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Alkaloid induced asymmetric electrocarboxylation of 4-methylpropiophenone

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ABSTRACT

The alkaloid-induced electrocarboxylation of 4-methylpropiophenone is examined in mild conditions. Comparative studies with several inductors indicate that the efficient enantiodiscrimination of the electrocarboxylation depends on the nucleophilic quinuclidine nitrogen atom and the OH group of the inductors.

1. Introduction

The electrochemical activation of aromatic ketones is one of the most important reactions in organic electrochemistry. In recent decades, an electrochemical methodology based on the use of an undivided cell equipped with a sacrificial anode (Mg, Al) has been a very convenient and cheap way to generate carboxylic acids via the coupling of CO_2 and aromatic ketones.[1–7] These acids are an important class of compounds, used to cure certain skin diseases, or used as pharmaceutical/fine chemical intermediates in the production of certain anti-inflammatory drugs.[8] One of the most active current areas of chemical research focuses on how to synthesize chiral compounds, because different enantiomers of a biomolecule can display dramatically different biological activities. Drawing inspiration from generic electrocarboxylation, there is a great need to synthesize chiral carboxylic acids in organic electrochemistry.

However, only a few electrocarboxylic reactions have been reported for the synthesis of chiral carboxylic acids. To the best of our knowledge, most of the preparations of optically active carboxylic acids are based on the electrocarboxylation of chiral substrates in an aprotic solvent.[9–11] Indeed, the exploration of an efficient route for the asymmetric electrocarboxylation reaction between CO_2 and prochiral substrates remains a challenge due to the difficulty in the selective fixation of the small molecule carbon dioxide. Our recent study found two alkaloids, cinchonidine (**CD**) and cinchonine (**CN**), to be efficient inductors for the asymmetric electrocarboxylation of acetophenone.[12]

Pursuant to our efforts toward the asymmetric electrocarboxylation of acetophenone under mild conditions, and to understand the mechanism of asymmetric electrocarboxylation of aromatic ketones, we are interested in studying the role of chiral inductors on enantiodifferentiation. To our knowledge, the specific role of inductors in asymmetric electrocarboxylation has not been reported. Herein, we describe a convenient route to optically active α-ethyl-α-hydroxy-4-methylbenzeneacetic acid (**2**) through the coupling reaction of CO_2 and 4-methylpropiophenone (**1**) using simple and easily accessible inductors. The electrocarboxylation of **1** was involved in several competitive reactions that lead to the formation of the target carboxylic acid **2**, and the corresponding alcohol and pinacol. In this Letter, we focus on the preliminary exploration of efficient inductors in the enantiodifferentiation of carboxylic acids.

2. Result and discussion

Electrolysis were carried out at 0 °C in *N*,*N*-dimethylformamide (DMF), under constant current conditions, in an undivided glass cell tank of cylindrical geometry fitted with sacrificial Mg rod anodes and a stainless steel cathode. The results are summarized in Scheme 1 and Table 1. No reaction occurred in the absence of current (Table 1, entry 1). No chiral induction occurred in the absence of alkaloids and *n*-butanol (Table 1, entry 2). Recently, our research[12] found that *n*-butanol as the co-catalyst is essential for the enantiodifferentiation of carboxylic acids. Without the *n*-butanol, only a racemic carboxylated product is obtained in the asymmetric electrocarboxylation of prochiral acetophenone. The remarkable similarities of the effect of **CN** in the asymmetric electrocarboxylation of acetophenone and **1** indicate that the sub-

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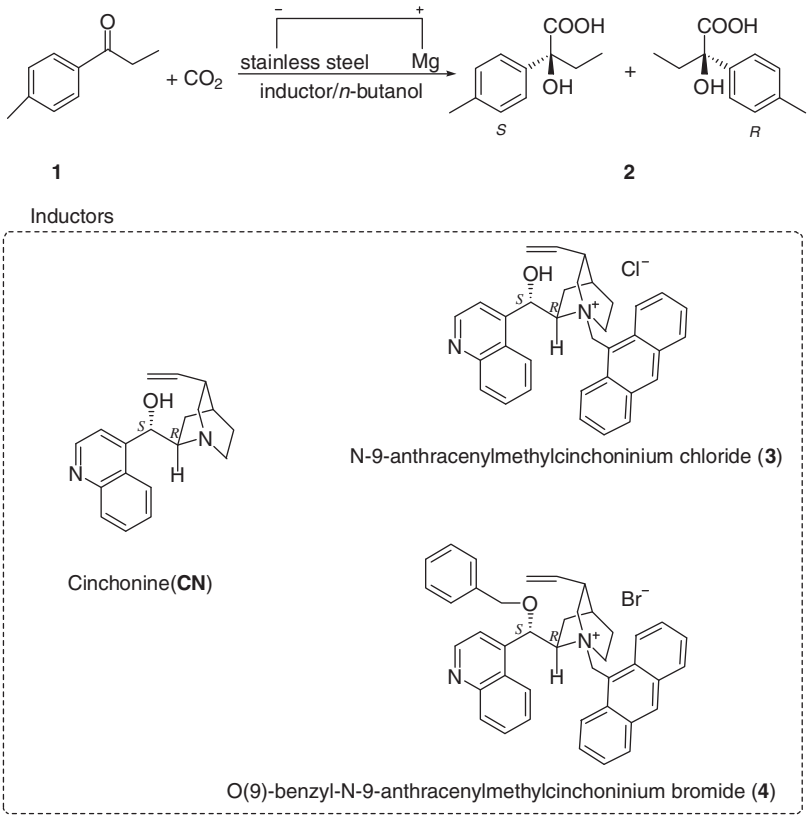

Scheme 1. Asymmetric electrocarboxylation of 4-methylpropiophenone.

Table 1
Asymmetric electrocarboxylation of 4-methylpropiophenone[a]

Entry	Inductor	Inductor (mM)	Yield[b] (%)	ee[c] (%)
1	**CN**	2.50	0	—
2[d]	—	0	40.0	—
3	**CN**	1.25	26.9	S-19.7
4	**CN**	2.50	31.4	S-28.4
5	**CN**	3.75	31.6	S-30.4
6	**CN**	5.00	37.4	S-32.8
7	**CN**	6.75	34.6	S-29.8
8	**3**	2.50	28.8	S-2.9
9	**4**	2.50	29.7	S-1.3

[a] Experimental conditions: 0 °C, stainless steel cathode, 4-methylpropiophenone 0.1 M, tetrabutylammonium iodide (TBAI) 0.1 M, *n*-butanol 25 mM, DMF 10 mL, current density 1.1 mA cm^{-2}, charge 193 C and CO_2 pressure 1 atm.
[b] The yield based on starting substrate.
[c] The enantiopurity of **2** was determined by HPLC.
[d] Run in the absence of *n*-butanol.

strates were transformed to the corresponding optically active carboxylic acids via the same reaction pathway. Therefore, **CN** should be adsorbed on the surface of the cathode to act as a chiral inductor in DMF. The *n*-butanol could act as co-catalyst by facilitating cinchona protonation. In the induction of **CN**, the *S* enantiomer of **2** was more abundant than the *R* enantiomer. The effect of **CN** concentration on the enantiomeric excess (ee) value has been studied in the asymmetric electrocarboxylation of **1** (Table 1, entries 3–7). The solubility of the cinchona alkaloids was clearly restricted in DMF. The dependence of the ee value (28.4%) on the **CN** concentration was approximately 2.50 mM (Table 1, entry 4). However, with higher concentration of **CN**, the ee value of **2** slightly increased (Table 1, entries 5 and 6). Moreover, when the concentration of **CN** was 6.75 mM (Table 1, entry 7), the asymmetric electrocarboxylation of **1** resulted in an ee value of 29.8% and a 34.6% yield. With replacement of **CN** with the same concentration of **3**, a low ee value was obtained (Table 1, entry 8). With **4** as the inductor, only a 1.3% ee value and 29.7% yield were obtained (Table 1, entry 9).

CN consists of three basic functional groups, a quinoline aromatic ring, a quinuclidine ring (a tertiary amine) containing the vinyl group, and a methylenic alcohol group linking the two. Multiple studies[13,14] have indicated that the catalytic activity of cinchona alkaloids is due to the nucleophilicity of the nitrogen of the quinuclidine ring. Therefore, the very low ee value when **3** was used as an inductor in the asymmetric electrocarboxylation of **1** is a strong indication that the key structural feature for **CN** is the nucleophilic quinuclidine nitrogen atom. Arx et al.[15] also showed that methylation of the quinuclidine nitrogen of **CD** leads to a complete loss of enantioselectivity in the heterogeneous enantioselective hydrogenation of trifluoromethyl ketones. Similarly, with **4** as inductor, the OH group of the modifiers was involved in the process of enantiodiscrimination. Most reports[16,17] on cinchona-promoted chiral catalysis have referred to this combination of the tertiary amine and the OH group to contribute to the enantioselectivity. The synergistic effect between the OH group of inductors and the enantioselectivity may provide valuable information on the reaction mechanism, and is currently being studied.

From a mechanistic point of view (Scheme 2), the inductor could obtain a proton from the co-catalyst of *n*-butanol. Studies have shown that the alkaloids could be adsorbed at the cathode surface as a chiral proton-donating species after the protonation of the quinuclidine nitrogen by the co-catalyst of *n*-butanol. Compound **1** accepts an electron at the cathode to form an anion radical intermediate (**1a**). As noted by Amatore et al.[18] the cyclodextrins act mostly as weak proton donors to the electronegative acetophenone anion radical in DMF. Similarly, the protonated inductor (**CN**–**H**) is implied to act as a weak proton donor to the electronegative