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Organocatalyzed α-Oxyamination of Aldehydes Using Anodic Oxidation

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Electrochemical oxidation was performed during the organocatalyzed α-oxyamination of aldehydes by using a one-compartment electrolytic cell under galvanostatic conditions. In the presence of substoichiometric amounts of *sec*-amines, the desired coupling products were formed in good yield. The asymmetric variant of the α-oxyamination of aldehydes was examined by using chiral *sec*-amines. Control experiments and cyclic voltammetry confirmed the key intermediate of this reaction to be the cationic radical of the enamine derived from the *sec*-amine catalysts and aldehydes.

Introduction

Electrochemical oxidation and reduction have been used as powerful and clean methods for the synthesis of complicated organic molecules.[1] In particular, cationic radicals and cations generated by electrochemical oxidation are involved in further chemical reactions, which can avoid the use of toxic chemical oxidants, leading to green chemical processes.[1,2] As part of an ongoing investigation aimed at developing green catalytic reactions, this study examined the anodic oxidation of enamines, forming the cationic radical intermediate to perform radical-mediated reactions.[3,4] In the context of oxidized enamine radical-mediated reactions, enantioselective α-substitution reactions of aldehydes catalyzed by chiral secondary amines have been reported.[5,6] During the reaction, the enamine generated in situ from the chiral amine and aldehyde undergoes oxidation by transition-metal oxidants (Fe^{3+} or Ce^{4+}) to produce cationic radicals. Subsequently, the cationic radicals react with the coupling partner to give α-substituted aldehydes. This paper reports the *sec*-amine-catalyzed coupling of an aldehyde to TEMPO by using electrochemical oxidation, where the cationic radicals are formed by the anodic oxidation of the enamine intermediates, rendering a reaction with the TEMPO radical. Although a wide range of electrooxidation reactions have been reported, there are no papers on the organocatalyzed α-substitution of an aldehyde by anodic oxidation.[2,7–9]

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Results and Discussion

Prior to conducting the α-oxyamination of aldehydes by anodic oxidation, the electrochemical properties of hydrocinnamaldehyde (**1a**), pyrrolidine (organocatalyst), and enamine **1b** were evaluated by cyclic voltammetry (CV) on a platinum electrode over the potential range 0.0 to 2.0 V (Figure 1). The structures of aldehyde **1a**, pyrrolidine, and enamine **1b** are illustrated in Scheme 1. No particular redox wave for aldehyde **1a** (0.01 M) was observed in a dichloromethane solution containing 0.1 M tetrabutylammonium perchlorate (TBAP) as the electrolyte. During the anodic scan, an oxidation wave for pyrrolidine peaking was observed at 1.41 V vs. a silver wire pseudoreference electrode at a scan rate of 0.1 $V s^{-1}$, but no reduction wave was observed during the reverse scan. The absence of a reverse reduction peak of the oxidized pyrrolidine during the oxidation scan was attributed to the subsequent chemical reaction of the oxidized species.[10] Enamine **1b** exhibits an electrochemically irreversible redox pattern at the platinum electrode. In the range 0.0 to 2.0 V, two oxidation waves appeared at $E_{p,a}$ = 0.71 and 0.95 V, which are assumed to be the cationic radical and the allylic cation, respectively[11] (Scheme 2).

Cyclic voltammetry of a mixture containing compound **1a** (0.01 M) and pyrrolidine (0.005 M) was performed to obtain more information on the electrochemical properties of the intermediates formed during the catalytic reaction conditions. To consume pyrrolidine completely, 2 equivalents of the aldehyde was used with respect to pyrrolidine (1 equiv.). An oxidation wave appeared with a peak potential at 0.72 V, whereas the oxidation current peak at 1.41 V corresponding to the oxidation of pyrrolidine disappeared. The anodic wave at 0.72 V was attributed to the first oxidation of enamine **1b** derived from pyrrolidine and compound **1a**, which was verified by the CV of enamine **1b** prepared independently. The second oxidation current peak of enamine

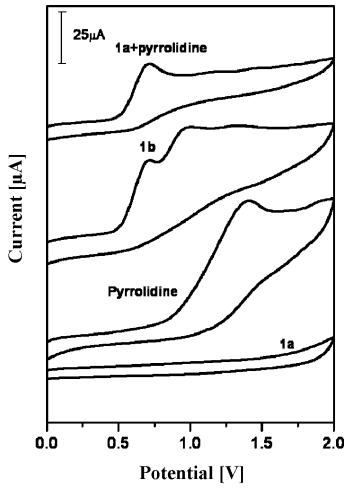
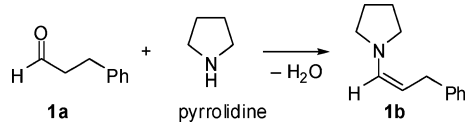
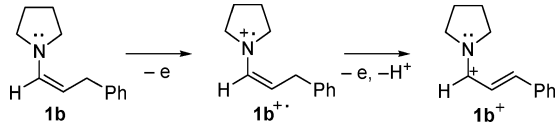


Figure 1. Cyclic voltammograms of **1a** (0.01 M), pyrrolidine (0.01 M), **1b** (0.01 M), and the mixture of **1a** (0.01 M) and pyrrolidine (0.005 M) in 0.1 M TBAP dichloromethane solution at a scan rate of 100 mV s^{-1}.



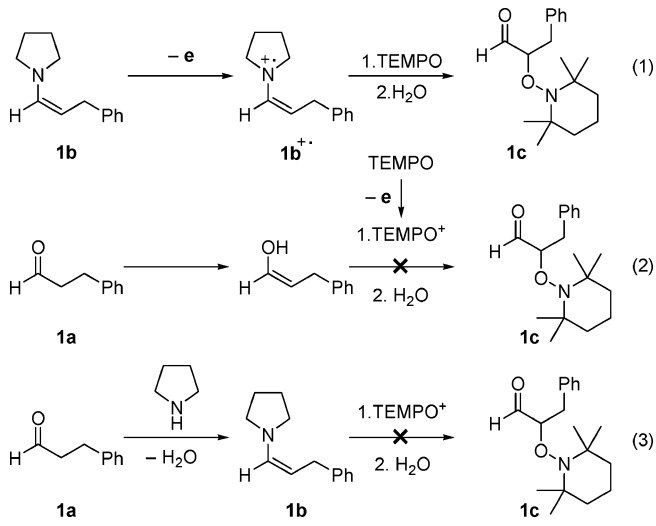
Scheme 1. The reaction of aldehyde **1a** with pyrrolidine.



Scheme 2. Electrooxidation of enamine **1b**.

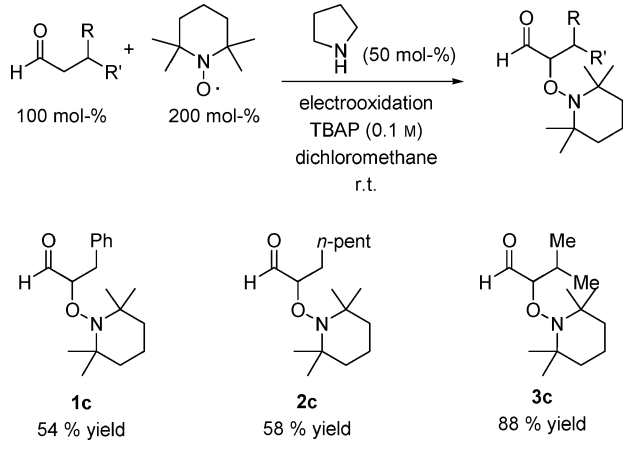
1b at 0.95 V was not observed in the CV of the solution containing compound **1a** (2 equiv.) and pyrrolidine (1 equiv.). Presumably, the cationic radical species generated from the first oxidation readily underwent a chemical reaction with the excess amount of the aldehyde.

In accordance with the electrochemical analysis of each component and their mixtures in Figure 1, a mechanism involving cationic radical **1b**$^{\cdot+}$ generated from the electrooxidation of **1b** and its reaction with TEMPO was considered to provide product **1c** (Scheme 3, Equation 1). Because the electrophilic addition of TEMPO$^+$ to enols has been reported,[7,12] oxidized TEMPO$^+$, and not cationic radical **1b**$^{\cdot+}$, might react with the enolized aldehyde to form compound **1c** under anodic electrolysis conditions (Scheme 3, Equation 2). To clarify the mechanism, the electrochemical oxidation of a solution containing **1a** and H$^+$ (*p*-toluenesulfonic acid) for enol formation was carried out in the presence of TEMPO, but no product was obtained. In addition, the possible route involving the electrophilic addition of TEMPO$^+$ to enamines (Scheme 3, Equation 3) was excluded on the basis of the following experiment. A chemical reaction of compound **1b** prepared independently with a commercially available oxopiperidinium salt (TEMPO$^+$) was carried out but no product was obtained. As a result, the electrophilic addition of TEMPO$^+$ to the enol or enamine to form compound **1c** was excluded under these reaction conditions.



Scheme 3. Plausible mechanisms for the formation of compound **1c**.

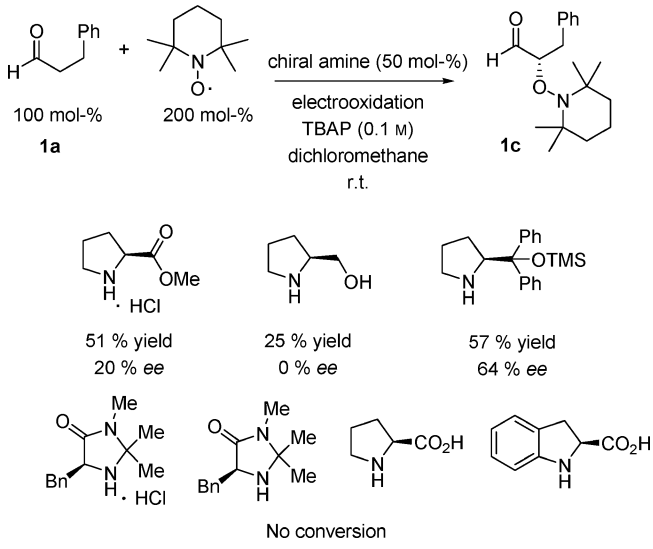
With the cyclic voltammetry and control experimental results indicating that the enamine-radical-mediated reaction is possible by an anodic oxidation, the electrolytically organocatalyzed α-oxyamination of aldehydes was conducted in a simple undivided cell under a constant anodic current. As shown in Scheme 4, the desired radical coupling products were obtained in good yield with a pyrrolidine catalyst. Hydrocinnamaldehyde (**1a**) and octanal (**2a**) participated in the reaction, providing coupling products **1c** and **2c** in 54 and 58% yield, respectively. The reaction of isovaleraldehyde (**3a**) and TEMPO showed higher yield compared to those of compounds **1a** and **2a**.



Scheme 4. Pyrrolidine-catalyzed α-oxyamination using anodic oxidation.

Various chiral *sec*-amines for the α-oxyamination of aldehydes were examined under the anodic electrolysis conditions to perform asymmetric conversion. Among the *sec*-

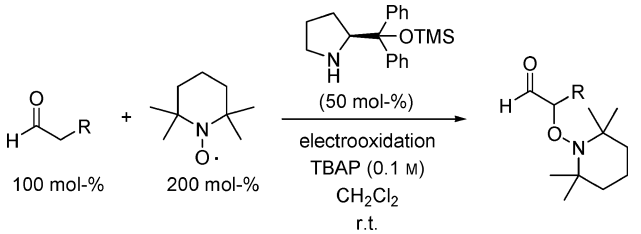
amine compounds listed, L-proline methyl ester hydrochloride, (*S*)-pyrrolidine methanol, and (*S*)-α,α-diphenyl-2-pyrrolidine methanol trimethylsilyl ether promoted this transformation (Scheme 5). In terms of the enantioselectivity, (*S*)-α,α-diphenyl-2-pyrrolidine methanol trimethylsilyl ether catalyzed the reaction to provide a product with higher enantioselectivity (64%*ee*) than the other catalysts, and it was chosen for study of the substrate scope. The absolute stereochemistry of compound **1c** was assigned as *S* by comparing the HPLC data reported in the literature.[5]



Scheme 5. Chiral amine-catalyzed α-oxyamination using anodic oxidation.

As shown in Table 1, enantioselective organocatalyzed α-oxyaminations of octanal (**2a**) and isovaleraldehyde (**3a**) were tested under the electrolysis conditions. Using **2a**, the desired coupling product was obtained in 23% yield and 70%*ee*. In the case of **3a**, 49% yield and 60%*ee* were observed under the electrolysis conditions.

Table 1. Substrate scope.



Entry	R	Time [h]	Yield [%]	*ee* [%][a]
1	Ph (**1a**)	9	57	64
2	$(CH_2)_5CH_3$ (**2a**)	10	23	70
3	$CH(CH_3)_2$ (**3a**)	9	49	60

[a] The enantioselectivity was measured by HPLC after modifying the product, as stated in the Supporting Information.

Conclusions

The organocatalyzed α-oxyamination of aldehydes by anodic oxidation was conducted in the presence of an achiral *sec*-amine (pyrrolidine) and chiral *sec*-amines, showing good yield and enantioselectivity. Despite the enormous effort to employ the electrolysis in a wide range of organic reactions including asymmetric reactions, this study is the first to show that anodic oxidation can be used to promote enamine-mediated organocatalytic reactions, where the cationic radical enamine intermediates are formed for singly occupied molecular orbital (SOMO) catalysis. Cyclic voltammetry and control experiments were carried out to confirm the mechanism.

Supporting Information (see footnote on the first page of this article): General experimental procedures and spectroscopic data for compound **2** and **3**.

Acknowledgments

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