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Electro-Organocatalysis: Enantioselective α-Alkylation of Aldehydes

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The asymmetric organocatalyzed α-alkylation of aldehydes via a cationic radical enamine intermediate was performed under environmentally benign electro-oxidation conditions without the use of chemical oxidants. To promote the desired α-alkylation reaction of aldehydes, various aldehydes with xanthene or cycloheptatriene groups were exposed to electro-organocatalytic conditions to afford optically active α-substituted aldehydes (α-alkylated aldehydes) in good yield. A reaction mechanism involving the cationic radical enamine was proposed based on the cyclic voltammetry (CV) results, DFT calculations, and control experiments.

Introduction

With the aim of broadening the scope and applications of conventional enamine-mediated organocatalytic reactions with electrophiles, a range of organocatalytic processes involving enamine radicals, which are formed from the 1-electron oxidation of the enamine, have been reported.[1,2] For the oxidation of the enamine, either stoichiometric amounts of transition-metal oxidants [ceric ammonium nitrate (CAN) and Fe^{3+}] or catalytic amounts of metal complexes with inorganic oxidants ($Cu^{2+}/Na_2S_2O_8$) are commonly used to generate a cationic radical enamine, which undergoes asymmetric coupling reactions with nonpolar hydrocarbon substrates or radical species. This new concept was proposed by MacMillan as a singly occupied molecular orbital (SOMO) concept.[2a]

In parallel with the development of SOMO protocols, including the in situ oxidation of enamine species to form cationic enamine radicals, a variety of methods for selectively oxidizing nonconventional coupling partners under organocatalytic reaction conditions by using metal complexes and organic oxidants have also been proposed.[3] In a photoredox transition-metal-mediated protocol presented by MacMillan, the direct alkylation of aldehydes occurs in the presence of photoredox transition-metal complexes and organocatalysts upon the irradiation of light. A catalytic amount of photoredox metal complexes {$[Ru(bpy)_3]^{2+}$ or $[Ir(ppy)_2(dtb\text{-}bpy)]^+$; bpy = bipyridine, ppy = 2-phenylpyridine, dtb-bpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl} promotes the redox process of the catalytic reaction without generating the cationic radical enamine.[3b,3c] As a transition-metal free method, a stoichiometric amount of an organic oxidant, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), was used to oxidize the benzylic C–H bond that participates in the reaction with the enamine.[3e]

Our research interest has been directed toward the development of green catalytic processes by avoiding the use of large amounts of toxic organic/inorganic chemicals. Accordingly, we have explored new catalytic reactions merging electro-oxidation and organocatalysis to establish green organocatalytic reactions.[4] By using electro-oxidation, enamine radicals could be generated, performing radical coupling reactions with 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) under environmentally benign conditions. Although there have been extensive studies on the application of electro-oxidation to organic synthesis,[5] there are few reports demonstrating electro-organocatalysis.[6] Therefore, we have examined a wide range of asymmetric transformations by using our electro-organocatalysis method under simple, aerobic and environmentally friendly conditions. This paper reports the first asymmetric organocatalyzed α-alkylation of aldehydes under galvanostatic conditions and electrochemical studies as well as DFT calculation results to provide mechanistic information. By using the electro-organocatalysis method, the direct incorporation of a benzylic carbon unit into synthetically versatile aldehydes was accomplished in a stereoselective manner.

Results and Discussion

The optimization began with an achiral *sec*-amine catalyst, pyrrolidine (**A**), which promoted the coupling of hydrocinnamaldehyde (**1a**) with xanthene (**2a**) under galvanostatic conditions to afford the desired product (**3a**) in 43% yield (Table 1, entry 1). With this result in mind, a range of proline derivatives and imidazolidinone-based catalysts were evaluated for the electro-organocatalytic coupling reaction, as shown in Table 1. Relative to compounds **B** and

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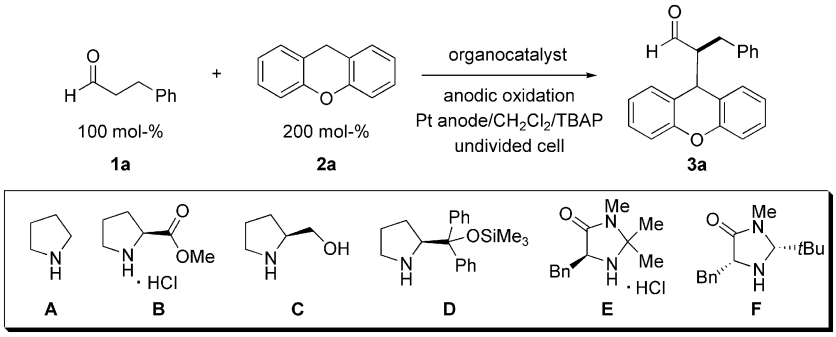
Table 1. Organocatalytic coupling reaction of **1a** and **2a** under galvanostatic conditions.[a]



Entry	Organocatalyst (mol-%)	*t* [h]	*T*	% Yield	*ee* [%]
1	**A** (50)	4	r.t.	43	–
2	**B** (50)	3	r.t.	81	3
3	**C** (50)	3	r.t.	25	17
4	**D** (50)	4	r.t.	14	68
5	**E** (50)	3	r.t.	18	65
6	**F** (50)	4	r.t.	74	70
7	**F** (50)	6	4 °C	80	70
8	**F** (20)	4	r.t.	68	68

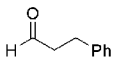
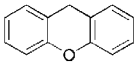
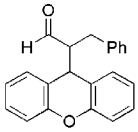
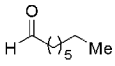
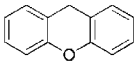
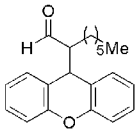
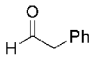
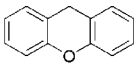
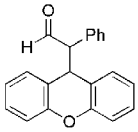
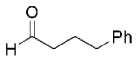
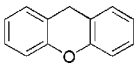
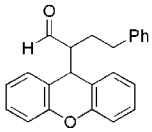
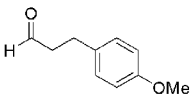
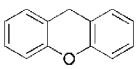
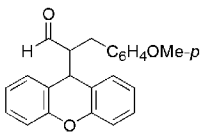
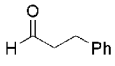
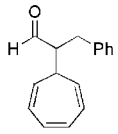
[a] Experimental procedure: organocatalyzed coupling reactions of **1a** and **2a** were conducted in an undivided cell with a dichloromethane solution [30 mL; tetrabutylammonium perchlorate (TBAP), 0.1 M] under galvanostatic conditions. The mixture of compound **1a** (1 mmol), **2a** (2 mmol), and catalyst was allowed to react at the indicated temperature until the starting material was completely consumed. Platinum gauze (2.5 cm × 2.5 cm) was used as the anode and cathode materials. A regulated power supply (Hanil Electric Co, maximum output power;180 W) was used for the constant current electrolyses. With this power supply, a fine adjustment of small current was not possible and around 50 mA of the current was applied. Over the course of the electrolysis, around 11–13 V of the potential was observed for each reaction.

C, compounds **D**, **E**, and **F** catalyzed the reaction and afforded the product with high enantioselectivity at room temperature (Table 1, entries 2–6). Compound **F** was chosen as a catalyst for further optimization considering the good enantioselectivity (70% *ee*; *ee* = enantiomeric excess) and yield (74%) of the reaction (Table 1, entry 6). To improve the enantioselectivity, the reaction was run at a lower temperature (4 °C) with a prolonged reaction time. However, the yield and enantioselectivity did not increase dramatically (entry 7). With the reduced catalyst loading (20 mol-%), a similar yield (68%) and enantiomeric excess (68% *ee*) of the reaction were observed (Table 1, entry 8). In contrast to dichloromethane as a solvent, acetonitrile, DMF, and acetone did not provide the desired product. Therefore, the reaction conditions of entry 8 were used to examine the substrate scope. The stereochemical outcome of this product was assigned by comparing its optical rotation with that of the previously reported compound **3a**.[3e]

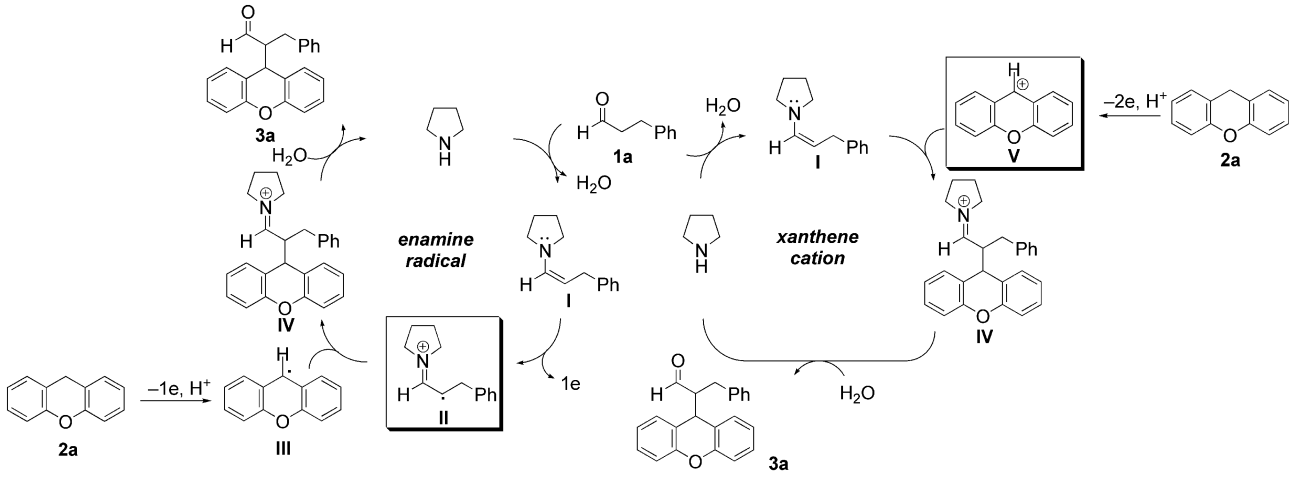
The α-alkylation of various aldehydes with xanthene (**2a**) and cycloheptatriene (**2b**) was examined. The results are summarized in Table 2. With organocatalyst **F** in 30 mL of a dichloromethane solution containing TBAP, a mixture of one equivalent of compounds **1a**–**e** and two equivalents of compounds **2a** and **2b** was exposed to the current controlled electrolysis conditions in an undivided cell equipped with platinum gauze as the anode and cathode. The aliphatic aldehyde **1b** and xanthene (**2a**) subjected to the reaction conditions produced the desired coupling product **3b** in 84% yield and with 24% *ee* (Table 2, entry 2). The enantioselectivity observed with **3b** was dramatically lower than that of **3a**. The possibility that the existence of a phenyl ring at the aldehyde would affect the enantioselectivity was examined. Aldehydes **1c** and **1d** were tested for the coupling reaction. The phenyl ring of **1c** is closer to the aldehyde than that of **1a** and the phenyl ring of **1d** is three carbon atoms away from the aldehyde. Based on the results of Table 2, entries 1, 3, and 4, each enantioselectivity of products **3a**, **3c**, and **3d** appears to be related to the distance of the phenyl ring position from the aldehyde. With *p*-methoxy-substituted hydrocinnamaldehyde **1e**, product **3e** was obtained in modest yield and enatioselectivity (Table 2, entry 5). When a disubstituted aldehyde at the β-position (isovaleraldehyde) was applied, the reaction did not proceed, which is not shown in Table 2. Other than xanthene (**2a**), cycloheptatriene (**2b**) was also applied for the reaction with **1a**, yielding a coupling product in 8% yield and with 10% *ee* (Table 2, entry 6).

To account for the product formation under anodic oxidation conditions, two possible routes (enamine radical pathway and xanthene cation pathway) were considered (Scheme 1). The enamine radical pathway involves the 1-electron oxidation of both the enamine intermediate and xanthene, followed by the coupling of two radical species. On the other hand, the reaction may proceed though two-electron oxidation and the C–H bond cleavage of xanthenes, generating xanthene cations during oxidation.[7] Since the benzylic C–H bond can be oxidized to form cationic species **V** in the presence of chemical oxidants, the

Table 2. Scope of the reaction.[a]

Entry	Compound 1	Compound 2	Product 3	Yield	*ee*
1[b]	 **1a**	 **2a**	 **3a**	68 %	68 %
2[c]	 **1b**	 **2a**	 **3b**	84 %	21 %
3[b]	 **1c**	 **2a**	 **3c**	46 %	20 %
4[b]	 **1d**	 **2a**	 **3d**	40 %	58 %
5[c]	 **1e**	 **2a**	 **3e**	67 %	55 %
6[c]	 **1a**	 **2b**	 **3f**	8 %	10 %

[a] Experimental procedure: under galvanostatic conditions, **F**-catalyzed reactions of the aldehyde (1 mmol) and **2a** or **2b** (2 mmol) were conducted in an undivided cell with a dichloromethane solution (30 mL; TBAP, 0.1 M). Platinum gauze (2.5 cm × 2.5 cm) was used as the anode and cathode materials. A regulated power supply (Hanil Electric Co, maximum output power, 180 W) was used for the constant current electrolyses. With this power supply, a fine adjustment of small current was not possible, and around 50 mA of the current was applied. Over the course of the electrolysis, around 11–13 V of the potential was observed for each reaction. The reaction times of each reaction are provided in the Supporting Information. [b] Catalyst **F** (20 mol-%). [c] Catalyst **F** (50 mol-%).

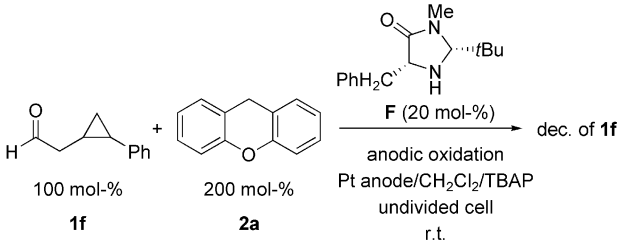


Scheme 1. Plausible catalytic cycles.

xanthene cation pathway was also considered as a possible mechanism.[3e,8]

To determine the mechanism for the organocatalyzed aldehdyes and xanthene coupling reactions under anodic oxidation conditions, the electrochemical properties of each component and the reaction mixtures of the substrates and catalyst were evaluated by cyclic voltammetry (CV) on a platinum electrode in a dichloromethane solution containing 0.1 M TBAP as the electrolyte (Figure 1). During the anodic scan over a potential range 0.0 to 2.5 V (or 3.0 V), **1a** (0.01 M), pyrrolidine (0.01 M), and **2a** (0.01 M) showed an oxidation peak at 2.7, 1.4, and 2.0 V, respectively versus a silver-wire pseudoreference electrode at a scan rate of 0.1 Vs^{-1} (Figure 1, a).[4,9] An oxidation peak for a mixture of compound **1a** (0.01 M) and pyrrolidine (0.005 M) was observed at 0.8 V, which was confirmed to be the oxidation peak potential corresponding to the enamine formed from **1a** and pyrrolidine (Figure 1, b).[4] In the cyclic voltammetry of a mixture of **1a** (0.01 M), pyrrolidine (0.005 M), and **2a** (0.02 M), three oxidation waves appeared at $E_{p,a}$ = 0.8, 2.3, and 2.9 V, respectively, which corresponded to the oxidation of in situ formed enamines **1b** and **1a**. No reduction wave was observed during the reverse scan. In accordance with the analysis of the cyclic voltammograms shown in Figure 1, the 1-electron oxidation of enamine intermediates was presumed to be facile, affording catalytically competent cationic radical species. Subsequently, the 1-electron oxidation of xanthene[8] and the immediate coupling of oxidized enamine and xanthene radicals are believed to occur (enamine radical pathway).

The effect of the radical inhibitor (2,6-di-*tert*-butyl-4-methylphenol, BHT) was examined to gain additional support for the proposed enamine radical pathway. During the organocatalytic coupling of **1a** and **2a** under anodic oxidation conditions, the desired product was not formed in the presence of 50 mol-% of BHT with respect to **1a**, which indicated the existence of radical intermediates as catalytically competent species. Next, compound **1f** containing a cyclopropyl group was exposed to these reaction conditions, as indicated in Scheme 2. The formation of the cationic radical enamine species during the reaction conditions is expected to provide the radical character at the α-position of the aldehyde, rendering the ring opening of the cyclopropyl ring on **1f**. Although no coupling product was obtained from the reaction of **1f** and **2a**, the disappearance of the cyclopropyl ring from the aldehyde was observed under the reaction conditions shown in Scheme 2.



Scheme 2. Reaction of **1f** and **2a**.

Assuming the catalytically competent intermediate of this reaction is the enamine radical, the ground-state-optimized geometries and relative energies of the enamine radical derived from compound **1a** and **F** were calculated at B3LYP/6-31G(d) level of theory with the Gaussian 03 program package. The structures of the three lowest-energy conformers (geometries 1, 2, and 3) devoid of solvents are given in Figure 2. Other geometries that lie much higher in energy (>7 kcal/mol) are not considered. Relative energies and abundances at 25 °C of the three conformers are given in Table 3. Relative abundances were calculated by as-

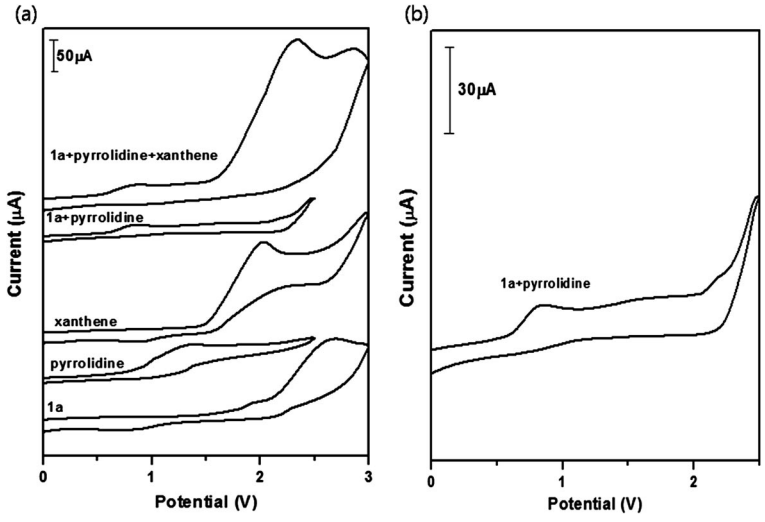


Figure 1. (a) Cyclic voltammograms of **1a** (0.01 M), pyrrolidine (0.01 M), **1b** (0.01 M), a mixture of **1a** (0.01 M) and pyrrolidine (0.005 M), and a mixture of **1a** (0.01 M), pyrrolidine (0.005M), and **2a** (0.02 M) in a 0.1 M $TBAClO_4$ (TBA = tetrabutylammonium) dichloromethane solution at a scan rate of 100 mV/s. (b) A cyclic voltammogram of a mixture of **1a** (0.01 M) and pyrrolidine (0.005 M) with a different current scale bar (30 μA).

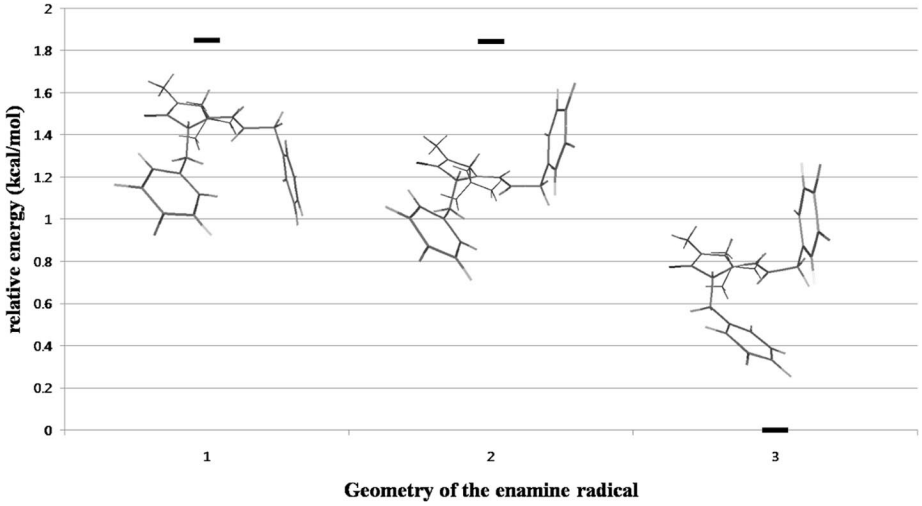


Figure 2. Ground-state-optimized geometries and relative energies of the enamine radical intermediate derived from compounds **1a** and **F**.

suming a Boltzmann distribution. As illustrated in Figure 2 and Table 3, the enamine radical mostly has the geometry 3 in vacuo, with a minor contribution from geometries 1 and 2. The geometry 3 has internal π hydrogen bonding, in which a hydrogen atom of one aromatic ring points to the other aromatic ring, making the geometry 3 stabilized. In geometry 3, the benzene ring from compound **F** efficiently blocks the lower side of the reaction center. As a result, xanthene is added to the top side of the enamine radical, providing the coupling product with the indicated stereochemistry of **3a**.

Table 3. Relative energies and abundances of the conformers (geometries 1, 2, and 3) of the enamine radical intermediate derived from compounds **1a** and **F**.

Geometry	Relative energy [kcal/mol]	Abundance [%]
1	1.847	4.06
2	1.842	4.10
3	0	91.84

Conclusions

The organocatalytic reaction protocol was extended to the enantioselective coupling of aldehydes and xanthene by utilizing anodic oxidation, affording the α-alkylation products in good yields and enantioselectivities. This study is the first to show that anodic oxidation can be applied to benzylic C–H functionalization for coupling with the enamine in the absence of large amounts of chemical oxidants. In addition, DFT calculations were conducted to understand the origin of the reaction selectivity. A pathway involving an enamine radical intermediate is believed to be suitable for the present reaction based on electrochemical studies and control experiments. However, the xanthene cation pathway cannot be ruled out completely because the homocoupling product of the radical intermediates supporting the enamine radical mechanism was not isolated from the reaction mixture. Further studies to extend the scope of this reaction and identify the reaction mechanism are currently underway.

Experimental Section

General: Dichloromethane was distilled from calcium hydride. ^{1}H NMR spectra were recorded with a Varian Mercury plus (400 MHz) spectrometer. Chemical shifts are reported as delta (δ) values (ppm) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz). ^{13}C NMR spectra were recorded with a Varian Mercury plus (100 MHz) spectrometer. Chemical shifts are reported as delta (δ) values, part per million (ppm) relative to the center of the triplet at δ = 77.00 ppm for deuteriochloroform. Electrochemical data were recorded on a potentiostat/galvanostat [PARC (Princeton Applied Research), model 263] with the Electrochemistry Power Suite Module and Cyclic Voltammetry software. The three-electrode cell consisting of a Pt disc (working electrode), a Ag wire (pseudo reference electrode), and a Pt wire (auxiliary electrode) was employed. Each compound was dissolved in a dichloromethane solution containing 0.1 M $TBAClO_4$. The resulting solutions were subject to cyclic voltammetry experiments at a scan rate of 100 mV/s. The enantiomeric excess (*ee*) of the products was determined by chiral stationary-phase HPLC. Optical rotations were measured on a DIP370 (JASCO) polarimeter. Product **3a** and **3b** exhibited spectral properties consistent with previous literature reports.[3e,10]

Representative Experimental Procedure of the α-Alkylation of Aldehydes Under Anodic Oxidation Conditions: Organocatalyzed couplings of aldehydes and xanthene or cycloheptatriene were conducted in an undivided cell in a dichloromethane solution (30 mL; TBAP, 0.1 M). The mixture of the aldehyde (1 mmol), **2a** or **2b** (2 mmol), and catalyst was exposed to constant current electrolysis conditions until the aldehyde was consumed completely. Platinum gauze (2.5 × 2.5 cm) was used as the anode and cathode materials. A regulated power supply (Hanil Electric Co, maximum output power, 180 W) was used for the constant current electrolyses. With this power supply, a fine adjustment of small current was not possible; ca. 50 mA of electric current was applied.

Supporting Information (see also the footnote on the first page of this article): Spectral data for compounds **3a**–**3f** and Table 2 with reaction times.

Acknowledgments

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