# Electrochemically Promoted Asymmetric Transfer Hydrogenation of 2,2,2-Trifluoroacetophenone

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C hiral compounds, especially chiral drugs, are increasingly in demand in today's society, so the research on the synthesis of chiral compounds is becoming more and more extensive. The preparation of chiral alcohols, which are important intermediates in the synthesis of many chiral drugs, is mainly realized by the asymmetric catalytic hydrogenation or transfer hydrogenation of prochiral ketones. In the past few decades, lots of transition metal complexes, such as Ir, Ru, and Rh complexes, have been developed and used as (pre)catalysts so that the product yields and enantiomeric excess (ee) values have gradually increased and achieved >99%.<sup>1-4</sup>

Recently, due to its mild reaction conditions, low energy consumption, and easy control of the reaction process, more and more research studies on electroorganic synthesis have been reported<sup>5,6</sup> and reviewed.<sup>7,8</sup> Among them, asymmetric electrosynthesis has attracted great attention, in view of the particularity of chiral products.<sup>9,10</sup> There have been many reports on the asymmetric electrosynthesis of chiral alcohols from aromatic ketones, starting from the perspectives of chiral media<sup>11</sup> and chiral inducers.<sup>12,13</sup> In our previous work, chirally functionalized electrodes, such as alkaloid@metal composites,<sup>14,15</sup> L-cysteine-functionalized CuPt alloy,<sup>16</sup> and mino acid-functionalized multiwalled carbon nanotubes,17,18 have been prepared, and the ee value has been increased to 40-70%. Although the performance of the target asymmetric reaction can be greatly improved by fixing the chiral inducer on the surface of the electrode, its reactivity is still not comparable to homogeneous chiral transition metal complexes.

Herein, we wish to report a possible electrochemical route for the asymmetric hydrogenation of 2,2,2-trifluoroacetophenone to form optically active  $\alpha$ -(trifluoromethyl) benzyl alcohol in the presence of the chiral RuCl<sub>2</sub>[(*R*)-xylbinap][(*R*)-daipen]complex (Scheme S1).

Initially, the influence of the solvent was studied by using 2,2,2-trifluoroacetophenone as the substrate and  $\operatorname{RuCl}_2[(R)-xylbinap][(R)-daipen]$  as the chiral catalyst in an undivided cell (Table 1). DMF, commonly used in an electroorganic synthesis system as an aprotic solvent, was tried first. When alcohols (e.g., EtOH, *i*-PrOH) were added into DMF as the hydrogen donor,

Table 1. Influence of Solvent on the Enantioselective Electroreduction of 2,2,2-Trifluoroacetophenone with a Ru Catalyst  $^a$ 

	CF <sub>3</sub> Mg(+) Pr	t(-) trolyte	H <sup>*</sup> CF <sub>3</sub>
entry	solvent	yield <sup>b</sup> (%)	$R ee^{b}$ (%)
1	DMF <sup>c</sup>	26	64
2	$DMF^d$	16	26
3	DMF/EtOH (1:1)	66	91
4	DMF/ <i>i</i> -PrOH (1:1)	24	83
5	EtOH/ <i>i</i> -PrOH (1:1)	96	94
6	EtOH	62	49
7	<i>i</i> -PrOH	56	78

<sup>*a*</sup>Reaction conditions: undivided cell, Mg anode, Pt cathode, solvent (20 mL), TEAI (0.1 M), 2,2,2-trifluoroacetophenone (0.1 M), RuCl<sub>2</sub>[(R)-xylbinap][(R)-daipen] (3 mM), *t*-BuOK (6 mM), current density = 3 mA cm<sup>-2</sup>, charge = 2 F mol<sup>-1</sup>, room temperature. <sup>*b*</sup>Determined by GC with a chiral column. <sup>*c*</sup>EtOH (0.2 M). <sup>*d*</sup>*i*-PrOH (0.2 M).

only 16–26% yield of desired product could be obtained (Table 1, entries 1 and 2). By increasing the volume ratio of alcohol to DMF to 1:1, the product yield also increases (Table 1, entries 3 and 4). More interestingly, when using mixed alcohols to replace DMF solvent, both yield and ee values have been greatly improved. As shown in Table 1, entry 5, (R)- $\alpha$ -(trifluoromethyl) benzyl alcohol with 96% yield and 94% ee was obtained in a EtOH/*i*-PrOH (1:1) mixed solvent, which is better than previous electrosynthesis reports and is comparable to

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homogeneous catalytic systems (Table S1). Pure EtOH and *i*-PrOH were also usable solvents, although the reactivity was lower than that in the mixed alcohols (Table 1, entries 6 and 7).

In addition to the solvent, the electrode material is also an important factor affecting electroorganic synthesis reactions. Here, conventional metal and nonmetal materials are tested for the enantioselective electroreduction of 2,2,2-trifluoroacetophenone (Table 2). Although a moderate yield can be obtained on a

Table 2. Influence of Cathode on the Enantioselective Electroreduction of 2,2,2-Trifluoroacetophenone with a Ru Catalyst  $^a$ 

entry	cathode	yield <sup><math>b</math></sup> (%)	$R ee^{b}$ (%)
1	GC	55	90
2	Ni	85	93
3	Cu	88	91
4	Pt	96	94

"Reaction conditions: undivided cell, Mg anode, solvent (EtOH/*i*-PrOH = 1:1, 20 mL), TEAI (0.1 M), 2,2,2-trifluoroacetophenone (0.1 M), RuCl<sub>2</sub>[(R)-xylbinap][(R)-daipen] (3 mM), *t*-BuOK (6 mM), current density = 3 mA cm<sup>-2</sup>, charge = 2 F mol<sup>-1</sup>, room temperature. <sup>b</sup>Determined by GC with a chiral column.

GC electrode (Table 2, entry 1), it is still significantly lower than those on metal electrodes. The order of metal electrodes in the reactivity was Pt > Cu  $\approx$  Ni (Table 2, entries 2–4). On the other hand, there is almost no difference in the enantioselectivity of the products on the tested electrodes. Therefore, it is inferred that, in the asymmetric electroreduction of the substrate participated by the Ru complex, the cathode material only affects the yield of the product but hardly affects the optical activity.

Then, the influence of charge amount was investigated. Generally, the electroreduction of aromatic ketones involves two electrons and two protons. In other words, the theoretical amount of electricity for electroreduction of aromatic ketones is  $2 \text{ F mol}^{-1}$ . As mentioned earlier, the product yield is 96%, which is very close to 100%, when the charge amount is  $2 \text{ F mol}^{-1}$ . It indicates that the efficiency of this electrosynthesis process is

very high at room temperature and normal pressure. As shown in Figure 1, the ee value is higher than 90% when the charge amount is larger than  $0.25 \text{ F} \text{ mol}^{-1}$ . However, unexpectedly, as the charge amount decreases, the product yield does not decrease linearly. The yield when the charge amount is 1 F mol<sup>-1</sup> is almost the same as that when the charge amount is  $2 \text{ F mol}^{-1}$ . Even when the charge amount is only  $0.5 \text{ F mol}^{-1}$ , which is a quarter of the theoretical amount, the yield is as high as 93% (isolated yield: 88%), and the corresponding current efficiency is 372%. A further decrease in charge amount will bring the current efficiency close to 600%. These results are completely inconsistent with the traditional electroreduction of aromatic ketones, which requires two electrons. Meanwhile, a control experiment without electricity was carried out. After stirring the solution for 9 h (similar to the electrolysis time for charge amount of 2 F  $mol^{-1}$ ) under room temperature and normal pressure, the yield of the desired product was only 5%. It shows that electrolysis is essential for this reaction process.

Is it possible that some intermediate generated by electrolysis will trigger the target reaction? In other words, is it possible that the electrogenerated intermediate can stably exist in the solution and can catalyze the reaction under room temperature and normal pressure? Therefore, a series of control experiments were carried out. After electrolysis for a certain charge amount, the current was disconnected, but the solution was continuously stirred for the same time as previous electrolysis. For instance, after electrolysis for a charge amount of 0.25 F mol $^{-1}$ (corresponding to electrolysis for 67 min), the solution was continuously stirred for another 67 min. Therefore, the total reaction time is equivalent to that of the experiment, which is electrolyzed for a charge amount of 0.5 F mol<sup>-1</sup>. As previously guessed, if the electrogenerated intermediate can continuously catalyze the target reaction, the reaction will continue for a period of time even if the current is disconnected. However, surprisingly, as shown in Figure 1, the continued stirring after electrolysis had almost no effect on the yield. The yield depends only on the electrolysis process.

In order to further understand the reaction system, cyclic voltammograms (CVs) have been carried out. Due to the serious



**Figure 1.** Influence of the charge amount on the enantioselective electroreduction of 2,2,2-trifluoroacetophenone. Red: electrolysis only (E). Blue: stirring for a certain time after electrolysis (E&S).



Figure 2. CVs recorded in DMF containing 0.1 M TEAI: (a) blank CV in DFM-0.1 M TEAI, (b) a + 50 mM 2,2,2-trifluoroacetophenon, (c) b + 1.5 mM Ru catalyst.

polarization of the EtOH/i-PrOH (1:1) mixed solvent, the electrochemical behavior of the substrate and  $\operatorname{RuCl}_2[(R)$ xylbinap][(R)-daipen] is mostly obscured (Figure S1). Therefore, the electrochemical behavior of each component in the reaction system was studied in DMF. As shown in Figure 2, curve b, two reduction peaks at -0.71 V and -1.20 V could be observed for 2,2,2-trifluoroacetophenone, corresponding to the two single-electron reduction of C=O bond. With the addition of RuCl<sub>2</sub>[(R)-xylbinap][(R)-daipen] (Figure 2, curve c), no new peak appeared, indicating the Ru complex itself is difficult to be reduced or oxidized in the scanning potential range. In previous studies,<sup>1,2</sup> it is reported that the oxidation state of the metal does not change during the catalytic reaction. This is completely different from our previous study about asymmetric electrocarboxylation of organic halides catalyzed by electrogenerated chiral [Co<sup>I</sup>(salen)]<sup>-</sup> complex.<sup>19</sup>

From the above electrochemical behavior, it can be shown that the Ru complex does not affect the process of electron transfer to the substrate. However, this does not seem to explain the experimental fact that only one-fourth of the theoretical charge amount can make the substrate close to complete conversion. It has been reported  $^{20}$  that the activation barrier could be lower ca. 10 kcal/mol by an oriented external electric field (OEEF), according to the DFT calculation. So judiciously applied OEEFs could manipulate the kinetics and improve the thermodynamics of chemical reactions. For example,<sup>21</sup> CH<sub>3</sub>-X bond activation in alkyl halides could be achieved with a palladium catalyst under room temperature conditions in the presence of an oriented external electric field. Moreover, the approximately linear relationship of the equilibrium of intermediate to other species with the applied bias voltage has been found.<sup>22</sup> On the basis of these reports, we speculate that during our electrolysis process, the current past the cell forms a certain electric field, which may greatly reduce the activation energy of the target reaction and make the reaction proceed quickly under room temperature and normal pressure. The specific reaction mechanism needs further investigation.

In summary, we have realized the electrochemically promoted hydrogen transfer reaction of 2,2,2-trifluoroacetophenone. (*R*)-

 $\alpha$ -(Trifluoromethyl) benzyl alcohol with 96% yield, and 94% ee was obtained at room temperature and normal pressure. Detailed mechanistic studies to the role of electrolysis and the origin of the enantioselectivity are ongoing.

# EXPERIMENTAL SECTION

**General Procedure for the Electrolysis.** A typical galvanostatic electrolysis was carried out in a mixture of 2,2,2-trifluoroacetophenon (2 mmol, 348 mg), RuCl<sub>2</sub>[(*R*)-xylbinap][(*R*)-daipen] (0.06 mmol, 73.3 mg), *t*-BuOK (0.12 mmol, 13.5 mg), TEAI (2 mmol, 514 mg), and EtOH/*i*-PrOH (20 mL, v/v = 1:1) in a one-chamber electrolytic cell with a sacrificial Mg anode and Pt cathode with a direct-current-regulated power supply (HY3002D, HYelec, China). The product yield and enantiomeric excess (ee) value (eq S1) were measured with Shimadzu GC-2010 equipped with a Stabilwax column (30 m × 0.32 mm i.d., 0.5  $\mu$ m film thickness). A total of 60  $\mu$ L of as-prepared L-cysteine-CuPt colloids was coated on carbon paper (2 × 2 cm) and used as a cathode.

**Cyclic Voltammetry.** Cyclic voltammograms were analyzed on a CHI 600c electrochemical station (Shanghai Chenhua Instruments Company). A three-electrode cell equipped a glassy carbon (GC, d = 2 mm) as a working electrode, a Pt gauze (1.5 cm × 1.5 cm) as a counter electrode, and Ag/AgI/0.1 M TEAI in MeCN as the reference electrode. All electrochemical measurements were performed at a scan rate of 0.1 V s<sup>-1</sup> in a N<sub>2</sub>-saturated solution.

**Characterization Data for Product.** *α*-(Trifluoromethyl) benzyl alcohol. Eluent: ethyl acetate/petroleum ether = 1:10 v/v. Light yellow oil (310 mg, 88%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>, *δ* ppm): 7.50–7.48 (m, 2H), 7.42–7.38 (m, 3H), 6.82–6.80 (m, 1H), 5.17–5.13 (m, 1H). <sup>13</sup>C{<sup>1</sup>H} NMR (125 MHz, DMSO-*d*<sub>6</sub>, *δ* ppm): 135.9, 128.8, 128.2, 127.6, 125.1 (q, *J* = 280 Hz), 70.4 (q, *J* = 30 Hz).

# ASSOCIATED CONTENT

## Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01030.

Equation, formula, cyclic voltammetry studies, and NMR spectra (PDF)

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## Notes

The authors declare no competing financial interest.

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