



Electro-oxidative kinetic resolution of *sec*-alcohols by using an optically active *N*-oxyl mediator

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Abstract

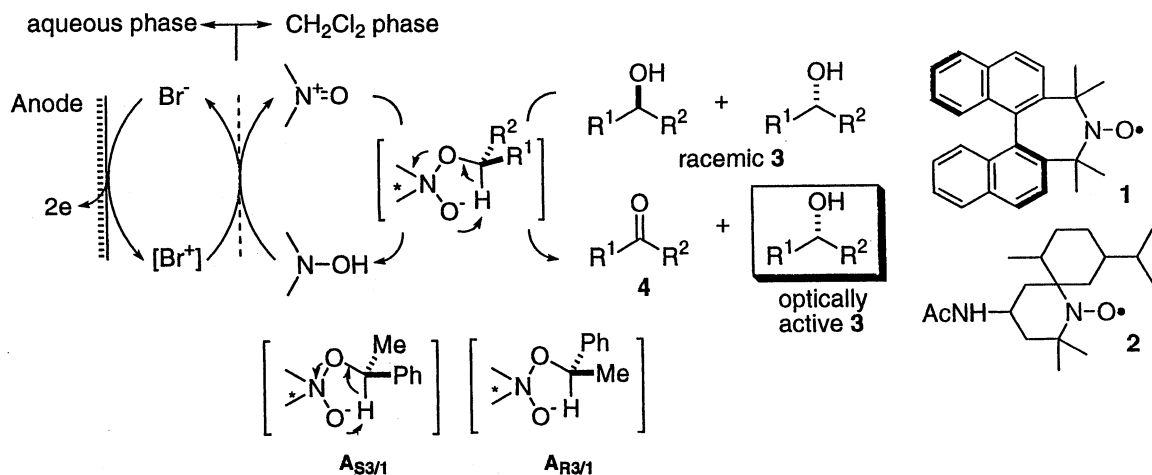
Electro-oxidative kinetic resolution of *sec*-alcohols mediated with a catalytic amount of an optically active *N*-oxyl was performed by use of a simple undivided cell under constant current conditions. The selectivity factor (*S*-value) increased remarkably when the reaction was performed at lower temperatures. The optically active *N*-oxyl was recovered and used repeatedly without any change in efficiency and selectivity. © 2000 Elsevier Science Ltd. All rights reserved.

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The preparation of chiral *sec*-alcohols is of importance for synthesis of chiral bioactive compounds and function materials. Among the methodologies developed for this purpose so far,¹ oxidative kinetic resolution using a chiral oxidant is a promising access to enantio-enriched alcohols from their racemates.² Electrochemical oxidation of alcohols has been well recognized as an environment-benign method since a catalytic amount of oxidant is enough to complete the oxidation through in situ electrochemical regeneration of the oxidant. Electrochemical kinetic resolution of *sec*-alcohols has been also developed by using an optically active *N*-oxyl compound as a mediator such as **2**,³ electrodes modified with a chiral *N*-oxyl,⁴ and a combination of an achiral *N*-oxyl-modified electrode and chiral amine, e.g. sparteine.⁵ Most of these reactions were, however, carried out in a divided cell; hence, a high concentration of a supporting electrolyte, such as a quaternary ammonium salt, was indispensable to attain a practically significant current of electricity, causing serious environmental problems in a practical scale of the electrolysis. Satisfactory selectivities (*S* value)⁶ were obtained only when *N*-oxyl was immobilized in a polymer matrix on the electrode under strict control of the electrode potential. Electrolysis in a simple undivided cell under constant current conditions is much more desirable

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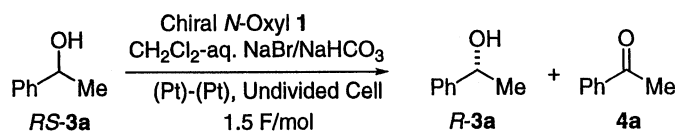
in the practical sense. We investigated electro-oxidation of alcohols in a double mediatory system comprising halide salts and *N*-oxyl compounds which can be operated in a simple undivided cell.⁷ In this report electro-oxidative kinetic resolution of *sec*-alcohols in a CH₂Cl₂–H₂O two-phase system involving bromide salts and an optically active *N*-oxyl mediator **1** is described. This is the first example of enantioselective electro-oxidation achieved in an undivided cell under constant current conditions, offering a simple operation for achieving high current efficiency as well as satisfactory selectivities (*S* = 13–20) (Scheme 1).



Scheme 1. Electro-oxidative kinetic resolution of *sec*-alcohols using an optically active *N*-oxyl mediator

The optically active *N*-oxyl **1** was prepared according to the literature.⁸ A typical procedure of the kinetic resolution is as follows (Table 1, entry 1): A mixture of (\pm)-1-phenyl-1-ethanol **3a** (0.56 mmol) and **1** (0.005 mmol) in a two-phase solution of CH₂Cl₂ (4 mL) and a saturated aq. NaHCO₃ (4 mL) containing 20w% of NaBr was placed in a beaker-type undivided electrolysis

Table 1
Kinetic resolution of (\pm)-1-phenyl-1-ethanol **3a**. Reaction temperature and selectivity



Entry	Temp/°C	4a		3a	<i>S</i> ^c
		Yield% ^a	Yield% ^a	Ee (<i>R</i>)/% ^b	
1	-15	57	43	91	16.4
2	-10	55	45	74	8.9
3	-5	46	53	52	6.3
4	0	40	57	44	5.7
5	18	52	47	16	1.6

^a Isolated yields.

^b Ee% were determined by HPLC using chiral column Daicel ChiralCel OD-H.

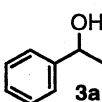
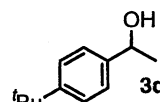
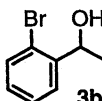
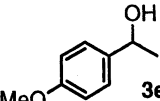
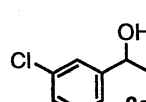
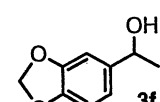
^c $S = \ln[(1-C)(1-ee)] / \ln[(1-C)(1+ee)]$ where ee is the fractional enantiomeric excess and *C* is the conversion.

cell. Two Pt plate electrodes (1.0×1.5 cm²) were immersed into the aqueous layer. Electrolysis was carried out at -15°C under constant current density (15 mA/cm²). After passage of 1.5 F/mol of electricity (ca 1.5 h),⁹ the mixture was poured into saturated aq. NaHCO₃, extracted with EtOAc, and dried over anhydrous Na₂SO₄. The organic layer was concentrated in vacuo, and the residue was chromatographed on a silica gel column to give the starting material **3a** (43%) and the corresponding ketone **4a** (57%). The recovered (*R*)-enriched **3a** was analyzed to be 91%ee by HPLC equipped with a chiral column Daicel ChiralCel OD-H. The selectivity factor, *S* value, was 16.4, which is much higher than that observed in the literature⁸ (0°C, 87% conv., 87%ee, *S*=7.1).

The ee% of **3a** and *S* value decreased significantly with increasing reaction temperature (Table 1). When the electrolysis was attempted at below -15°C, a part of the solvent was frozen and, consequently, no appreciable dc current could be passed and the electro-oxidation did not proceed at all.

The present optically active *N*-oxyl mediated electro-oxidation was successfully applied to the kinetic resolution of phenethyl alcohol derivatives **3** with a catalytic amount of **1**. Representative results are summarized in Table 2. When the aryl group of **3** was substituted with a chlorine, bromine, or alkyl group, stereoselectivity of the recovered **3** was high (**3b**, **3c**, **3d**). On the other hand, alkoxy-substituted phenethyl alcohols (**3e**, **3f**) were easily oxidized but in low ee% and *S* value. The low *S* value for the alkoxy-substituted substrates may be due to non-enantioselective oxidation such as direct oxidation. Indeed, when the electro-oxidation of 1-(4-methoxyphenyl)ethanol **3e** was performed without the *N*-oxyl **1**, a significant amount (ca 50%) of 4-methoxyphenyl methyl ketone was formed after passage of 2 F/mol of electricity, whereas no appreciable oxidation of 1-(4-chlorophenyl)ethanol was observed.

Table 2
Oxidation of phenethyl alcohol derivatives **3** using the optically active *N*-oxyl **1**

Substrate	4		3		<i>S</i> ^c	Substrate	4		3		<i>S</i> ^c
	Yield ^a	Yield ^a	Ee ^b	Yield ^a			Yield ^a	Ee ^b			
 3a	57	43	91 (<i>R</i>)	16	 3d	42	55	60 (<i>R</i>)	20		
 3b	54	42	81 (<i>R</i>)	13	 3e	61	37	56 (<i>R</i>)	5.3		
 3c	58	41	88 (<i>R</i>)	13	 3f	72	23	54 (<i>R</i>)	2.0		

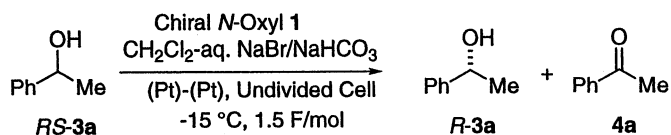
^a Isolated yields.

^b Determined by HPLC equipped with chiral column.

^c $S = \ln[(1 - C)(1 - ee)] / \ln[(1 - C)(1 - ee)]$ where ee is the fractional enantiomeric excess and *C* is the conversion.

It is noteworthy that the optically active mediator **1** could be recovered after electrolysis and used repeatedly without any appreciable change in efficiency and selectivity (Table 3). In each of the entries, the *N*-oxyl **1** was recovered almost quantitatively after the electro-oxidation.

Table 3
Recycle usage of the optically active *N*-oxyl **1**



Entry	4a		3a	<i>S</i> ^c
	Yield% ^a	Yield% ^a	Ee (<i>R</i>)/% ^b	
1	52	43	91	16
2	53	42	90	16
3	52	46	90	17

^a Isolated yields.

^b Determined by HPLC equipped with chiral column.

^c $S = \ln[(1 - C)(1 - ee)] / \ln[(1 - C)(1 + ee)]$ where ee is the fractional enantiomeric excess and *C* is the conversion.

Although the reaction mechanism is not clear at present, an optically active *N*-oxoammonium species would be formed from oxidation of *N*-oxyl **1** and/or *N*-hydroxyl with the bromonium species [Br⁺] generated by electro-oxidation of the bromide ion in aqueous media (Scheme 1). The *N*-oxoammonium would react with the alcohol **3** to give an intermediate **A**.^{7b} As the *N*-oxyl **1** is optically active, intermediate complexes with (*R*)-**3** (**A**_{R3/1}) and (*S*)-**3** (**A**_{S3/1}) are diastereomers of each other. Kinetic resolution might occur at this complex-formation stage: The steric environment of **1** would prefer the formation of the intermediate **A**_{S3/1} rather than the intermediate **A**_{R3/1}.⁸ The ketone **4** may be formed by hydride transfer in the intermediate **A**_{S3/1}, and (*S*)-**3** may be preferentially consumed. As a result, (*R*)-**3** might be retained predominantly.

In conclusion, electro-oxidative kinetic resolution of *sec*-alcohol using an optically active *N*-oxyl **1** proceeds smoothly in a CH₂Cl₂-H₂O two-phase system to give optically active *sec*-alcohols in high recovery and high ee%. The electrolysis can be performed in a simple undivided cell under self-potential controlled conditions. The enantiomeric selectivity was increased when the electro-oxidation was carried out at lower temperature (−15°C). The catalyst **1** can be used repeatedly without any change in efficiency and selectivity.

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6. Selective factor: $S = \ln[(1-C)(1-ee)] / \ln[(1-C)(1+ee)]$ where ee is the fractional enantiomeric excess of recovered **2a** and C is the conversion.²
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9. When 1.0 F/mol of electricity was passed, the ketone **4a** and alcohol **3a** were obtained in 37 and 61% yields, respectively.