62–78% and 4.7–5.8, respectively.**

Optically active amines are some of the most important chiral intermediates in organic synthesis. They have been prepared by many methods, including optical resolution of their racemates, usually by preferential crystallization.[1] Several enantioselective chemical oxidations for optical resolution of the racemates using chiral aminoxyl radicals have been reported, but these works were mainly carried out with secondary alcohols as the racemate.[2–4] On the other hand, 2,2,6,6-tetramethylpiperidin-1-yloxyl is known to be an effective redox mediator for the electrooxidation of amines to nitriles and carbonyl compounds.[5–7] Here we report the first efficient, enantioselective electrocatalytic oxidation of a number of racemic amines using (6*S*, 7*R*, 10*R*)-4-acetylamino-2,2,7-trimethyl-10-isopropyl-1-azaspiro[5.5]undecane *N*-oxyl **1**[3] as a chiral 1-azaspiro-[5.5]undecane *N*-oxyl radical.




The cyclic voltammetry† of **1** was carried out in a MeCN solution containing 0.1 M $NaClO_4$ as supporting electrolyte. Fig. 1 shows the cyclic voltammogram (CV) of **1**, in which a reversible redox couple was observed. This redox couple corresponds to one-electron oxidation of the oxoammonium ion. Similar electrochemical behavior has been reported by Bobbitt *et al.*[3] The redox potential and peak split between the anodic and cathodic peak potentials were +0.62 V (*vs.* Ag/AgCl) and 70 mV, respectively. These values are comparable to those for TEMPO derivatives.[8] In addition, the diffusion coefficient of **1** was estimated to be $1.3 \times 10^{-5}$ cm$^2$ s$^{-1}$ based on a plot of the peak current *vs.* the square root of scan rate in the cyclic voltammetry.[9] These observations suggest a possible use of **1** as catalyst in the electrocatalytic oxidation of amines.

The enantioselective oxidation of a chiral amine on **1** was investigated using (*R*)-(+)- and (*S*)-(−)-1-phenylethylamine [(*R*)-PEA and (*S*)-PEA] as substrates. The CVs of 0.1 M (*R*)-PEA and (*S*)-PEA in the presence of 0.8 M 2,6-lutidine as deprotonating agent are shown in Fig. 1. The anodic peak current for (*S*)-PEA was significantly enhanced in comparison with the blank voltammogram (**1** itself) and a small cathodic peak was observed on the reverse scan, showing that (*S*)-PEA was efficiently oxidized electrocatalytically. In contrast to the CV for (*S*)-PEA, the anodic peak current for (*R*)-PEA increased only slightly. These results clearly show that the electrocatalytic oxidation of (*S*)-PEA on **1** occurred in preference to that of (*R*)-PEA.

Preparative potential-controlled electrolysis was performed on a graphite felt electrode (Nippon Kynol Inc., $5 \times 5 \times 5$ mm) in MeCN–$H_2O$ (4:1) solution, using an 'H type divided cell separated by a cationic exchange membrane (Nafion 117). The anolyte contained 0.05 mmol of **1**, 1 mmol of substrate, 0.5 mmol of tetralin as a chromatographic standard, 4 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 MeCN–$H_2O$ (4:1) solution containing 0.5 mmol of $NaClO_4$. The 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.‡ The consumption of racemic 1-phenylethylamine and formation of acetophenone are plotted against electrolysis time in Fig. 2. 1-Phenylethylamine was probably oxidized to the corresponding imine, the expected oxidation intermediate, which can be easily hydrolyzed to acetophenone; imine was not actually detected. After 5 h of electrolysis, the (*R*)- and (*S*)-forms of 1-phenylethylamine were oxidized to acetophenone in 45.9 and 92.4% yield, respectively. The current efficiency and turnover number (given by ratio of mole of product ×2/mol of **1**) were 91.5% and 26.2, respectively, at 5 h of electrolysis. The remaining (*R*)-PEA and (*S*)-PEA equalled 56.1 and 7.6%, respectively. Thus, the ee of the unreacted amine was 78%. The efficiency of the resolution is characterized by the selectivity factor, *S* (= $k_s/k_R$).[9] The *S* value of this reaction was 5.3.

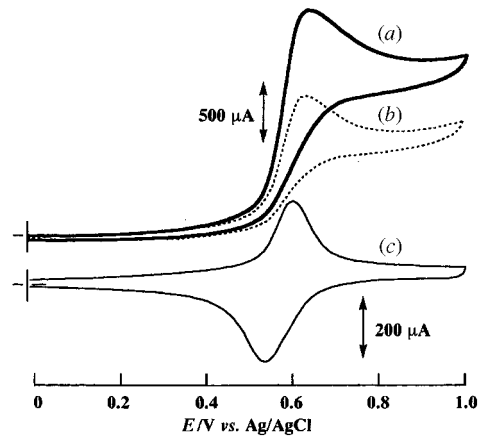
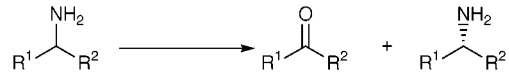



**Fig. 1** Cyclic voltammograms of 0.01 M **1** in 0.1 M $NaClO_4$/MeCN at the scan rate of 50 mV s$^{-1}$: (*a*) in the presence of 0.1 M (*S*)-PEA and 0.2 M 2,6-lutidine, (*b*) in the presence of 0.1 M (*R*)-PEA and 0.2 M 2,6-lutidine, and (*c*) blank.

**Table 1** Electrocatalytic oxidation of racemic secondary amines by **1**



| $R^1$ | $R^2$ | Amine | Charge/C | Efficiency[a] (%) | Ee (%) | Conversion (%) | *S* | TON[b] |
|---|---|---|---|---|---|---|---|---|
| Ph | Me | R | 137.9 | 91.5 | 78 | 65.4 | 5.3 | 26.2 |
| *p*-Tol | Me | R | 134.6 | 94.8 | 75 | 66.1 | 4.7 | 26.5 |
| 1-Naphthyl | Me | R | 115.5 | 90.7 | 62 | 54.3 | 5.8 | 21.7 |
| 2-Naphthyl | Me | R | 124.8 | 92.3 | 66 | 59.7 | 4.9 | 23.9 |
| $PhMeCHCH_2$ | H | — | 192.4 | 96.1 | 0 | 95.8 | 0 | 38.3 |

[a] Current efficiency. [b] Turnover number.

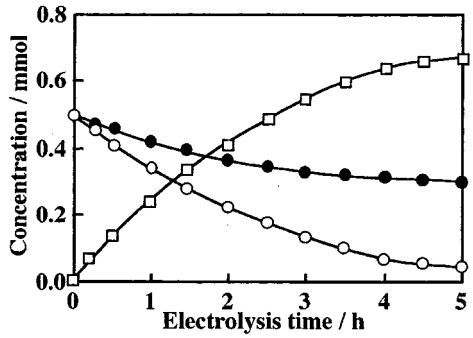



**Fig. 2** Macroelectrolysis of racemic PEA by **1** in the presence of 2,6-lutidine: (●) (*R*)-PEA, (○) (*S*)-PEA and (□) acetophenone.

The results from the enantioselective oxidation reactions of a variety of racemic amines are shown in Table 1. In the electrocatalytic oxidation of the racemic amines such as 1-(1-naphthyl)ethylamine, 1-(2-naphthyl)ethylamine and 1-(*p*-tolyl)ethylamine, which contain a chiral centre α to the amino group, the (*S*)-isomers were oxidized in preference to the (*R*)-isomers. After 5 h of electrolysis, the racemic amines were oxidized to the corresponding ketones in 90.7–94.8% current efficiency, 54.3–66.1% yield and 100% selectivity. The turnover numbers based on **1** are larger than 21. The enantiopurity of the remaining (*R*)-isomers and *S* values were 62–78% and 4.7–5.8, respectively. On the contrary, the electrooxidation of 2-phenylpropylamine, which has a chiral centre β to the amino group, was not enantioselective. After 5 h of electrolysis, it was oxidized to the corresponding aldehyde in 96.1% current efficiency, 95.8% yield and 100% selectivity. The turnover numbers based on **1** is 38.3. These facts mean that an α-hydrogen in a chiral centre adjacent to the amino group is necessary to attain an enantioselective oxidation in the present system. The enantioselective oxidation with **1** is applicable to the optical resolution of racemic secondary amines.

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## Notes and references

† A glassy carbon disk electrode (3 mm diameter) and a platinum wire were employed as working electrode and counter electrode, respectively. The anode potentials were referred to Ag/AgCl (saturated AgCl and $Me_2EtNCl$ in MeCN). Cyclic potential sweeps were generated by a Hokuto Denko Model HABF-501 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).

‡ The HPLC analysis was carried out using Daisel CHIRALCELL-OD column (46 mm $\phi \times 250$ mm). The column temperature was kept constant at 40 °C. The analytes were eluted by $Pr^iOH$–*n*-hexane (2:33) at 0.7 ml $min^{-1}$ flow rate, and detected by UV absorption at 254 nm.

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10 $S = \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$, where ee is the fractional enantiomeric excess and *C* is the conversion. For a discussion of kinetic resolutions see: H. B. Kagan and J. C. Fiaund, *Top. Stereochem.*, 1988, **18**, 249.

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