COMMUNICATION

ChemComm
www.rsc.org/chemcomm

# Asymmetric electrochemical lactonization of diols on a chiral 1-azaspiro[5.5]undecane *N*-oxyl radical mediator-modified graphite felt electrode

**Yoshitomo Kashiwagi,*[a] Futoshi Kurashima,[a] Shinya Chiba,[a] Jun-ichi Anzai,[a] Tetsuo Osa[a] and James M. Bobbitt[b]**

[a] *Graduate School of Pharmaceutical Sciences, Tohoku University, Aramaki, Aoba-ku, Sendai 980-8578, Japan. E-mail: kashi@mail.pharm.tohoku.ac.jp; Fax: +81-22-217-6840; Tel: +81-22-217-6842*

[b] *Department of Chemistry, University of Connecticut, Storrs, CT 06269-3060, USA*

***Received (in Cambridge, UK) 8th October 2002, Accepted 15th November 2002***
***First published as an Advance Article on the web 28th November 2002***

**A graphite felt electrode modified with (6*S*,7*R*,10*R*)-4-amino-2,2,7-trimethyl-10-isopropyl-1-azaspiro[5.5]undecane *N*-oxyl was prepared for electrocatalytic oxidation of diols; electrolysis of diols on the modified electrode yielded optically active lactones (92.0–96.4%), with an enantiopurity of 82–99% ee.**

The preparation of optically active lactones is of importance for the synthesis of chiral bioactive compounds and functional materials. 2,2,6,6-Tetramethylpiperidin-1-yloxyl (TEMPO) is known to be an effective redox mediator for the chemical or electrochemical oxidation of diols to lactones.[1–10] Bobbitt *et al.* demonstrated the asymmetric oxidation of *cis*-1,2-cyclohexanedimethanol to the corresponding optically active lactones using 4-acetylamino-2,2,7-trimethyl-10-isopropyl-1-azaspiro-[5.5]undecane *N*-oxyl (4-acetylamino-SPIROXYL) as a chiral nitroxyl radical *via* a non-electrochemical method.[11] In order to construct a clean and simple reaction system, we report here the first efficient asymmetric electrocatalytic oxidation of diols to the corresponding optically active lactones on a SPIROXYL-modified graphite felt (GF) electrode.

Four isomers of optically active 4-amino-SPIROXYL were prepared by the reaction of 2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine with (+)-dihydrocarvone as the starting material.[11] The SPIROXYL-modified GF electrode was prepared in a similar manner as in the preparation of a TEMPO-modified GF electrode[12] by attaching 4-amino-SPIROXYL to the carboxyl groups of a thin poly(acrylic acid) (PAA) layer coated on GF.[13] Fig. 1 shows the cyclic voltammogram (CV) of a (6*S*,7*R*,10*R*)-SPIROXYL-modified GF electrode, in which a reversible redox couple was observed. This redox couple corresponds to the one-electron oxidation of nitroxyl radical to oxoammonium ion. The immobilized (6*S*,7*R*,10*R*)-SPIROXYL on the electrode surface was quite stable and no deactivation was observed in CV after repeated potential scanning. The oxidation potential was found at +0.58 V *vs.* Ag/AgCl and the peak separation between the positive and negative peak potentials was 65 mV. The amount of electroactive (6*S*,7*R*,10*R*)-SPIROXYL on the electrode surface as determined by integrating the oxidation current peak of the CV and applying Faraday's law was *ca.* $8.4 \times 10^{-6}$ mol cm$^{-3}$. This means that *ca.* 20% of the carboxyl groups of the PAA layer on the GF electrode were modified with (6*S*,7*R*,10*R*)-SPIROXYL. When 3-methyl-1,5-pentanediol was added to the electrolytic solution bathing the (6*S*,7*R*,10*R*)-SPIROXYL-modified GF electrode, an increase of the nitroxyl radical oxidation current was observed (Fig. 1). The oxoammonium ion reduction current disappeared, and the new oxidation peak current was proportional to the concentration of 3-methyl-1,5-pentanediol. The ratio of this new oxidation peak's height to the reversible nitroxyl radical oxidation peak height decreased as the scan rate increased. 3-Methyl-1,5-pentanediol is not oxidized directly on a bare GF electrode below +1.0 V *vs.* Ag/AgCl. All these results

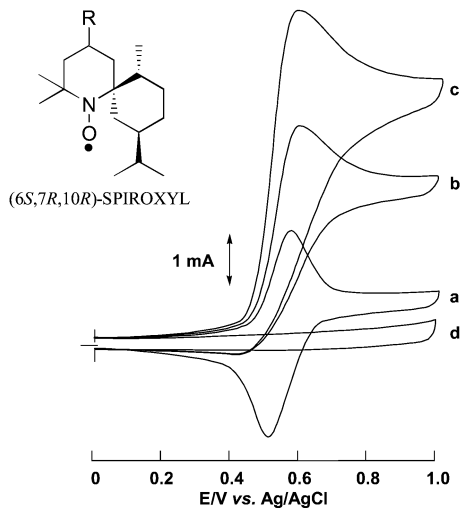



**Fig. 1** Cyclic voltammograms of a (6*S*,7*R*,10*R*)-SPIROXYL-modified GF electrode ($1.0 \times 1.0 \times 0.5$ cm) at 50 mV s$^{-1}$ in 0.1 M $NaClO_4/CH_3CN$: with (a) 0 M 3-methyl-1,5-pentanediol; (b) 0.1 M 3-methyl-1,5-pentanediol and 0.2 M 2,6-lutidine; (c) 0.2 M 3-methyl-1,5-pentanediol and 0.2 M 2,6-lutidine; (d) 0.1 M 3-methyl-1,5-pentanediol on a bare GF electrode.

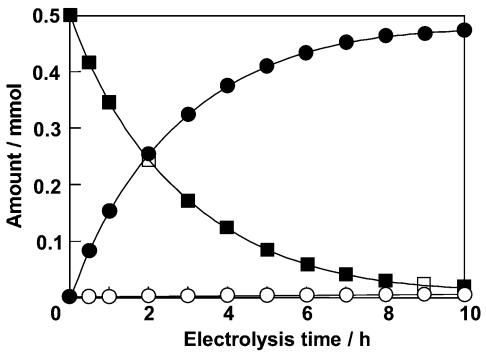



**Fig. 2** Macroelectrolysis of 3-methyl-1,5-pentanediol using the (6*S*,7*R*,10*R*)-SPIROXYL-modified GF electrode in the presence of 2,6-lutidine: (■) 3-methyl-1,5-pentanediol, (○) (*R*)-3-methyl-δ-valerolactone and (●) (*S*)-3-methyl-δ-valerolactone.

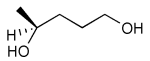
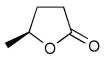
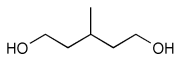
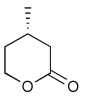
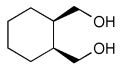
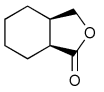
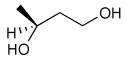
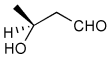
**Table 1** Asymmetric oxidation of 3-methyl-1,5-pentanediol to (*S*)-3-methyl-δ-valerolactone[a]

| Method | Current efficiency (%) | Ee (%) | Isolated yield (%) | Turnover number |
|---|---|---|---|---|
| Electrocatalysis on (6*S*,7*R*,10*R*)-SPIROXYL-modified GF | 97.0 | 98 | 96.4 | 459.0 |
| Electrocatalysis on bare GF[b] | 78.5 | 38 | 86.5 | 34.7 |
| Reagent oxidation[c] | — | 16 | 85.0 | 34.0 |

[a] In the presence of 0.5 mmol 3-methyl-1,5-pentanediol and 2 mmol 2,6-lutidine in each reaction. [b] 0.05 mmol (6*S*,7*R*,10*R*)-4-acetylamino-SPIROXYL. [c] Ref. 11.

DOI: 10.1039/b209871g

**Table 2** Electrocatalytic oxidation of diols using the (6*S*,7*R*,10*R*)-SPIROXYL-modified GF electrode

| Substrate | Product | Config. | Current efficiency (%) | Ee[a] (%) | Isolated yield (%) | Turnover number |
|---|---|---|---|---|---|---|
|  |  | *S* | 96.5 | 99 | 94.8 | 451.4 |
|  |  | *S* | 97.0 | 98 | 96.4 | 459.0 |
|  |  | 1*R*,6*S* | 94.9 | 82 | 92.0 | 438.1 |
|  |  | *S* | 84.6 | 99 | 80.4[b] | 191.4 |

[a] Determined by GC or HPLC. [b] Isolated yield of (*S*)-(+)-3-hydroxybutyric acid.

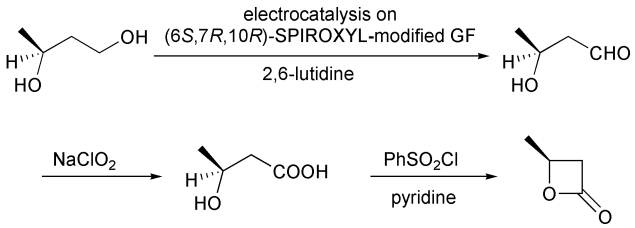
are characteristic of electrochemical catalysis[14,15] of the oxidation of 3-methyl-1,5-pentanediol. Similar results were seen with the other diols used.

Preparative potential-controlled electrolysis was performed on the (6*S*,7*R*,10*R*)-SPIROXYL-modified GF electrode (1.0 × 1.0 × 0.5 cm) in MeCN solution, using an 'H' type divided cell separated by a cationic exchange membrane (Nafion 117). The anolyte contained 0.5 mmol of substrate, 2 mmol of 2,6-lutidine as a deprotonating agent, 0.5 mmol of tetralin as a chromatographic standard and 0.5 mmol of $NaClO_4$ as a supporting electrolyte in a total volume of 5 ml. The catholyte was 5 ml of MeCN solution containing 0.5 mmol of $NaClO_4$. The electrolysis was carried out at +0.8 V *vs.* Ag/AgCl. During electrolysis, aliquots of anolyte were analyzed occasionally by GC† and HPLC.‡ The consumption of 3-methyl-1,5-pentanediol and formation of 3-methyl-δ-valerolactone are plotted against electrolysis time in Fig. 2. After 10 h of electrolysis, 3-methyl-1,5-pentanediol was oxidized to the (*R*)- and (*S*)-forms of 3-methyl-δ-valerolactone in 1.0% and 95.4% yield, respectively. Thus, the ee of the formed lactone was 98%. The current efficiency and turnover number (given by ratio of mole of product × 4/mol of (6*S*,7*R*,10*R*)-SPIROXYL) were 97.0% and 459.0, respectively, at 10 h of electrolysis. The catalytic activity of the modified electrode remained high after several runs.

When we carried out the oxidation reaction of 3-methyl-1,5-pentanediol on a bare GF with (6*S*,7*R*,10*R*)-4-acetylamino-SPIROXYL in solution or in a homogeneous chemical system under similar conditions, the stereoselectivity was rather poor (Table 1). Thus, this asymmetric oxidation reaction was achieved only on the (6*S*,7*R*,10*R*)-SPIROXYL-modified GF electrode.

The results from the oxidation reactions of a variety of diols are shown in Table 2. (*S*)-(+)-1,4-Pentanediol was converted to (*S*)-(−)-2-methyl-γ-butyrolactone in high enantiomeric excess of 99%. *cis*-1,2-Cyclohexanedimethanol was also oxidized to the corresponding *cis*-(1*R*,6*S*)-(+)-8-oxabicyclo[4.3.0]nonan-7-one in an enantioselectivity of 82%. They were oxidized to the corresponding lactones in 94.9–97.0% current efficiency and 92.0–96.4% yield. The turnover numbers based on (6*S*,7*R*,10*R*)-SPIROXYL are greater than 430. (*S*)-(+)-1,3-Butanediol did not lead directly to the corresponding β-lactone; however, it was oxidized to a optically active hydroxyaldehyde without loss of optical purity (99% ee). The current efficiency and turnover number (given by ratio of mole of product × 2/mol of (6*S*,7*R*,10*R*)-SPIROXYL) were 84.6% and 191.4, respectively. This hydroxyaldehyde was oxidized directly with sodium chlorite to the corresponding hydroxy acid in 80.4% yield to give an unstable compound, and the closure of the hydroxy acid to β-lactone was carried out using $PhSO_2Cl$ (Scheme 1).[16]

We have described the first efficient, asymmetric oxidation of a number of diols using a chemically modified electrode. Electrolysis on the (6*S*,7*R*,10*R*)-SPIROXYL-modified GF electrode gave selectively (*S*)-isomers of lactones. We are now investigating the other isomer-modified GF electrodes for the asymmetric oxidation of diols.




**Scheme 1**

This work was supported in part by the Foundation for Earth Environment, and by a Grant-in-Aid for Scientific Research on Encouragement Research (No. 13750792) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

## Notes and references

† The GC analysis was carried out using a CP-Cyclodextrin-B-2,3,6-M-19 capillary column (0.25 mm ϕ × 25 m). The column temperature increased at 3 °C $min^{-1}$ from 80 to 150 °C. The injection and detector temperatures were constant at 200 and 240 °C, respectively.

‡ The HPLC analysis was carried out using a Daisel CHIRALCEL® OD column (4.6 mm ϕ × 250 mm). The column temperature was 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.

1 T. Miyazawa and T. Endo, *J. Org. Chem.*, 1985, **50**, 3930.
2 T. Miyazawa and T. Endo, *J. Mol. Catal.*, 1985, **32**, 357.
3 P. L. Anelli, S. Banfi, F. Montanari and S. Quici, *J. Org. Chem.*, 1989, **54**, 2970.
4 T. Inokuchi, S. Matsumoto, T. Nishiyama and S. Torii, *J. Org. Chem.*, 1990, **55**, 462.
5 R. Siedlecka, J. Skarzewski and J. Mlochowski, *Tetrahedron Lett.*, 1990, **31**, 2177.
6 Z. Ma and J. M. Bobbitt, *J. Org. Chem.*, 1991, **56**, 6110.
7 M. F. Semmelhack, C. S. Chou and D. A. Cortes, *J. Am. Chem. Soc.*, 1983, **105**, 4492.
8 T. Inokuchi, S. Matsumoto and S. Torii, *J. Org. Chem.*, 1991, **56**, 2416.
9 T. Osa, Y. Kashiwagi, K. Mukai, A. Ohsawa and J. M. Bobbitt, *Chem. Lett.*, 1990, 75.
10 H. Tanaka, Y. Kawakami, K. Goto and M. Kuroboshi, *Tetrahedron Lett.*, 2001, **42**, 445.
11 Z. Ma, Q. Huang and J. M. Bobbitt, *J. Org. Chem.*, 1993, **58**, 4837.
12 Y. Kashiwagi, H. Ono and T. Osa, *Chem. Lett.*, 1993, 257.
13 T. Osa, Y. Kashiwagi, M. Nakamura and M. Ohba, *JP Pat.*, 12 776, 1999.
14 R. W. Murray, in *Electroanalytical Chemistry*, vol. 13, ed. A. J. Bard, Marcel Dekker, New York, 1984, p. 191.
15 R. W. Murray, *Molecular Design of Electrode Surfaces, Techniques of Chemistry Series 22*, ed. R. W. Murray, Wiley-Interscience, New York, 1992.
16 P. M. Wovkulich, K. Shankaran, J. Kiegiel and M. R. Uskoković, *J. Org. Chem.*, 1993, **58**, 832.