

# Enantioselective Asymmetric Electrochemical Oxidation of Enol Acetates Using Chiral Supporting Electrolyte

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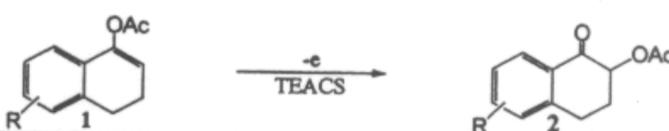
Enantioselective asymmetric synthesis by electrochemical methods has been one of the most challenging subjects in organic electrochemistry.<sup>1, 2)</sup>

In this study, we wish to present novel enantioselective introduction of an acetoxy group to the  $\alpha$ -position of the carbonyl group of ketones by anodic oxidation of enol acetates using a chiral supporting electrolyte. Thus, anodic oxidation of 1-acetoxy-3,4-dihydronaphthalenes (1) and 1-acetoxystyrenes (2) was carried out at  $-78^\circ\text{C}$  in a mixed solvent of AcOH and  $\text{CH}_3\text{CN}$  containing tetraethylammonium camphor-sulfonate (TEACS) as a chiral supporting electrolyte. Enantioselectivity and yield of the products, the corresponding  $\alpha$ -acetoxyketones (3,4) were found to be largely influenced by a variety of reaction conditions, especially temperature, solvent composition, and structure of the substrates. It was found that lowering of reaction temperature and decrease in solvent polarity resulted in remarkable increase in enantioselectivity of the products, as shown in Table 1. It may be noteworthy that introduction of a methoxy group to the 7-position of 1 brought about much better yield of the product 2c from the reaction in AcOH (entry 4 and 7, Table 1), and higher enantioselectivity for 2c (entry 6 and 9, Table 1) from the reaction in a mixed solvent of  $\text{CH}_3\text{CN}$ , THF and AcOH than that to the 6-position of 1. This remarkable phenomena may be elucidated by the following proposed mechanism, as shown in Scheme. The first electron transfer from 1 to an anode may generate a cation radical 6, which is subjected to alternative two pathways A or B. In the path A, nucleophilic attack of an acetoxy anion to the 2-position of 6 followed by the second electron transfer takes place to generate diacetoxy carbocation 8, which exclusively give the desired 2-acetoxy ketone 2. The electron-withdrawing character of the 7-methoxy group may accelerate this path A by distribution of the positive charge on the 1-carbon atom to the 2-carbon atom. On the other hand, elimination of an acetyl cation generates  $\alpha$ -keto radical 9, which leads to side reactions or formation of an unstable  $\alpha$ -keto carbocation 10 in the path B, unfavorable for the formation of 2. This path B is enhanced by the electron donating character of the 6-methoxy group by localization of the positive charge at the 1-carbon atom. In the interaction of the cation radical intermediate 6 with the chiral supporting electrolyte (TEACS), the interaction at the two points, the one between the  $\text{SO}_3^-$  anion of TEACS and 1-carbon atom of 6, and the other between the carbonyl oxygen of TEACS and 2-carbon atom of 6 are more available for the 7-methoxylated intermediate 6 than for the 6-methoxylated one, and may indicate that an approach of TEACS shown in Figure B is more favorable than that in shown Figure A owing to steric repulsion between the methylene group of TEACS and those of 2.

Furthermore, the increase in steric bulkiness of a 2-alkyl(R) group of enol acetates 2 led to proportional increase in the enantioselectivity of the products 4, although the incorporation a phenyl group as the

substituent R resulted in no stereoselectivity, possibly because of easy racemization of the product through isomerization via a cyclic intermediate under the reaction condition. Comparison of chiral liquid chromatographic behaviors of the enantiomeric mixture obtained of  $\alpha$ -acetoxypropiophenone with those of authentic (S)- $\alpha$ -acetoxypropiophenone indicated that the (R)-isomer was preferentially obtained in the present anodic oxidation.

Table 1 Enantioselective Anodic Oxidation of Enol Acetates of  $\alpha$ -Tetralone Derivatives

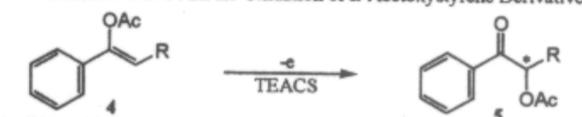


Entry	R	Solvents <sup>a)</sup>	Conv. (%) <sup>b)</sup>	Yield (%) <sup>b)</sup>	e. e. (%) <sup>c)</sup>
1 <sup>d)</sup>	H [1a]	AcOH	100	31 [2a]	-
2	H [1a]	MeCN:AcOH 9:1	70	10 [2a]	11
3	H [1a]	MeCN:THF:AcOH 27:9:1	76	8 [2a]	36
4 <sup>d)</sup>	6-MeO [1b]	AcOH	100	39 [2b]	-
5	6-MeO [1b]	MeCN:AcOH 9:1	67	12 [2b]	1
6	6-MeO [1b]	MeCN:THF:AcOH 27:9:1	60	8 [2b]	2
7	7-MeO [1c]	AcOH	100	81 [2c]	-
8	7-MeO [1c]	MeCN:AcOH 9:1	83	8 [2c]	37
9	7-MeO [1c]	MeCN:THF:AcOH 27:9:1	76	7 [2c]	44

Reaction Conditions: Substrate (10mmol), Solvent (40ml), Current density (15mA/cm<sup>2</sup>), Supporting electrolyte (10mmol), Supplied electricity (6.0F/mol), Temperature ( $-78^\circ\text{C}$ ), under  $\text{N}_2$  atmosphere.

a) Volume Ratio. b) GC Yield. c) Analyzed by HPLC. d) NaOAc was added (0.3eq.mol).

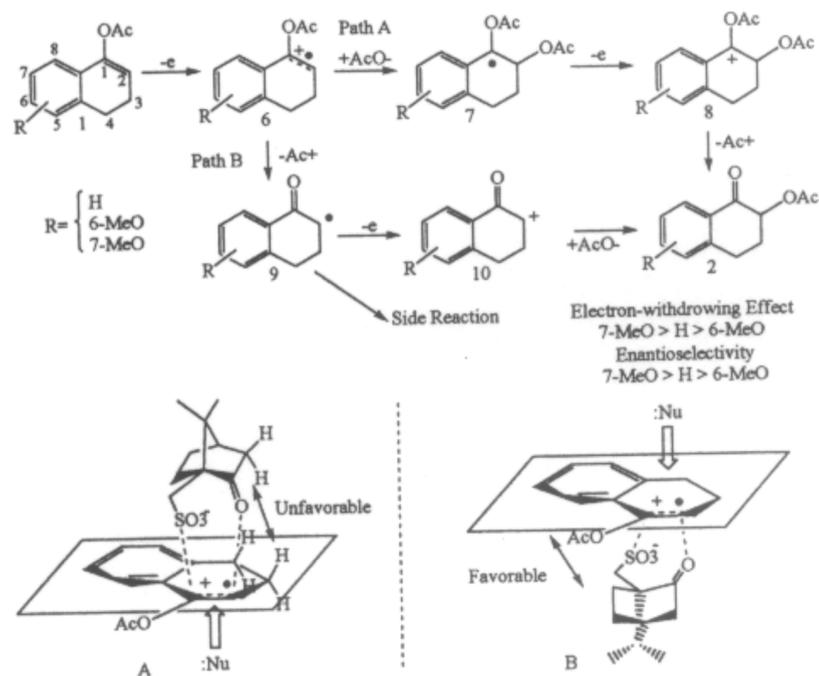
Table 2 Enantioselective Anodic Oxidation of  $\alpha$ -Acetoxystyrene Derivatives [4]



Entry	R	Solvents <sup>a)</sup>	S.E. (F/mol) <sup>b)</sup>	Conv. (%) <sup>c)</sup>	Yield (%) <sup>c)</sup>	e. e. (%) <sup>d)</sup>
1 <sup>e)</sup>	Me [4a]	AcOH	3.0	100	68 [5a]	-
2	Me [4a]	MeCN:AcOH 9:1	6.0	73	15 [5a]	7
3 <sup>e)</sup>	Pr [4b]	AcOH	3.0	100	60 [5b]	-
4	Pr [4b]	MeCN:AcOH 9:1	6.0	75	13 [5b]	17
5 <sup>e)</sup>	Bu [4c]	AcOH	3.0	100	71 [5c]	-
6	Bu [4c]	MeCN:AcOH 9:1	6.0	62	10 [5c]	21
7 <sup>e)</sup>	Ph [4d]	AcOH	3.0	100	64 [5d]	-
8	Ph [4d]	MeCN:AcOH 9:1	6.0	81	15 [5d]	<1

Reaction Conditions: Substrate (10mmol), Solvent (40ml), Current density (15mA/cm<sup>2</sup>), Supporting electrolyte (10mmol), Supplied electricity (6.0F/mol), Temperature ( $-78^\circ\text{C}$ ), under  $\text{N}_2$  atmosphere.

a) Volume Ratio. b) Supplied Electricity. c) GC Yield. d) Analyzed by HPLC. e) NaOAc was used as a supporting electrolyte at room temp.



Scheme 3-7 Proposed Mechanism