Letter

Oxidation of alcohols with nitroxyl radical under polymer-supported two-phase conditions

Yoshitomo Kashiwagi,* Shinya Chiba and Jun-ichi Anzai

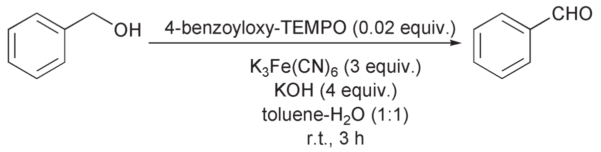
Graduate School of Pharmaceutical Sciences, Tohoku University, Aramaki, Aoba-ku, Sendai 980-8578, Japan. E-mail: kashi@mail.pharm.tohoku.ac.jp; Fax: +81-22-217-6840; Tel: +81-22-217-6842

Received* (*in Montpellier, France*) *24th June 2003, Accepted 12th August 2003
First published as an Advance Article on the web 19th September 2003

The oxidation of alcohols to carbonyl compounds was studied using potassium hexacyanoferrate(III) mediated by nitroxyl radical as the catalyst under polymer-supported organic–aqueous two-phase conditions. Primary alcohols are readily oxidized to the corresponding aldehydes in excellent yield with no over-oxidation to carboxylic acids. Secondary alcohols are converted to the corresponding ketones with a much lower efficiency. The oxidation reactions of primary alcohols in the presence of secondary alcohols is strongly favored. Primary-secondary diols are selectively transformed into hydroxy aldehydes with small amounts of ketoaldehydes, the amount of isomeric keto alcohols remaining is less than 1%.

Oxoammonium ions[1] are known as nonmetallic oxidizing reagents of alcohols to the corresponding carbonyl compounds under mild reaction conditions[2] and are easily available from the corresponding nitroxyl radicals by one-electron oxidation. Several oxidation reactions of alcohols in organic–aqueous two-phase solutions have been reported using regenerating oxidants such as positive halogen sources[3–6] and high valency metal salts,[7,8] which were mediated by the oxidation of nitroxyl radical to oxoammonium ion. However, almost all of the reactions require the same amount of organic solvent as water. The use of water instead of organic solvents is strongly desired from the viewpoint of environmental safety and economical cost. For this reason, we tried to use a small amount of swelled organic solvent, which may be kept in a polystyrene (PS) resin by hydrophobic interactions, as the organic layer of a two-phase reaction system. Herein we report on the first efficient oxidation of alcohols to carbonyl compounds using potassium hexacyanoferrate(III) [$K_3Fe(CN)_6$] mediated by nitroxyl radical as the catalyst under polymer-supported organic–aqueous two-phase conditions (Fig. 1).

We first tried the oxidation of benzyl alcohol using $K_3Fe(CN)_6$ mediated by 4-benzoyloxy-2,2,6,6-tetramethylpipridin-1-yloxyl (4-benzoyloxy-TEMPO) as the nitroxyl radical catalyst in a two-phase system of toluene and 1 M aqueous KOH (1:1) at room temperature; the corresponding benzaldehyde was obtained quantitatively in 3 h.



Therefore, the oxidation reactions of alcohols under polymer-supported organic–aqueous two-phase conditions were performed based on these experimental conditions. About 2 ml of a toluene solution containing alcohol and 4-benzyloxy-TEMPO was completely absorbed by 300 mg of PS resin, by mixing the two. Then, the swelled resin was added to 10 ml of a 1 M aqueous KOH solution containing 2.45 g (7.5 mmol) of $K_3Fe(CN)_6$. The leakage of toluene from the polymer under the reaction conditions was *ca.* 1.5%. The reaction mixture was stirred at room temperature. During the oxidation reaction, aliquots of the reaction mixture were occasionally analyzed by GC and HLPC. The results from the oxidation reactions of benzyl alcohol are shown in Fig. 2 and Table 1. If only small amounts of the catalyst were employed, the yield of benzaldehyde was low although the turnover number (given

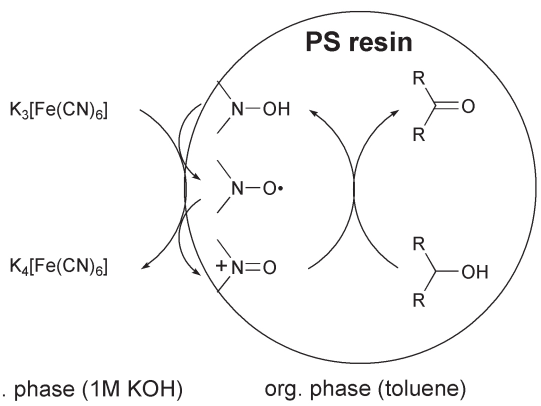


Fig. 1 Oxidation of alcohols with $K_3Fe(CN)_6$ mediated by the nitroxyl radical catalyst in a resin-supported organic–aqueous two-phase solution system.

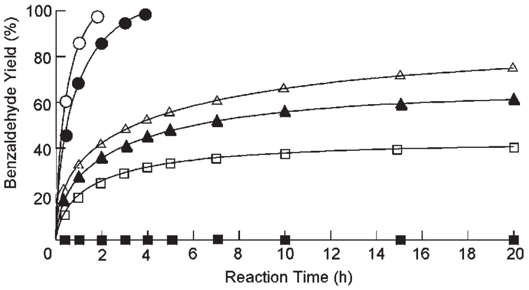


Fig. 2 PS resin-supported two-phase oxidation of benzyl alcohol to benzaldehyde with $K_3Fe(CN)_6$ mediated by 4-benzoyloxy-TEMPO. The reaction was performed under the same conditions as those given in the Experimental. Amount of 4-benzoyloxy-TEMPO: (○) 0.05, (●) 0.02, (△) 0.01, (▲) 0.005, (□) 0.001 and (■) 0 equiv.

DOI: 10.1039/b307190c

Table 1 PS resin-supported two-phase oxidation of benzyl alcohol with $K_3Fe(CN)_6$ mediated by 4-benzoyloxy-TEMPO

Run	4-benzoyloxy-TEMPO[a] / equiv.	Time/h	% Benzaldehyde yield[b]	TON of 4-benzoyloxy-TEMPO[c]
1	0.05	2	98	39
2	0.02	4	98	98
3	0.01	20	75	150
4	0.005	20	62	248
5	0.001	20	40	800
6	0	20	0	–

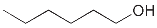
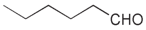
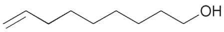
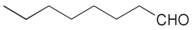
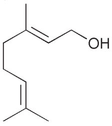
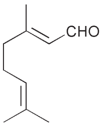
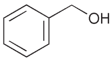
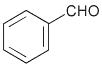
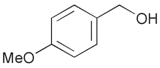
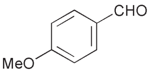
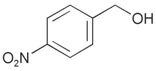
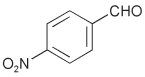
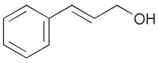
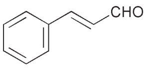
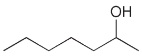
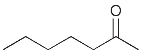
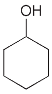
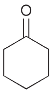
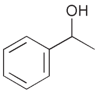
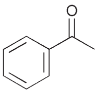
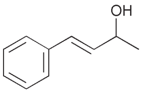
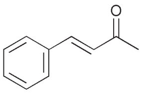
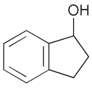
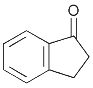
[a] Based on benzyl alcohol. [b] Yield was determined by calibrated quantitative HLPC analysis using an internal standerd. [c] Turnover number given by the ratio of mol of products × 2 per mol of 4-benzoyloxy-TEMPO.

by the ratio of mol of products × 2 per mol of nitroxyl radical catalyst) was high, as shown in Table 1. The results depicted in Fig. 2 indicate that more than 2 mol % nitroxyl radical based on benzyl alcohol is needed to obtain quantitative oxidation.

The results of the oxidation of a variety of primary and secondary alcohols are given in Table 2. The primary alcohols (entries 1–7) such as 1-hexanol, 7-octen-1-ol, nerol, benzyl alcohol, 4-methoxybenzyl alcohol, 4-nitrobenzyl alcohol and cinnamyl alcohol were oxidized to the corresponding aldehydes. Under standard reaction conditions aliphatic and benzylic primary alcohols are oxidized within 0–8 h. The turnover number based on the amount of 4-benzoyloxy-TEMPO was calculated to be >97. In the case of benzylic alcohols, electron-donating groups slow down the reaction (entry 5) whereas electron-withdrawing groups accelerate it (entry 6). Allyl alcohols (entries 3 and 7) are also oxidized to the corresponding aldehydes in adequate yields.

On the other hand, the secondary alcohols (entries 8–12) such as 2-hexanol, cyclohexanol, 1-phenylethanol, 4-phenyl-3-buten-2-ol and 1-hydroxyindan are converted to the corresponding ketones with a much lower efficiency under the same conditions. This observation suggests the possible chemoselective oxidation of primary alcohols in the presence of secondary alcohols. The results from the oxidation of a 1:1 mixture of 1-hexanol and 2-hexanol are shown in Fig. 3 and Table 3 (entry 1). Indeed, the present oxidation system proved to be

Table 2 PS resin-supported two-phase oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones with $K_3Fe(CN)_6$ mediated by 4-benzoyloxy-TEMPO

Entry	Substrate	Time/h	Product	% Yield[a]	TON of 4-benzoyloxy-TEMPO[b]
1		4		97	97
2		24		92	92
3		3		98	98
4		2		98	98
5		8		96	96
6		0.5		98	98
7		3		85	85
8		6		28	28
9		6		30	30
10		4		72	72
11		24		58	58
12		3		64	64

[a] Yields were determined by calibrated quantitative GC and HPLC analysis using an internal standard. [b] Turnover number given by the ratio of mol of products × 2 per mol 4-benzoyloxy-TEMPO.

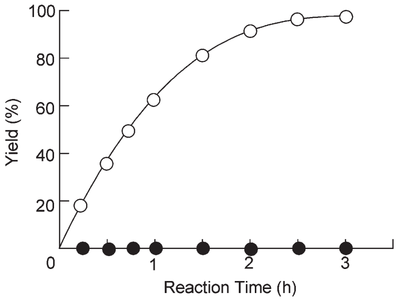


Fig. 3 PS resin-supported two-phase oxidation of a 1:1 mixture of 1-hexanol and 2-hexanol with $K_3Fe(CN)_6$ mediated by 4-benzoyloxy-TEMPO. The reaction was performed under the same conditions as those shown in Table 3. (○) 1-hexanol, (●) 2-hexanol.

exceptionally chemoselective: under standard reaction conditions the primary alcohol was converted quantitatively into aldehyde after 3 h whereas virtually no ketone ($<0.1\%$) could be detected by GC. The competitive oxidation of benzyl alcohol and 1-phenylethanol exhibits a similar degree of selectivity. An even more difficult problem of selectivity is that of cinnamyl alcohol *versus* 4-phenyl-3-buten-2-ol as allyl alcohols. A 88:5 ratio of aldehyde to ketone was obtained after 4 h.

The results of the oxidation of various diols are shown in Table 4. Oxidative cyclization of 1,4- and 1,5-diols to γ- and δ-lactones, respectively, proceeded nicely (entries 1, 2, 6 and 7). *cis*-Cyclohexane-1,2-dimethanol is also converted into a cyclization product (entry 5). However, 1,*n*-diols ($n > 5$) gave predominately non-cyclization products such as 1,*n*-dialdehyde or *n*-hydroxyalkanal (entries 3 and 8). 1,4-Benezenedimethanol, a benzylic primary-primary diol, is oxidized to the corresponding dialdehyde with excellent yield (entry 4). As an example of interamolecular competition between primary and secondary alcohols, oxidation of 1,10-undecanediol gave an 82% isolated yield of 10-hydorxyundecanal with 5% ketoaldehyde, the amount of isomeric keto alcohol remaining being less than 0.1% (entry 8). Even in the case of doubly activated secondary alcohols the method ensures oxidation of the primary alcohols with a high chemoselectivity (entry 9). The oxidation of an end 1,2-diol produced an intermolecular hemiacetal (entry 10). The oxidation of 6,7-dodecanediol as a secondary-secondary diol produced the corresponding diketone in 60% yield without any cleavage of the carbon-carbon bonds (entry 11).

A possible reaction mechanism is shown in Fig. 4. The nitroxyl radical catalyst is first oxidized by Fe(III) to give oxoammonium ion at the organic–aqueous interface. Subsequently, the alcohol is oxidized by the oxoammonium ion in the organic phase of the PS resin to give an adduct made up of the alcohol and the oxoammonium ion, which is attacked by a Lewis base to form the second intermediate. This leads to the carbonyl compound,[9] hydroxylamine and a protic acid such as $H^+K_3[Fe^{II}(CN)_6]^-$, which is neutralized by KOH to give potassium ferrocyanide. Either the hydroxylamine is oxidized to the nitroxyl radical by Fe(III) or the reaction of the hydroxylamine and the oxoammonium ion produces the nitroxyl radical. In either case, the nitroxyl radical is re-oxidized chemically by Fe(III) to complete a catalytic cycle.

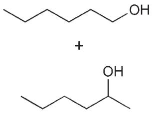
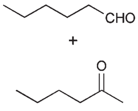
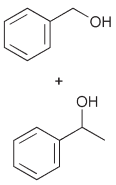
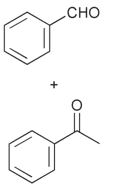
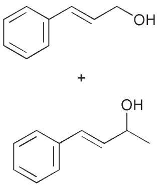
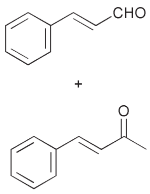
In conclusion, we have demonstrated the first efficient oxidation of alcohols using $K_3Fe(CN)_6$ mediated by 4-benzoyloxy-TEMPO in a polymer-supported organic–aqueous two-phase solution system. Primary alcohols are readily oxidized with no over-oxidation to carboxylic acids. Furthermore, this process exhibits chemoselectivity for the oxidation of primary hydroxy groups in the presence of secondary hydroxy groups.

Experimental

Materials

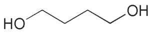
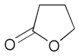
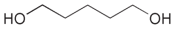
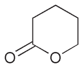
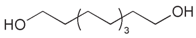
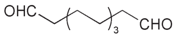
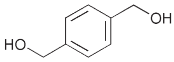
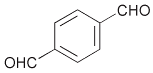
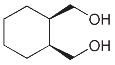
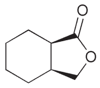
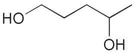
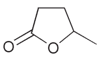
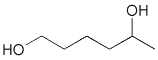
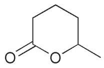
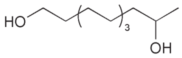
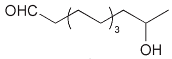
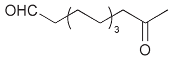
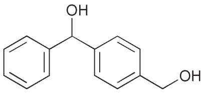
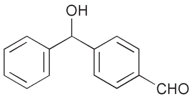
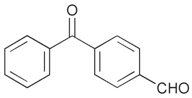
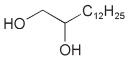
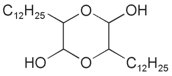
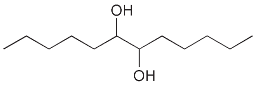
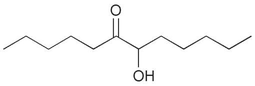
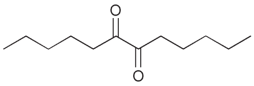
PS resin (1% cross-linked, 75–150 mesh) was purchased from Agronaut Technologies Inc. 4-Benzoyloxy-TEMPO was purchased from Tokyo Chemical Industry. Potasium hydroxide and $K_3Fe(CN)_6$ were purchased from Nakari Tesque. All alcohols and symmetrical diols used for the oxidations were of commercially available reagent grade except *trans*-4-phenyl-3-buten-2-ol obtained in 70% yield by reduction of 4-phenyl-3-buten-2-one as the commercial ketone by $NaBH_4/CeCl_3$.[10] Primary-secondary diols, already known, were prepared

Table 3 PS resin-supported two-phase oxidation of primary alcohols in the presence of secondary alcohols with $K_3Fe(CN)_6$ mediated by 4-benzoyloxy-TEMPO[a]

Entry	Substrate	Time/h	Product	% Yield[b]	TON of 4-benzoyloxy-TEMPO[c]
1		3		98 < 0.1	49
2		3		98 < 0.1	49
3		4		88 5	47

[a] The reactions were carried out, on a 1:1 mixture of primary and secondary alcohols. [b] Yields were determined by calibrated quantitative GC and HPLC analysis using an internal standard. [c] Turnover number given by the ratio of mol of products × 2 per mol 4-benzoyloxy-TEMPO.

Table 4 PS resin-supported two-phase oxidation of various diols with $K_3Fe(CN)_6$ mediated by 4-benzoyloxy-TEMPO

Entry	Substrate	Time/h	Product	% Yield[a]	TON of TEMPO[b]
1		4		96	192
2		3		97	194
3		4		92	184
4		6		95	190
5		2		94	188
6		6		88	176
7		5		90	180
8		2	 + 	80[c] 5	90
9		3	 + 	76[d] 12	100
10		5		70	70
11		8	 + 	12 60	132

[a] Yields based on weight of pure product after chromatography. [b] Turnover number given by the ratio of mol of products such as lactones, ketoaldehydes, dialdehydes and diketones × 4 per mol of 4-benzoyloxy-TEMPO. [c] Ketoalcohol could not be detected. [d] 0.5% ketoalcohol and 7% starting diol were isolated.

by simplified procedures except for 1,4-pentanediol, 1,5-hexanediol and 1,2-tetradecanediol as commercial diols; 1,10-undecenediol[11] was prepared with a 78% yield by oxymercuration-demercuration of 10-undecene-1-ol and α-phenyl-1,4-benzenedimethanol[12] in 90% yield by borane/THF reduction of 4-benzoylbenzoic acid.

General procedure for the oxidation of alcohols

PS resin (300 mg) was added to the toluene solution (4 ml) containing alcohol (2 mmol), 4-bezoyloxy-TEMPO (0.04 mmol) and tetralin (0.5 mmol; internal standard). This PS resin dispersed solution was stirred for 1 h at room temperature and then was separated. The swelled resin was washed three times with water and then was added to 10 ml of a 1 M aqueous KOH solution containing 2.45 g (7.5 mmol) of $K_3Fe(CN)_6$. The reaction mixture was stirred at room temperature and the reaction monitored by HPLC and/or GC. The HPLC analysis was carried out using a Daisel CHIRALCEL® OD column (46 mm ϕ × 250 mm). The column temperature 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 adsorption at 254 nm. The GC analysis was carried out using CP-cyclodextrin-b-2,3,6-M-19 capillary column (0.25 mm ϕ × 25 m). The column temperature was increased at 3 °C min^{-1} from 80 to 150 °C. The injection and detector temperatures were 200 °C and 240 °C, respectively. At the end of the reaction, the swelled resin was separated, washed three times with water, extracted three times with toluene and filtered *in vacuo*. This extracted solution was dried with magnesium

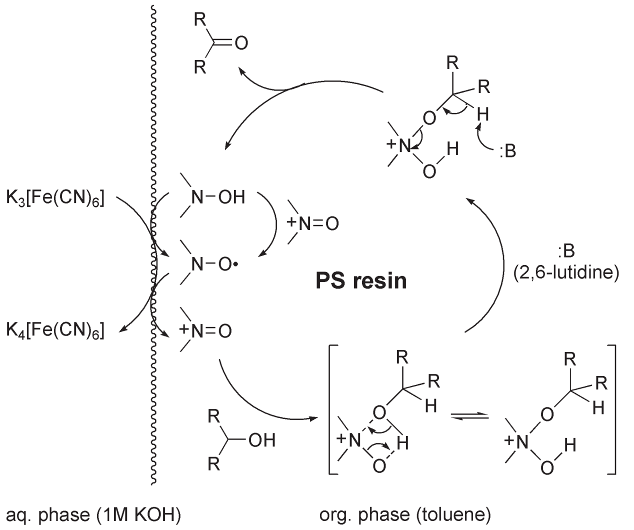


Fig. 4 Schematic diagram of PS resin-supported two-phase oxidation of alcohols with $K_3Fe(CN)_6$ mediated by 4-benzoyloxy-TEMPO.

sulfate and evaporated. The residue was distilled or isolated by column chromatography on silica gel.

Oxidation products

Simple aldehydes, ketones and lactones obtained by oxidation were characterized by the usual spectral data (mass, IR, ^1H and ^{13}C NMR) and compared with the literature values. The oxidation products of primary-secondary diols were already described: 10-hydroxyundecanal,[4c] 10-oxoundecan-1-ol,[11] 10-oxoundecanal,[3b] 4-(α-phenylhydroxymethyl)benzaldehyde,[13] 4-(hydroxymethyl)benzophenone,[12] 4-benzoyl benzaldehyde.[12]

Acknowledgements

This work was supported in part 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.

References

1 E. G. Rozantsen and V. D. Sholle, *Synthesis*, 1971, 401.
2 A. E. J. de Nooy, A. C. Besemer and H. van Bekkum, *Synthesis*, 1996, 1153.
3 NaOCl: (*a*) P. L. Anelli, C. Biffi, F. Montanari and S. Quici, *J. Org. Chem.*, 1987, **52**, 2559; (*b*) P. L. Anelli, S. Banfi, F. Montanari and S. Quici, *J. Org. Chem.*, 1989, **54**, 2970; (*c*) P. L. Anelli, F. Montanari and S. Quici, *Org. Synth.*, 1990, **69**, 212; (*d*) R. Siedlecka, J. Skarzewski and J. Mlochowski, *Tetrahedron Lett.*, 1990, **31**, 2177; (*e*) G. Tong, J. W. Perich and R. B. Johns, *Tetrahedron Lett.*, 1990, **31**, 3759; (*f*) T. S. Straub, *J. Chem. Educ.*, 1991, **68**, 1048; (*g*) N. J. Davis and S. L. Flitsch, *Tetrahedron Lett.*, 1993, **34**, 1181; (*h*) N. J. Davis and S. L. Flitsch, *J. Chem. Soc., Perkin Trans. 1*, 1994, 359; (*i*) C. Bolm and T. Fey, *Chem. Commun.*, 1999, 1795; (*j*) M. Zao, J. Li, E. Mano, Z. Song, D. M. Tschaen, E. J. J. Grabowski and P. J. Reider, *J. Org. Chem.*, 1999, **64**, 2564.
4 NaBr: (*a*) M. R. Leanna, T. J. Sowin and H. E. Morton, *Tetrahedron Lett.*, 1992, **33**, 5029; (*b*) T. Inokuchi, S. Matsumoto, T. Nishiyama and S. Torii, *Synlett.*, 1990, 57; (*c*) T. Inokuchi, S. Matsumoto and S. Torii, *J. Org. Chem.*, 1991, **56**, 2416; (*d*) Y. N. Ogibin, A. K. Khusid and G. I. Nikishin, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 941; Y. N. Ogibin, A. K. Khusid and G. I. Nikishin, *Bull. Acad. Sci., USSR Div. Chem. Sci. (Engl. Transl.)*, 1992, 735; (*e*) M. Kuroboshi, H. Yoshihara, M. N. Cortona, Y. Kawakami, Z. Gao and H. Tanaka, *Tetrahedron Lett.*, 2000, **41**, 8131.
5 $NaBrO_2$: (*a*) T. Inokuchi, S. Matsumoto, T. Nishiyama and S. Torii, *J. Org. Chem.*, 1990, **55**, 462; (*b*) T. Inokuchi, P. Liu and S. Torii, *Chem. Lett.*, 1994, 1411; (*c*) S. Saito, T. Hara, K. Naka, T. Hayashi and T. Moriwake, *Synlett.*, 1992, 241; (*d*) S. Saito, T. Ishikawa and T. Moriwake, *Synlett.*, 1993, 139.
6 Bu_4NBr_3: T. Inokuchi, S. Matsumoto, M. Fukushima and S. Torii, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 796.
7 $CuCl_2$: (*a*) T. Miyazawa and T. Endo, *J. Mol. Catal.*, 1985, **31**, 217; (*b*) T. Miyazawa and T. Endo, *J. Polym. Sci., Chem. Ed.*, 1985, **23**, 2487.
8 $K_3Fe(CN)_6$: (*a*) T. Miyazawa and T. Endo, *J. Mol. Catal.*, 1985, **32**, 357; (*b*) T. Miyazawa and T. Endo, *J. Mol. Catal.*, 1988, **49**, L31.
9 (*a*) S. Kishioka, T. Ohsaka and K. Tokuda, *Chem. Lett.*, 1988, 343; (*b*) S. Kishioka, S. Ohki, T. Ohsaka and K. Tokuda, *J. Electroanal. Chem.*, 1998, **452**, 176.
10 A. Gemal and L. Luche, *J. Am Chem. Soc.*, 1981, **103**, 5454.
11 S. Kanemoto, H. Tomioka, K. Ohshima and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 105.
12 C. F. Nutaitis and G. W. Gribble, *Tetrahedron Lett.*, 1983, **24**, 4287.
13 C. C. Leznoff and J. Y. Wong, *Can. J. Chem.*, 1973, **51**, 3756.