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Highly Enhanced Enantioselectivity in the Memory of Chirality via Acyliminium Ions†

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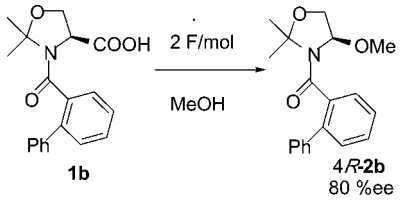
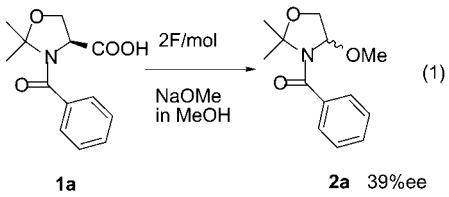
ABSTRACT



Electrochemical oxidation of N-acylated serine derivative 1b in methanol gave optically active methoxylated compound 2b with an enantiomeric excess of up to 80%. The bulky *o*-phenyl benzoyl N-protecting group was found to be the main contributing factor for the enhanced enantioselectivity. The mechanistic aspect of this methoxylation reaction was investigated and found to proceed via a retention mechanism.

The synthesis of optically active compounds on the basis of "memory of chirality" continues to attract much attention in asymmetric synthesis.[1] Memory of chirality can be defined as a phenomenon in which the chirality of a starting material having a chiral sp^3-carbon is preserved in the reaction product even though the reaction proceeds at the chiral carbon as a reaction center through reactive intermediates such as carbanion, singlet monoradicals,[2] biradicals,[3] or carbenium ions.[4,5] Reactions involving all the above intermediates except the carbenium ion have been reported to proceed well affording products with very high enantiomeric excesses.

In the first memory of chirality via carbenium ion chemistry, we reported the generation of optically active **2a** (39% enantiomeric excess (ee)) when N-benzoylated serine derivative **1a** was electrochemically oxidized (eq 1),[4a] but the ee was generally low.



To increase the enantioselectivity, we envisioned that the modification of the N-protecting group could enhance the ee since protecting groups of amino compounds are known to affect selectivity of the reactions[6] especially asymmetric reactions.[7] On the basis of this hypothesis, we synthesized a serine derivative **1b** bearing a bulky *o*-phenylbenzoyl group

† This paper is dedicated to Professor Hans J. Schäfer on the occasion of his 65th birthday.

(1) Kawabata, T.; Chen, J.; Suzuki, H.; Nagae, Y.; Kinoshita, T.; Chancharunee, S.; Fuji, K. *Org. Lett.* **2000**, *2*, 3883−3885.

(2) (a) Schmalz, H. G.; de Koning, C. B.; Bernicke, D.; Siegel, S.; Pfletchinger, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1620−1623. (b) Sauer, S.; Schumacher, A.; Barbosa, F.; Giese, B. *Tetrahedron Lett.* **1998**, *39*, 3685−3688. (c) Giese, B.; Wettstein, P.; Stahelin, C.; Barbosa, F.; Neuburger, M.; Zehnder, M.; Wessig, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2586−2587.

(3) Griesbeck, A. G.; Kramer, W.; Lex, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 577−579.

(4) (a) Matsumura, Y.; Shirakawa, Y.; Satoh, Y.; Umino, M.; Tanaka, T.; Maki, T.; Onomura, O. *Org. Lett.* **2000**, *2*, 1689−1691. (b) Matsumura, Y.; Tanaka, T.; Wanyoike, G. N.; Maki, T.; Onomura, O. *J. Electroanal. Chem.* **2001**, *507*, 71−74. (c) Davies, S. G.; Donohoe, T. J. *Synlett* **1993**, 323−332.

(5) The original chirality is conformationally memorized in those reactive intermediates. Thus, the well-known retention of configuration caused by neighboring effects in carbocation chemistry is excluded from the definition.

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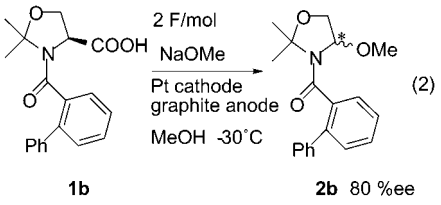
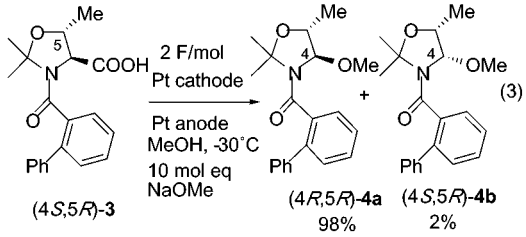
as the N-protecting group. Electrolysis of this compound **1b** in methanol afforded α-methoxylated serine derivative **2b** with an interestingly high ee of up to 80%[8] (eq 2).



The electrolysis was carried out in methanol at −30 °C using an excess of base (NaOMe) and platinum as both the anode and the cathode.[9]

Having obtained a convenient method for synthesizing optically active **2b**, we finally had to determine the absolute configuration and hence deduce the reaction mechanism. The absolute configuration of **2b** could not be determined directly but was inferred on the basis of the following reactions.

Threonine derivative **3** was synthesized and subjected to electrolysis under the optimized reaction conditions. This electrolysis afforded α-methoxylated diastereomers **4a** and **4b** in a 98:2 ratio (eq 3).[10,11]



The relative configuration of the oxidation products **4a** and **4b** was confirmed by NOE experiments. Particularly diagnostic were the presence of strong NOE between the 5-methyl group protons and the H(4) and the NOE between methoxyl protons and H(5) of **4a** (Figure 1). In the case of

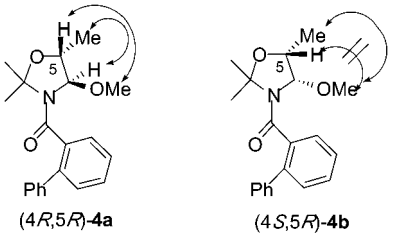
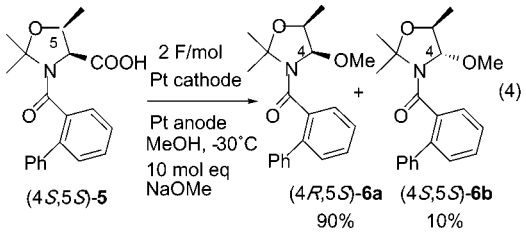


Figure 1. NOESY for **4a** and **4b**

4b, these signals were absent but the NOE between the methoxyl and methyl groups was observed, implying that these groups had a cis relationship (Figure 1).

It was deduced from this result that the methoxylation process proceeded mainly by introduction of the methoxyl group from the same side (syn) as the carboxylate group to afford a retention product **4a**. This information was necessary for inferring the absolute configuration of **2b**, but it was not sufficient because the presence of the methyl group at the C(5) could have had a directing effect on the incoming nucleophile due to steric effects. The steric hindrance could favor the formation of the trans isomer, which was the main product. To investigate whether the stereochemical course of reaction of **3** was governed by the chirality at C(5), an L-*allo*-threonine derivative **5** was prepared and electrolyzed under similar reaction conditions (eq 4).



Electrolysis of the L-*allo*-threonine derivative **5** afforded a mixture of α-methoxylated diastereomers **6a** and **6b** in a ratio of 90:10. The strong NOE between methyl protons and the methoxy protons of **6a**, which was absent in the minor isomer **6b**, confirmed the relative stereochemistry of the major product **6a** (Figure 2).

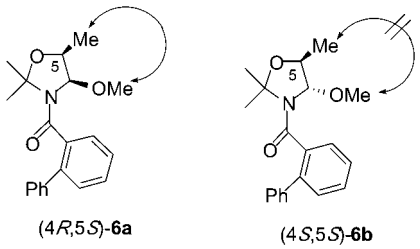


Figure 2. NOESY for **6a** and **6b**

This result also shows that the major oxidation product **6a** resulted from attack of the methoxide from the much more

(6) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons: New York, 1991; pp 315−403, 41−452.

(7) Shibasaki, M.; Takamura, M.; Funabashi, K.; Kanai, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327−6328; **2001**, *123*, 6801−6088.

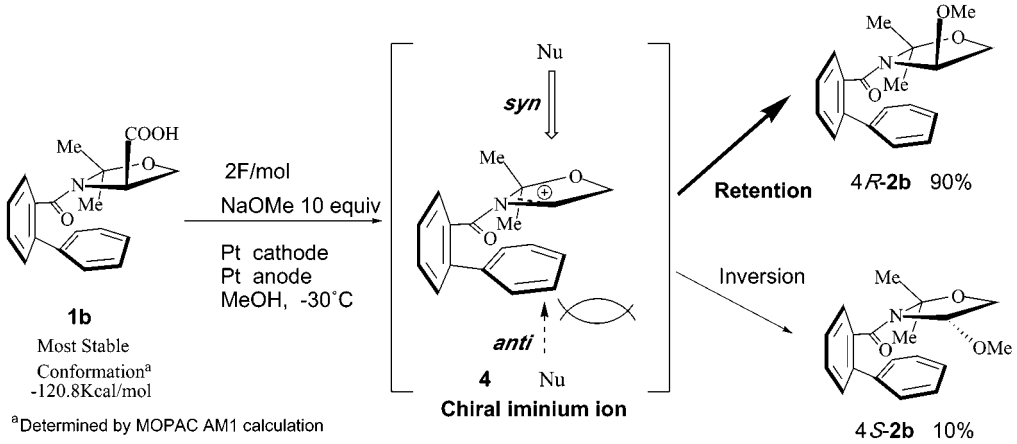
(8) The ee of **2b** was determined by HPLC analysis employing a Daicel Chiralpak OD.

(9) A solution of serine derivative **1b** (0.5 mmol) and NaOMe (5 mmol) in methanol (10 mL) was put into an undivided cell, stirred continuously, and cooled to −30 °C. The cell was then equipped with platinum plate electrodes (1 × 2 cm). Electrolysis of the solution with 2 F/mol at a constant current (50 mA) afforded **2b** (40% yield at 2 F/mol, 74% yield at 8 F/mol) with a recovery of **1b** (no racemization) after the usual workup.[4a]

(10) Treatment of a 98:2 mixture of **4a** and **4b** with acidic methanol at room temperature for 12 h afforded a 37:63 thermodynamic ratio of of **4a** and **4b**. Also, an acid treatment of a 90:10 mixture of **6a** and **6b** in methanol resulted in the formation of a 63:37 mixture of **6a** and **6b**.[11]

(11) The de for the methoxylated product of threonine and *allo*-threonine derivatives **3** and **5**, respectively, were determined using both Daicel Chiralpak OD and YMC-Pac SIL HPLC columns.

Scheme 1. Reaction Mechanism



[a] Determined by MOPAC AM1 calculation.

hindered syn side to form (4*R*,5*S*)-**6a**. On the basis of the stereochemical results of the oxidation products of both threonine and *allo*-threonine derivatives, it was deduced that the chirality at C(4) in **4a** and **6a** was memorized in the corresponding iminium ion intermediates. The memorized chirality made a major contribution to the stereochemical course of the reaction, while chirality at the adjacent chiral center C(5) had little effect. It is therefore inferred that the major oxidation product for **1b** is also the *R*-isomer.

Although the mechanistic details of this reaction are not well understood, a plausible mechanism for the electrochemical oxidation of these non-Kolbe reactions is illustrated in Scheme 1.

The initial step involves the oxidative decarboxylation of **1b** to form the iminium ion **4**, which can be attacked by nucleophiles (Nu) from the syn or the anti side. The observed 80% ee could be attributable to the presence of the bulky *o*-phenyl group beneath the carboxylic group and the fixation of the conformation of **1b** and of iminium ion intermediate **4** at low temperature.[12] The restricted rotation could have favored the formation of a chiral iminium ion with the conformation of an *o*-phenyl group similar to that of the precursor **1b**. The bulky *o*-phenyl group could have precluded an effective approach from the anti side, and hence the nucleophilic attack was predominantly from the less hindered syn side resulting in *R*-isomer **2b**.

In conclusion, we have found that the electrochemical oxidation of the serine derivative **1b** in methanol at −30 °C afforded optically active α-methoxylated compound **2b** with 80% ee, while that of threonine derivative **3** and *allo*-threonine derivative **5** afforded α-methoxylated products with 96 and 80% de, respectively. The high ee observed is attributable to the bulky *o*-phenylbenzoyl protecting group. Investigation is under way to find a more efficient protecting group than the *o*-phenylbenzoyl group for the improvement of enantioselectivity.

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Supporting Information Available: Experimental procedures and characterization for **1a**, **2b**, **3**, **4a**, **5**, and **6a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Electrolysis of **1b** at room temperature afforded **2b** (57% ee). The fact that this ee of **2b** was lower than that obtained when the reaction was performed at −30 °C (80% ee) indicated that the facial selectivity was dependent on the temperature.