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Alkaloid induced enantioselective electroreduction of acetophenone

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ABSTRACT

The feasibility of the enantioselective electroreduction of pro-chiral acetophenone was investigated at the silver cathode in an undivided cell for the first time. Electroreduction of acetophenone in the presence of cinchonidine (CD) yielded two main products: the optically active alcohol, and the dimer product pinacol with no optical rotation. The influence of water in the co-solvent (MeCN/H_2O), supporting electrolyte, electrode material, current density, and the alkaloid type on the enantiomeric excesses (ee) and yield was investigated. Under the optimized conditions, the alcohol was obtained with a 21.6% ee and a 3.6% yield, whereas, an 83.2% yield and a 5.5 dl/meso ratio were obtained for pinacol. The electrochemical behavior of the samples was also studied through cyclic voltammetry (CV). Finally, we proposed a possible induction mechanism based on the results of the electrolysis and CV.

1. Introduction

Asymmetric synthesis by diastereoselective reduction, which change intrinsic optical substrate conformation by diastereoselective reduction due to the presence of a prochiral and a chiral center in the substrate, has attracted increasing attention in the last few decades. Chiral drugs have caused great concerns from scientists because of the dependence of their pharmacologic activity on structure, wherein only one isomer is effective and the other one is inert or even has opposite effects. Thus, methods for the enantioselective preparation of chiral products are urgently needed to synthesize biologically active compounds for pharmaceutical and agrochemical use [1]. Organic asymmetric reduction and catalysis are efficient methods for producing chiral compounds and they have made great progress during the last few decades [2–12]. However, these procedures have disadvantages, such as the use of toxic transition metal compounds, costly chiral ligands and high-pressure conditions. Consequently, electrochemical techniques [13–15] which deals with a clean reagent, the electron [16], becomes a viable alternative because of its mild and safe conditions. The electrochemical methods are useful tools because they are the only pathway for some organic transformations [17]. In addition, electrochemical reactions generate highly energetic intermediates in a facile and precise way by controlling the electrode potential [18].

Asymmetric electrochemical reduction has developed since the 1960s. Furthermore, this method has considerably progressed in both theory and application in the past 20 years. The pioneering work has been performed in field of enantioselective electrochemical reduction of organic compounds, especially those that contain activating bonds, such as C—X, C=C and C=O [1,19–27]. A number of methods for creating a chiral environment have been reported for electrochemical enantioselective synthesis, such as the use of chiral solvents [28,29], chiral supporting electrolytes [29–31], intrinsic optical substrate conformation [17,32,33], chiral electrodes [22–24,34–36], and chiral catalytic systems [37]. Recently, we successfully synthesized the pharmaceutically active intermediates 2-hydroxy-2-phenylpropionic acid (atrolactic acid) and α-ethyl-α-hydroxy-4-methylbenzeneacetic acid through the asymmetric electrochemical carboxylation of pro-chiral ketone in the presence of a chiral alkaloid inducer [38,39]. The electroreduction of ketone in the presence of hydrogen source yields two main products: alcohol and pinacol, as shown in Scheme 1. The alcohol is produced through the use of two-electron reduction and the pinacol is produced through the use of one-electron reduction. Optically active alcohol can be obtained if the ketone is reduced in a chiral environment; otherwise, only the racemic alcohol is produced.

The electrochemical asymmetric reduction of pro-chiral ketones to alcohols has been observed in many systems [24]. Vago [25] reported the enantioselective electrocatalytic hydrogenation of ethyl pyruvate on carbon-supported Pd electrodes modified with cinchonidine (CD) to yield ethyl lactate with 13% enantiomeric excesses (ee). On one hand, acetophenone is one of the simplest aromatic ketones. On the other hand, one of its products, chiral alcohol,

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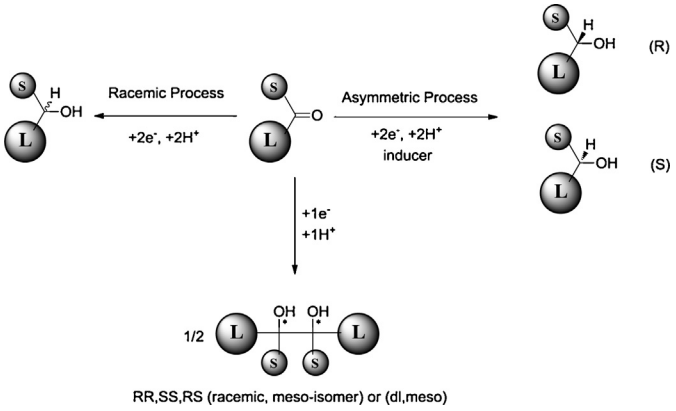


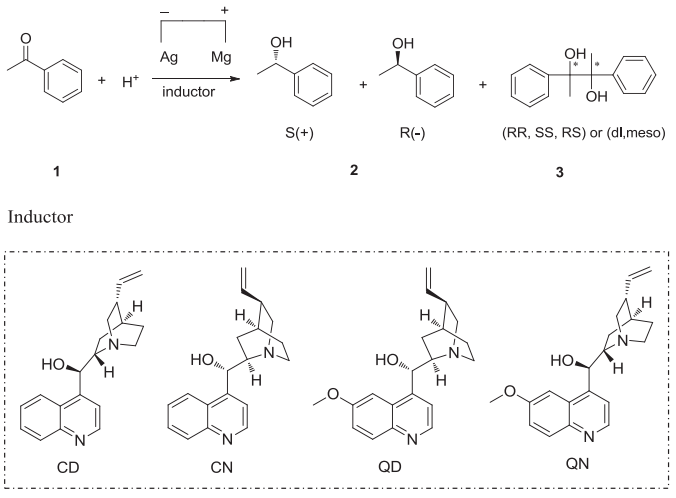
Scheme 1.

is a very useful chiral building block for the production of pharmaceuticals, agrochemicals, and natural products. In 1998, Moutet [26] studied the asymmetric induction of acetophenone on a chiral poly [2,2′-bipyridyl rhodium (III) complex] film electrode with 12% ee; however, the electrode preparation process is complex. In addition, the induction of several alkaloids during ketone electroreduction on a mercury cathode has been reported in preliminary studies, with particular reference to the catalytic concentrations of certain alkaloids that are strongly adsorbed onto the cathode and provided a chiral environment [20,23] with the highest ee of 14.9%. However, toxic Hg electrode, which contradicts the principles of green chemistry, was used. In the current study, we established a novel method for the enantioselective electroreduction of pro-chiral acetophenone that uses nontoxic electrode materials and four different alkaloids [cinchonidine (CD), cinchonine (CN), quinidine (QD) and quinine (QN)] under mild conditions (Scheme 2).

2. Experimental

2.1. Chemicals and instruments

All reagents were used as received. Cyclic voltammograms were measured with CHI 600c electrochemical Station (Shanghai Chenhua Instruments Company). The galvanostatic electrolysis was done with a dc regulated power supply HY12001 E (Hangzhou Huayi Electronics Industry Co., Ltd.). The product yields and the ee value were determined by a high performance liquid chromatography (HPLC) instrument (DIONEX Ultimate 3000 pump) equipped



Scheme 2.

with a UV (RS Variable Wavelength) detector and a chiralcel OD-H column [DAICEL Chiral technologies (China) CO., Ltd.]. GC–MS spectra was obtained on a 5973N spectrometer which was connected with a HP 6890 gas chromatograph.

2.2. Electroanalytical procedure

The electroanalytical experiments were carried out in acetonitrile (MeCN) or co-solvent (MeCN–H_2O, MeCN–EtOH, MeCN–HOAc) with 0.1 M tetraethylammonium tetrafluoroborate ($TEABF_4$) as the supporting electrolyte in an undivided glass cell equipped with a gas inlet and outlet, a glassy carbon (GC) electrode (d = 2 mm) as the working electrode, a platinum spiral (Pt) as the counter electrode and a Ag/AgI/0.1 M TBAI in DMF as the reference electrode. All experiments were performed at 25 °C under an atmospheric pressure. In addition, the oxygen was removed by continuous bubbling with nitrogen before the experiment.

2.3. General electrolysis procedure

The galvanostatic electrolysis was carried out in a mixture of substrate acetophenone (0.1 M), supporting electrolyte (0.1 M) and 1 mM alkaloid in 10 ml co-solvent bubbled with N_2 to remove the oxygen in an undivided glass cell, equipped with a sacrificial magnesium rod (Mg) anode and a cathode such as Ag (9.8 cm^2), Cu (10.6 cm^2), C (3.8 cm^2), Zn (10.6 cm^2), Ti (10.4 cm^2), Pt (4.0 cm^2), Ni (8.0 cm^2), 316 stainless steel (Ss) (10.7 cm^2). The electrolyte solution was continuously stirred during electrolysis. At the end of each set of experiment, the co-solvent was distilled off in vacuo. The residue was hydrolyzed and extracted three times with diethyl ether. In addition, the organic layers were washed with saturated brine, dried over anhydrous $MgSO_4$, eventually, evaporated in vacuo. After isolation and identification, the product yields, based on the starting material, were determined by high performance liquid chromatography (HPLC), also for the enatiomeric excesses (ee) of the alcohol and the dl/meso ratio of pinacol. The ee of optically active alcohol is defined as follows:

$$ee = \frac{[R] - [S]}{[R]+[S]} \times 100\%$$

3. Results and discussion

3.1. Electroanalytical results

The cyclic voltammograms of acetophenone using a glass carbon (GC) electrode at different scan rates in MeCN are shown in Fig. 1. Two successive one-electron reduction peaks at −1.68 V and −2.15 V, which correspond to the two-electron transfer of the ketone group (C=O) of acetophenone [40], were observed at a scan rate of 0.1 V s^{-1} (Fig. 1, curve a). When the scan rate was increased, the two reduction peaks became more negative, with the peak current increasing concomitantly (Fig. 1, curves a–e). The first peak current varied linearly with $v^{1/2}$ (Fig. 1, inset), which confirms the diffusion control for the electrochemical reduction process [41,42]. Meanwhile, the ratio of the two peak current (I_pc2/I_pc1) decreased with increasing scan rate (Table 1). This behavior indicates that the intermediate reducted at the second peak come from a slow reaction following the first electron transfer (Scheme 3). In addition, the experimental result suggests that producing alcohol from acetophenone consists of an ECEC mechanism [38,43] (E: electron transfer, C: chemistry), not an EECC mechanism.

To study the cyclic voltammograms of acetophenone in the presence of water, the aprotic MeCN solution (Fig. 2A) was replaced with the protic co-solvent (MeCN/H_2O) at a 9/1 volume ratio (Fig. 2B). The voltammetric behavior (Fig. 2) was strongly modified by the

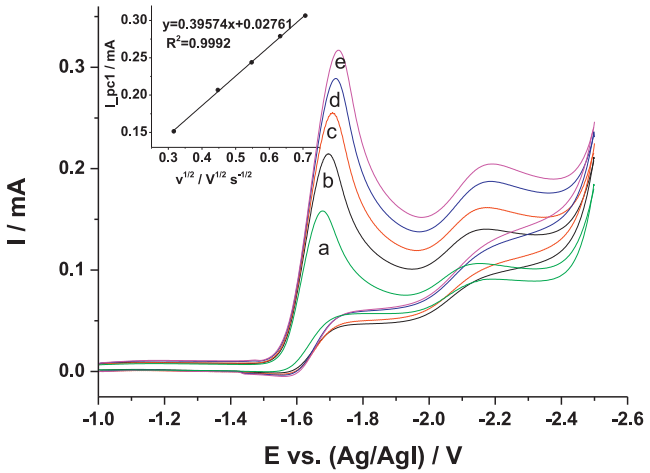
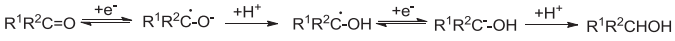


Fig. 1. Cyclic voltammograms of 10 mM acetophenone in MeCN–0.1 M $TEABF_4$ at different scan rates: (a) 0.1 V s^{-1}, (b) 0.2 V s^{-1}, (c) 0.3 V s^{-1}, (d) 0.4 V s^{-1}, (e) 0.5 V s^{-1}, T = 25 °C. Inset: variation of the first peak current (I_pc1) of 10 mM acetophenone vs. square root of scan rate ($v^{1/2}$).

Table 1
Effect of scan rate to the ratio of the two reduction peak (I_pc2/I_pc1).[a]

v (V s^{-1})	I_pc1(mA)	I_pc1 (mA)	I_pc2/I_pc1
0.1	0.151364	0.0311085	0.205521
0.2	0.206789	0.0393741	0.190407
0.3	0.243745	0.0496153	0.180566
0.4	0.278821	0.0496153	0.177947
0.5	0.306317	0.0526049	0.171734

[a] Experiment condition as Fig. 1.



Scheme 3.

water content in the solvent, which may be attributed to the abundant proton source in the system after the addition of water. As shown in Fig. 2B curve c, when water was added, the first cathodic peak (peak I in Fig. 2A, curve c) shifted to a more positive potential region with a minimal increase in the peak current, whereas the second peak (peak II in Fig. 2A curve c) disappeared completely.

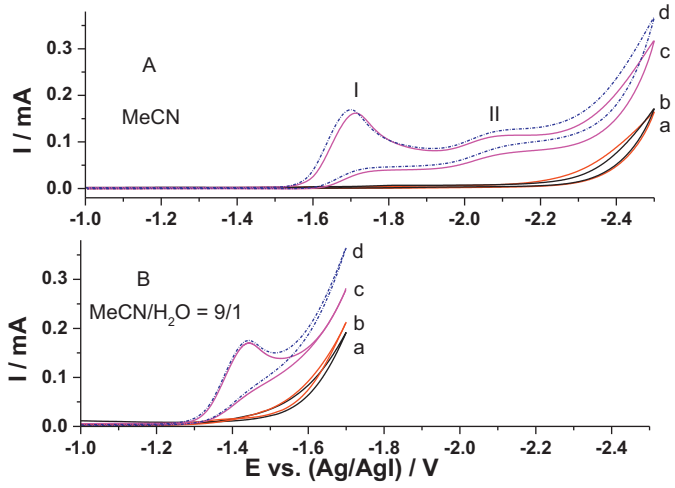


Fig. 2. Cyclic voltammograms recorded at GC electrode at 25 °C with the scan rate of 0.1 V s^{-1}: (a) blank cyclic voltammetry in solvent–0.1 M $TEABF_4$, (b) as (a) +0.1 mM CD, (c) as (a) +10 mM acetophenone, (d) as (c) +0.1 mM CD. (A) The solvent is 10 ml MeCN. (B) The solvent is 10 ml co-solvent ($MeCN/H_2O$ = 9/1, volume ratio).

The second peak mainly disappeared because it was concealed by the current for the reduction of the protic co-solvent. To determine the number of electrons transferred in the reduction peak of curve c in Fig. 2B, potential controlled electrolysis experiment was carried out at −1.35 V. The electrolysis was interrupted after the current dropped to ca. 6% of its initial value, which corresponded to total conversion of the acetophenone. Reduction of acetophenone consumes ca. 1e^-/molecule of acetophenone. After electrolysis, the sample was analyzed using GC–MS, which indicated that only the dimerization product pinacol was obtained, and no alcohol was detected. The result further illustrates that the peak (curve c in Fig. 2B) is a one-electron reduction of acetophenone into pinacol. The positive shift in the reduction potential for the peak I (curve c in Fig. 2A and B) of acetophenone caused by the addition of water into the solvents may be ascribed to both the protonation and hydrogen-bonding effects of H_2O [42,44,45]. In addition, the peak potential of the peak I exhibited a positive shift (curve c in Fig. 2B) and the minimal increase in the acetophenone reduction peak current in the present of H_2O are consistent with the ECEC mechanism [38] of the acetophenone reduction, which can be caused by subsequent chemical reactions between the anion radicals and a proton source.

To further study the effect of alkaloid on the voltammetric behavior of acetophenone, 0.1 mM CD was added into the aprotic electrolyte (Fig. 2A) and protic co-solvent ($MeCN/H_2O$ = 9/1) (Fig. 2B), respectively. As shown in curves c and d in Fig. 2A, the two reduction peak currents both increased slightly, with the first reduction peak potential shifting to a more positive value, which (i) indicates the strong interaction between CD and the 1-(1-phenyl-1-hydroxy)-ethyl anion; (ii) most probably because acetophenone is activated by a hydrogen bond from the protonated alkaloid or the HO-group of the alkaloid to yield after a proton and electron transfer the 1-(1-phenyl-1-hydroxy)-ethyl radical. No obvious peak was detected in the potential region when 0.1 mM CD was added into the MeCN–0.1 M $TEABF_4$ system, which demonstrated that the increase of the peak current does not correspond to the direct reduction of CD (Fig. 2A, curve b). Moreover, CD favored acetophenone reduction. Fig. 2B plots the change after adding 0.1 mM of CD to the protic co-solvent system. The reduction peak potential slightly shifted to a more positive region, and the peak current increased minimally (Fig. 2B, curves c and d). Similar to curve b in Fig. 2A, no obvious peak was observed in the potential region when only 0.1 mM CD was in the protic co-solvent ($MeCN/H_2O$ = 9/1)–0.1 M $TEABF_4$, demonstrating that the increase in peak current did not correspond to the direct reduction of CD (Fig. 2B, curve b). Therefore, the protonated CD can act as proton donor, which favored the reduction of acetophenone [1].

3.2. Preparative electrolysis

The preparative electrolysis (Scheme 2) was carried out in co-solvent ($MeCN/H_2O$ = 9/1)–0.1 M $TEABF_4$ containing 0.1 M acetophenone and 1 mM CD in an undivided cell equipped with a Mg rod anode and a Ag cathode at 25 °C. After 2 F mol^{-1} charge was passed, the current was switched off. The electrolyte was then extracted with ethyl ether. The yield and the dl/meso ratio of pinacol with three stereoisomers (Scheme 2) were both detected by HPLC analysis. Two products, optically active alcohol (**2**) and dimer product pinacol (**3**) with no optical rotation, were obtained with 3.6% yield and 83.2% yield, respectively (Table 2, entry 2). In the presence of CD, the R enantiomer was more abundant than the S enantiomer with 21.6% ee for alcohol, whereas the pinacol exhibited no optical rotation. The peak areas in the HPLC suggest the presence of equal amounts of the two enantiomers; that is, the pinacol is optically inactive. To optimize the synthesis condition, the effect of water in the co-solvent, supporting electrolyte, electrode material, current density, and alkaloid type were investigated systematically.

Table 2
Effect of water content in the co-solvent and supporting electrolyte on the enantioselective electroreduction of acetophenone.[a]

Entry	MeCN/H_2O volume ratio	Supporting electrolyte	Alcohol yield[b] (%)	Pinacol yield[b] (%)	ee[b] (R-%)	Pinacol dl/meso[b]
1	9.5/0.5	TEAI	0.9	88.0	39.4	6.7
2	9/1	TEAI	3.6	83.2	21.6	5.5
3	8.5/.5	TEAI	6.7	55.2	6.8	4.9
4	8/2	TEAI	10.1	51.5	2.0	4.2
5	7.5/2.5	TEAI	16.1	62.5	1.2	4.0
6	7/3	TEAI	16.8	43.8	1.0	3.6
7	6/4	TEAI	28.7	38.6	0.5	3.1
8	5/5	TEAI	45.2	14.7	trace	2.8
9	9/1[c]	TEAI	1.9	43.7	25.6	2.0
10	9/1[d]	TEAI	0.9	34.5	5.7	1.2
11	9/1	TEABr	1.5	65.9	22.3	6.2
12	9/1	TEACl	1.2	87.5	30.2	6.3
13	9/1	$TEABF_4$	2.5	79.8	15.2	5.4
14	9/1	TBAI	3.2	88.0	6.7	5.6
15	9/1	TBABr	0.9	81.3	46.5	6.0
16	9/1	KCl	3.9	7.8	4.5	3.3
17	9/1	NaCl	1.1	2.3	8.9	2.7
18	9/1	$KClO_4$	3.2	13.7	8.4	4.9

[a] Cathode: silver. Anode: Mg. Acetophenone concentration: 0.1 M. Charge passed: 2 F mol^{-1}. CD concentration: 1 mM. Supporting electrolyte concentration: 0.1 M. Current density: 3 mA cm^{-2}. Temperature: 25 °C.
[b] The yield based on the starting materiel, enantioselectivity of alcohol and the ratio of dl/meso of pinacol were determined by HPLC analysis.
[c] MeCN/EtOH.
[d] MeCN/HOAc.

3.2.1. *Effect of water in the co-solvent and effect of the electrolyte*

The effect of water amount of the co-solvent on enantioselective electroreduction was first investigated. In our study, the best result was achieved with 21.6% ee and 3.6% chemical yield for alcohol. For pinacol, a chemical yield of 83.2% and a dl/meso ratio of 5.5 were found (Table 2, entry 2). As shown in Table 2 (entries 1–8), with the decreasing MeCN/H_2O volume ratio in the co-solvent, (i) the alcohol yield increased whereas the pinacol yield decreased. This result is due to the increase of the water amount as proton donor. The ratio of alcohol to pinacol should depend on the competing dimerization and reduction of the intermediate carbonyl radical [phenyl(CH_3)(OH)C•] [44]. A rich proton source is more conducive to the reduction of the intermediate carbonyl radical, because the resulting anion is faster protonated. Competing with the dimerization, the radical was reduced to 1-(1-phenyl-1-hydroxy)-ethyl anion, which is protonated though intermolecular proton transfer, water, and/or CD. These results are probable but not experimentally well supported for the moment. (ii) The ratio of the dl to meso decreases with decreasing pH [46,47]. The pH of the electrolyte increases near the cathode during electrolysis because of hydrogen evolution. At a higher water content, the increase should be lower, and then caused the decrease in the dl/meso ratio. Third, the ee value of the alcohol decreased. The H_2O, not the protonated alkaloid, probably acted as the proton donor when the amount of water was higher. For the ee and chemical yield of alcohol, the MeCN/H_2O = 9/1 volume ratio was used for the next optimization. In addition, replacing the H_2O in the co-solvent with other proton donors such as ethanol (EtOH) and acetic acid (HOAc) (Table 2, entries 9 and 10) did not improve the product yield (alcohol and pinacol) and the enantioselectivity except for the enantioselectivity in the MeCN/EtOH co-solvent. The result is consistent with the acetophenone voltammograms obtained using the MeCN/EtOH, MeCN/HOAc (Fig. 3), and MeCN/H_2O co-solvents (Fig. 2B). Figs. 2B and 3A indicate that the voltammetric curve of acetophenone in the MeCN/EtOH co-solvent is similar to that obtained using the MeCN/H_2O co-solvent, except the reduction peak potentials in MeCN/EtOH co-solvent were more negative than these in the MeCN/H_2O co-solvent. Thus, the yield using the MeCN/EtOH co-solvent (Table 2, entry 9) was lower than that using the MeCN/H_2O co-solvent (Table 2, entry 2). Fig. 3B shows a reduction current in MeCN/HOAc already at −0.8 V whilst in MeCN/EtOH the current starts at about −1.45 V. This result indicates that in MeCN/HOAc the current is mainly used for the reduction of the solvent, which explains the low yield in this solvent. In summary, the best co-solvent was MeCN/H_2O at a 9/1 volume ratio.

Table 2 (entries 2, 11–18) shows that with the regard to the chemical yield the best supporting electrolytes were tetraalkylammonium salts. The use of alkali salts as the supporting electrolyte (entries 16–18) decreased the alcohol and pinacol yields. The result could be attributed to the ability of the tetraalkylammonium cation to stabilize the acetophenone radical anion by forming an ion pair as has been assumed in related reaction [48–50]. As shown in Table 2 (entries 2, 11, 12), the alcohol yield decreased in dependence on the anion in the following order: $I^{-1} > Br^{-1} > Cl^{-1}$ under the same electrolytic conditions. However, the origin of the effect is unclear at this stage. In addition, the ammonium salt anions affected the enantioselectivity of alcohol. As shown in Table 2 (entries 2, 11–12), in the same TEA^+ case, the ee value of alcohol increased in the following order: $I^{-1} < Br^{-1} < Cl^{-1}$. Also this effect remains unclear.

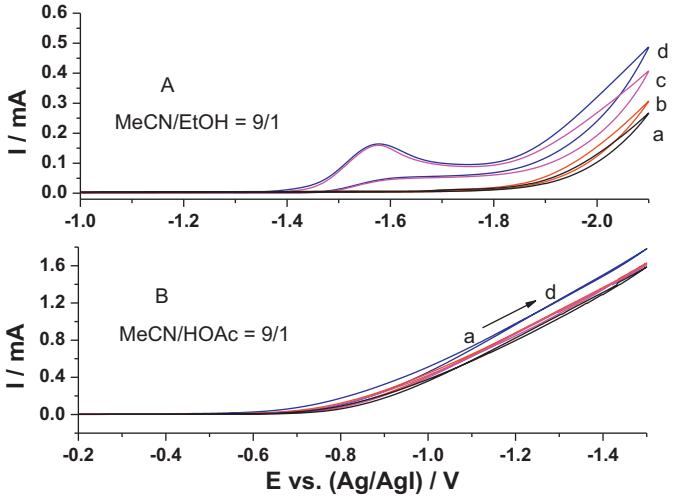


Fig. 3. Cyclic voltammograms recorded at GC electrode at 25 °C with the scan rate of 0.1 V s^{-1}: (a) blank cyclic voltammogram in co-solvent–0.1 M $TEABF_4$, (b) as (a) +0.1 mM CD, (c) as (a) +10 mM acetophenone, (d) as (c) +0.1 mM CD. (A) Co-solvent MeCN/EtOH = 9/1, volume ratio. (B) Co-solvent MeCN/HOAc = 9/1, volume ratio.

Table 3
Effect of electrode material and current density on the enantioselective electroreduction of acetophenone.[a]

Entry	Electrode materials	Current density (mA cm^{-2})	Alcohol yield[b] (%)	Pinacol yield[b] (%)	ee[b] (R-%)	Pinacol dl/meso[b]
1	Ag	3	3.6	83.2	21.6	5.5
2	Pt	3	trace	trace	–	–
3	Ni	3	trace	trace	–	–
4	Ss	3	trace	trace	–	–
5	Zn	3	1.3	87.2	32.1	5.9
6	Ti	3	1.2	88.1	53.3	5.6
7	Cu	3	0.7	71.5	58.6	5.6
8	C	3	3.8	70.5	7.2	6.3
9	Ag	5	2.6	85.6	9.2	5.7
10	Ag	4	2.7	84.5	12.6	5.6
11	Ag	3.5	2.8	83.2	15.8	5.6
12	Ag	2.5	4.2	65.0	7.9	5.4
13	Ag	2	3.1	41.4	6.9	5.5
14	Ag	1	2.1	35.8	3.6	4.8

[a] Solvent: co-solvent (MeCN/H_2O = 9/1, volume ratio). Anode: Mg. Acetophenone concentration: 0.1 M. Charge passed: 2 F mol^{-1}. CD concentration: 1 mM. Supporting electrolyte: 0.1 M TEAI. Temperature: 25 °C.
[b] The yield based on the starting materiel, enantioselectivity of alcohol and the ratio of dl/meso of pinacol were determined by HPLC analysis.

3.2.2. *Effect of electrode material and current density*

The nature of the cathode material strongly affected the yield and ee value of the electroreductive reaction. The most effective cathode with regard to the enantioselectivity was the Ag electrode with a 21.6% ee and a 3.6% alcohol yield (Table 3, entry 1). Possibly the Ag electrode adsorbs the alkaloid similar as the Hg electrode [20,21,23] to create a chiral environment that eventually caused chiral induction. With Pt, Ni, and Ss cathodes (Table 3, entries 2–4) no desired reduction product was obtained, whereas a large number of unreacted substrate was detected. The result is consistent with the voltammetric behavior of acetophenone in the co-solvent at the Pt, Ni, and Ss cathodes (curves f, b, and e in Fig. 4): no reduction peak for the acetophenone, but high reduction currents for the hydrogen evolution due to the more anodic hydrogen evolution potential of these cathodes. Bubbles that corresponded to hydrogen were clearly observed in the surface of the three electrodes during electrolysis, but this phenomenon was not observed for the other materials in Table 3 (entries 1, 5–8). Table 3 (entries 1–8) also suggests that the total reduction yields depend on the cathode materials in the following order: Pt (trace, entry 2), Ni (trace, entry 3) and Ss (trace, entry 4) < Cu (72.2%, entry 7) < C (74.3%, entry 8) < Ag (86.8%, entry 1) < Zn (88.5%, entry 5) < Ti (89.3%, entry 6). The yield correlates with the reduction potential of acetophenone at the different electrodes: Cu (−1.50 V, curve d of Fig. 4) < Ag (−1.47 V, curve a of Fig. 4) < GC (−1.44 V, curve c of Fig. 4).

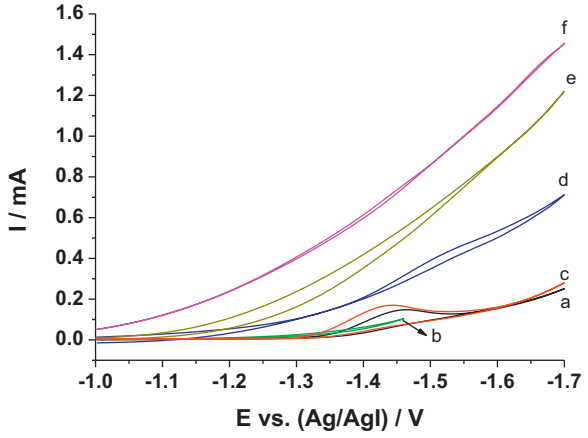
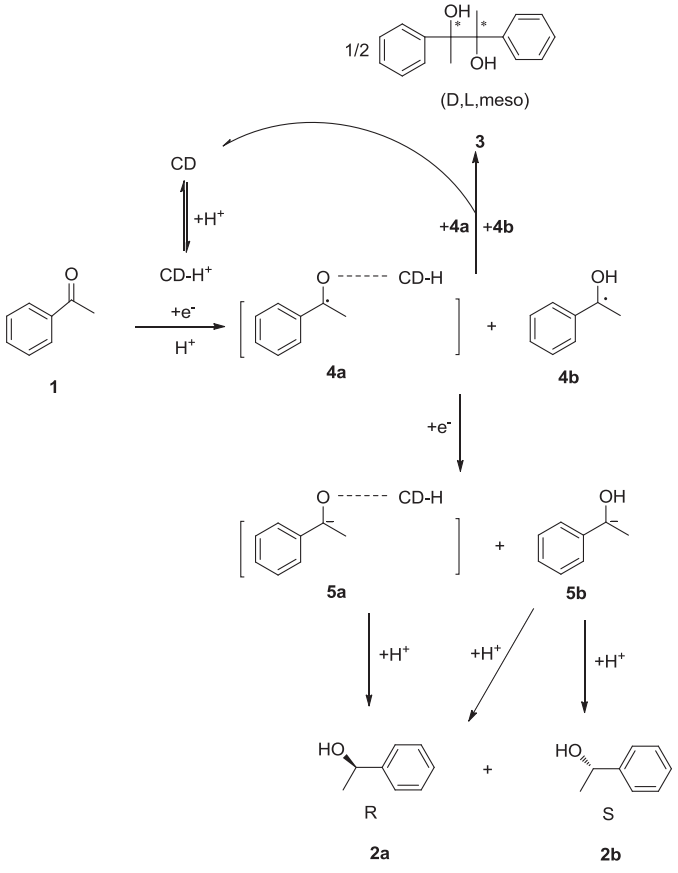


Fig. 4. Cyclic voltammograms of 10 mM acetophenone in co-solvent (MeCN/H_2O = 9/1, volume ratio)–0.1 M $TEABF_4$ with the scan rate of 0.1 V s^{-1} at different electrodes: (a) Ag, (b) Ni, (c) GC, (d) Cu, (e) Ss, (f) Pt, T = 25 °C.

The current density also affected the reaction. Table 3 (entries 1, 9–14) shows the chemical yield and enantioselectivity under various current densities. At a current density of 3 mA cm^{-2}, a high ee value and chemical yield was achieved. Higher or lower current densities resulted in lower ee values, although higher yields were obtained at 2.5 mA cm^{-2}. On the one hand, higher current densities accelerate the electron transfer rate between the electrode and the substrate [38]. Possibly the high concentration of generated radical anions (see Scheme 4) depletes the electrode surface from the alkaloid and the enantioselective protonation of the 1-(1-hydroxy-phenethyl)-anion (see Scheme 4) competes with the non-enantioselective protonation by water. On the other hand,



Scheme 4. Mechanism for the alkaloid induced enantioselective electroreduction of acetophenone.

Table 4
Effect of alkaloid types on the enantioselective electroreduction of acetophenone.[a]

Entry	Alkaloid	Alcohol yield[b] (%)	Pinacol yield[b] (%)	ee[b] (R-%)	Pinacol dl/meso[b]
1	CD	3.6	83.2	21.6	5.5
2	QD	4.1	79.9	4.7	5.5
3	QN	3.3	85.7	4.9	5.5
4	CN	3.6	74.3	4.0	5.4
5	–	2.8	79.2	–	5.4

[a] Solvent: co-solvent ($MeCN/H_2O$ = 9/1, volume ratio). Cathode: silver. Anode: Mg. Acetophenone concentration: 0.1 M. Charge passed: 2 F mol^{-1}. Alkaloid concentration: 1 mM. Supporting electrolyte: 0.1 M TEAI. Current density: 3 mA cm^{-2}. Temperature: 25 °C.
[b] The yield based on the starting materiel, enantioselectivity of alcohol and the ratio of dl/meso of pinacol were determined by HPLC analysis.

lower current densities slow the electron transfer rate between the electrode and the substrate. Under such conditions, the generated complex (**4a**) may diffuse or migrate again into the solution, and consequently decreased the ee value. Moreover, the electrolysis conducted at low current densities was very inefficient [Table 3, entries 13, 14]. Unreacted substrate was detected in HPLC after electrolysis. This is because lower current densities leading to more positive of electrode potential [51], thereby decreasing the electroreduction yield.

3.2.3. *Effect of alkaloid type*

Table 4 (entries 1–4) presents the results obtained using different alkaloids (CD, CN, QD, QN, structures shown in Scheme 2). The best result was obtained using CD as inducer (Table 4, entry 1), wherein, alcohol was obtained at 21.6% ee with 3.6% yield. When the inducer CD was replaced with CN, QD, or QN (Table 4, entries 2–4), no substantial change in chemical yield was observed, but the ee values were lower. Thus, an excess of the R enantiomer was formed in all cases (when CD was replaced with CN, QD, or QN). The mechanism of the asymmetric induction is discussed below. The successful asymmetric induction of alkaloid was attributed to complexation (**4a**) formed through the one-electron reduction of acetophenone (**1**) and the protonated alkaloid (e.g. CD-H) [1]. In addition, Table 4 (entries 1–5) revealed that the addition of any of the alkaloids tested increased the product yield, which is consistent with the cyclic voltammograms in Fig. 2. Moreover, it also increased the relative alcohol production during electrolysis [23].

3.3. *Mechanism of the alkaloid-induced enantioselective electroreduction of acetophenone*

Based on the results of the electrolysis and CVs discussed above, we accordingly propose an induction mechanism (Scheme 4). The alkaloid is probably adsorbed at the Ag electrode similar to the adsorption at the mercury cathode as a chiral proton donor after protonation. In the course of the reduction, at first the radical anion of acetophenone is formed and protonated by the protonated alkaloid or water. The resulting 1-(1-hydroxy-phenethyl)-radical bound to the alkaloid or not the hydroxy anion **4a** or being a free anion **4b** can couple to the pinacol (**3**) and/or be reduced to the corresponding anions **5a** and **5b**. **5a** can be enantioselectively protonated to the optically active alcohol (**2a**) in an inter- or intramolecular reaction, whereas **5b** must be protonated to the racemic alcohol (**2a** + **2b**) in an intermolecular reaction.

4. Conclusions

In summary, an electrochemical enantioselective reduction of acetophenone in the presence of alkaloids has been established at the Ag electrode. Thereby optically active 1-phenyl-1-ethanol and optically inactive pinacol is obtained. Under the optimized condition, the enantiomeric excess of alcohol was 21.6% ee and the yield 3.6%; additionally, the pinacol was obtained in 83.2% yield with a 5.5 dl/meso ratio.

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