

Efficient fixation of carbon dioxide by electrolysis - Facile synthesis of useful carboxylic acids

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Abstract

Electrochemical fixation of an atmospheric pressure of carbon dioxide to organic compounds is a useful and attractive method for a synthesis of various carboxylic acids. Electrochemical fixation of carbon dioxide, electrochemical carboxylation, to organic halides, organic triflates, alkenes, aromatic compounds and carbonyl compounds can readily take place in the presence of an atmospheric pressure of carbon dioxide to give the corresponding carboxylic acids in high yields when a sacrificial anode such as magnesium or aluminum is used in the electrolysis. The electrochemical carboxylation of vinyl bromides was successfully applied to a synthesis of the precursor of non-steroidal anti-inflammatory agents such as ibuprofen and naproxen. On the other hand, supercritical carbon dioxide (scCO₂) has significant potential as an environmentally benign solvent in organic synthesis and it could be used both as a solvent and a reagent in these electrochemical carboxylations by using a small amount of co-solvent.

Keywords: Fixation of carbon dioxide, Supercritical carbon dioxide, Electrolysis, Sacrificial anode, Carboxylic acid

1.0 Introduction

Efficient fixation of an atmospheric pressure of carbon dioxide to appropriate organic substrates is a very useful and attractive method for a synthesis of various carboxylic acids. Electrochemical methods for an efficient fixation of carbon dioxide have been studied since the electrochemical reactions usually proceed under mild conditions. Among them the electro-chemical reductive method using a platinum cathode and a sacrificial anode such as magnesium or aluminum metal in a one-compartment cell was found to be most convenient and most efficient for that purpose.¹⁻²⁾ We have also studied the electrochemical fixation of carbon dioxide to various types of organic compounds and prepared a variety of useful carboxylic acids in high yields. These electrochemical fixations, electrochemical carboxylations, were successfully applied to an efficient synthesis of the precursor of non-steroidal anti-inflammatory agents such as ibuprofen and naproxen.

On the other hand, supercritical carbon dioxide (scCO₂) has significant potential as an environmentally benign solvent to replace hazardous organic media in organic synthesis, since it is inexpensive and nontoxic, and can readily be recovered and reused after the reaction. We found that supercritical carbon dioxide could be used both as a solvent and a reagent in these electrochemical fixations.

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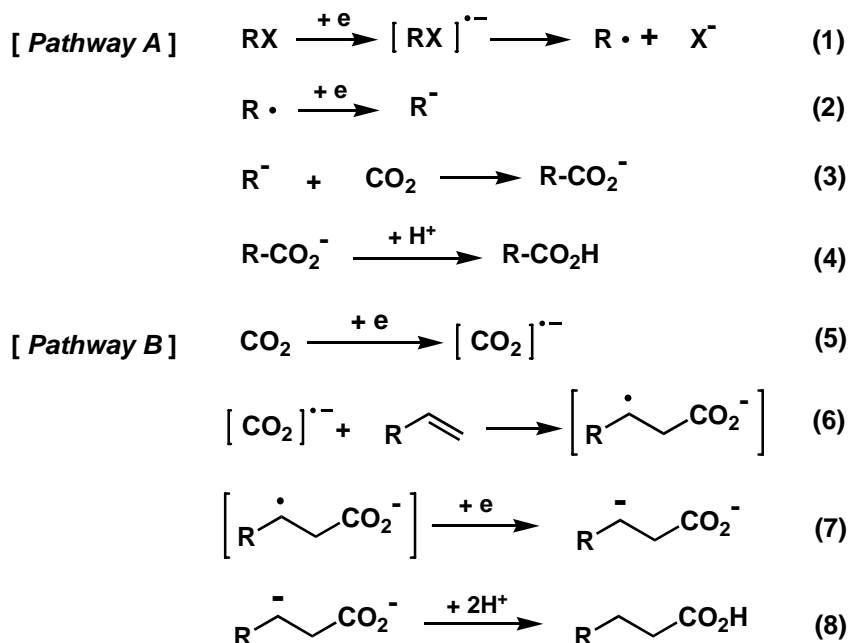
In this review, our results on an efficient electrochemical fixation of an atmospheric pressure of carbon dioxide and its application to a synthesis of various useful carboxylic acids including the precursor of anti-inflammatory agents are summarized. Use of supercritical carbon dioxide both as a solvent and a reagent in these electrochemical fixations is also described in this review.

2.0 Materials and Methods

2.1 Electrochemical fixation of carbon dioxide

Two cases may be considered for an electrochemical fixation of carbon dioxide to organic compounds. First case, the pathway **A**, includes anionic species generated by a two-electron reduction of organic substrates (Scheme 1, equations (1)-(4)). The carbanions undergo a nucleophilic attack on carbon dioxide to give the corresponding carboxylic acids. This case occurs when reduction potentials of organic substrates are more positive than that of carbon dioxide. On the other hand, an electrochemical fixation of carbon dioxide also takes place according to the pathway **B** when the reduction potentials of organic substrates are more negative than that of carbon dioxide (Scheme 1, equations (5)-(8)). In this carboxylation, an anion radical of carbon dioxide generated by a one-electron reduction reacts with organic substrates, typically such as alkenes, to give the corresponding carboxylic acids.

These electrochemical fixations of an atmospheric pressure of carbon dioxide to organic substrates can take place efficiently when the electrolysis is carried out in a one-compartment cell by using a platinum cathode and a sacrificial anode such as magnesium or aluminum.¹⁻²⁾ Such fixation, the electrochemical carboxylation, gives various useful carboxylic acids in good yields.

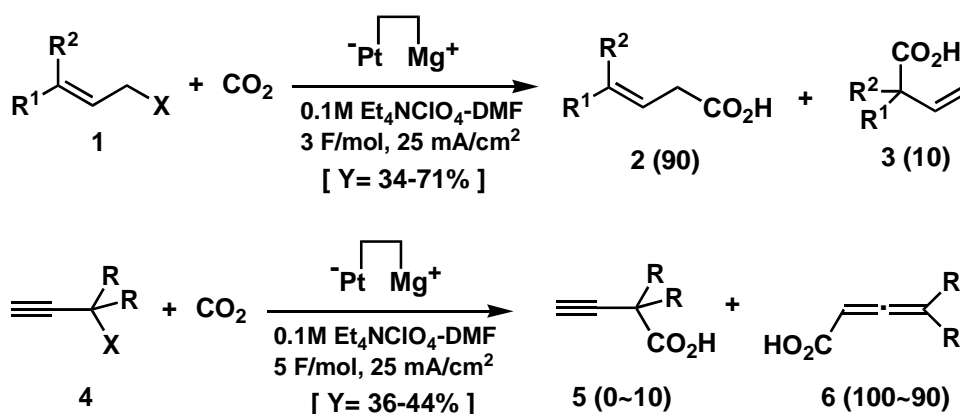


Scheme 1 Electrochemical fixation of carbon dioxide to organic substrates

2.2 Electrochemical carboxylation of allylic and propargylic halides

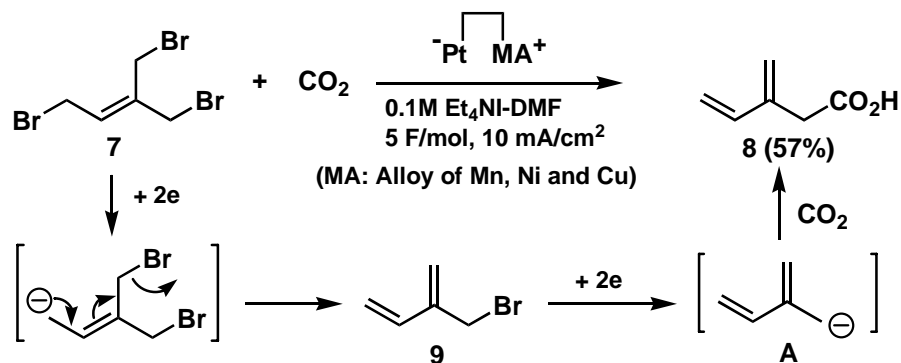
Electrolysis of allylic bromides (**1**) in the presence of an atmospheric pressure of carbon dioxide with a platinum cathode and a magnesium anode gave regioselectively the corresponding β,γ -unsaturated carboxylic acids **2** in 34-71% isolated yields (Scheme 2).³⁾ The electrolysis was carried out in a DMF solution containing 0.1M Et₄NClO₄ at a constant current by using a one-compartment cell. This electrochemical carboxylation giving the acids **2** is of synthetic interest since a carboxylation of allylic organometallic compounds derived from allylic halides **1** usually gives exclusively β,γ -unsaturated carboxylic acids **3**.⁴⁾

Similar electrochemical carboxylation of α,α -disubstituted propargyl bromides (**4**) gave exclusively allenic acids **6** (Scheme 2).⁵⁾ Carboxylation of propargylic organometallic compounds gives a mixture of acids **5** and **6** in very low yields. Both electrochemical carboxylations of allylic and propargylic halides would proceed *via* the pathway A in Scheme 1, since both halides are more readily reduced than carbon dioxide. In these cases the corresponding carbanions derived from allylic or propargylic halides are produced as intermediate species and the regioselectivity of the electrochemical carboxylations to give **2** or **6** can be elucidated by an addition of more stable form of the carbanions to carbon dioxide.



Scheme 2 Electrochemical carboxylation of allylic and propargylic halides

Convenient synthesis of the hitherto unknown 3-methylenepent-4-enoic acid (**8**) was achieved by the electrochemical carboxylation of allylic tribromide **7** (Scheme 3).⁶⁾ Tribromide **7** was readily prepared by 1,4-addition of bromide to isoprene followed by allylic bromination⁷⁾ and it can work as a synthetic equivalent for isoprenyl carbanion (**A**). A two-electron reduction of **7** gives isoprenyl bromide (**9**) and another two-electron reduction of **9** generates the carbanion **A** (Scheme 3).

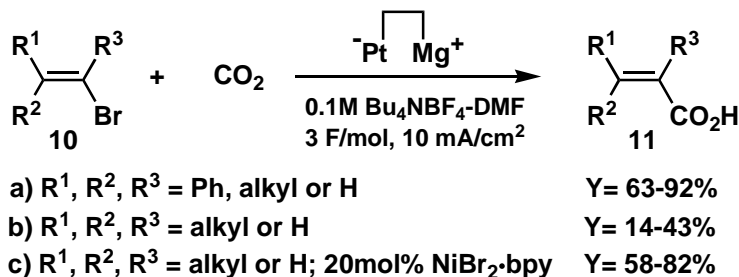


Scheme 3 Electrochemical carboxylation of isoprenyl anion equivalent **7**

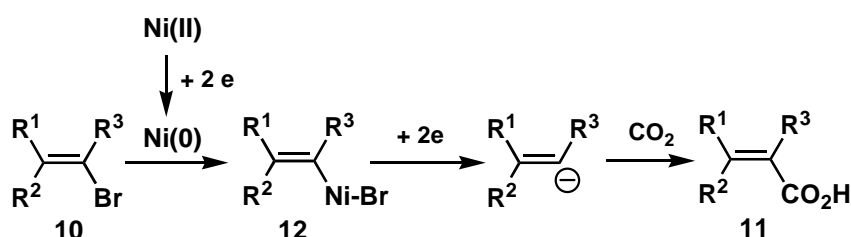
2.3 Electrochemical carboxylation of vinylic bromides

Reduction potentials of aryl-substituted vinyl bromides are more positive than that of carbon dioxide and, therefore, their electrochemical carboxylation would proceed *via* the pathway **A** in Scheme 1. Electrolysis of aryl-substituted vinyl bromides **10** in the presence of an atmospheric pressure of carbon dioxide with a platinum cathode and a magnesium anode gave the corresponding α,β -unsaturated carboxylic acids **11** in isolated yields of 63-92% (Scheme 4).^{8,9)} When all of R^1 , R^2 or R^3 are alkyl or hydrogen, the reduction potentials of the vinyl bromides are very negative and their electrochemical carboxylations gave α,β -unsaturated carboxylic acids **11** in lower yields. However, an addition of Ni(II) catalyst in this electrochemical reduction was found to enhance largely the yield of **11** and the desired α,β -unsaturated carboxylic acids **11** were obtained in the isolated yields of 58-82% (Scheme 4).¹⁰⁾

Probable reaction pathways of the electrochemical carboxylation of aliphatic vinyl bromides in the presence of Ni(II) catalyst are shown in Scheme 5. Reduction potentials of 1-bromocycloheptene and $\text{NiBr}_2(\text{bpy})$ are <-2.6 V and -1.25 V *vs* Ag/AgCl, respectively. A two-electron reduction of more reducible Ni(II) catalyst gives Ni(0) species and an oxidative addition of Ni(0) to vinyl bromide would produce vinyl nickel complex **12**. A two-electron reduction of the complex **12** gives the corresponding vinyl carbanion, which would be trapped by an atmospheric pressure of carbon dioxide to give the corresponding α,β -unsaturated carboxylic acids **11**. Cyclic voltammetry of 1-bromocycloheptene in the presence of $\text{NiBr}_2(\text{bpy})$ showed the existence of a new reduction peak at ca. -1.5 V, which is more positive potential than that of the original vinyl bromide.¹⁰⁾



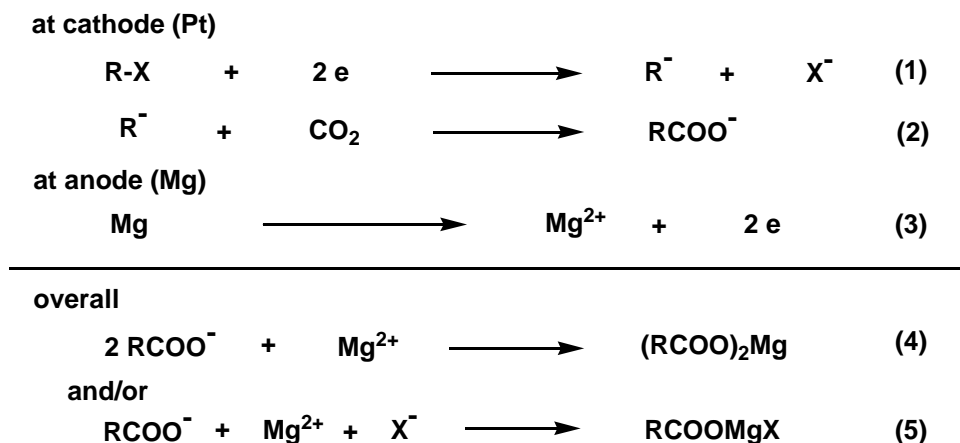
Scheme 4 Electrochemical carboxylation of vinylic bromides



Scheme 5 Proposed reaction pathways of the electrochemical carboxylation of aliphatic vinyl bromide using Ni(II) catalyst

Stereochemistry of the electrochemical carboxylation using Ni(II) catalyst was also examined. Electrochemical carboxylation of (*E*)- and (*Z*)- β -bromostyrene in the presence of 20 mol% of NiBr₂(bpy) proceeded with retention of the stereochemistry to give the corresponding (*E*)- and (*Z*)-cinnamic acids in high stereoselectivities.¹¹⁾

High efficiency in the electrochemical fixation of carbon dioxide using a sacrificial anode can be rationalized by the reaction pathways shown in Scheme 6. At the cathode, a two-electron reduction of organic halides occurs to give the corresponding carbanions (R⁻), which are trapped by carbon dioxide to give the corresponding carboxylates (RCOO⁻) (Scheme 6, equations (1) and (2)). At the anode, on the other hand, a dissolution of magnesium metal takes place to give magnesium ion (Mg²⁺) (equation (3)). The magnesium ion readily captures carboxylates to give stable magnesium carboxylates ((RCOO)₂Mg or RCOOMgX) (equation (4) or (5)). If there is no magnesium ion in the solution, most of the carboxylates would undergo decarboxylation to regenerate original carbanions or would decompose at an anode to give radicals followed by Kolbe coupling reaction. These decarboxylation and decomposition of carboxylate anions would result in lower yields of carboxylic acids.

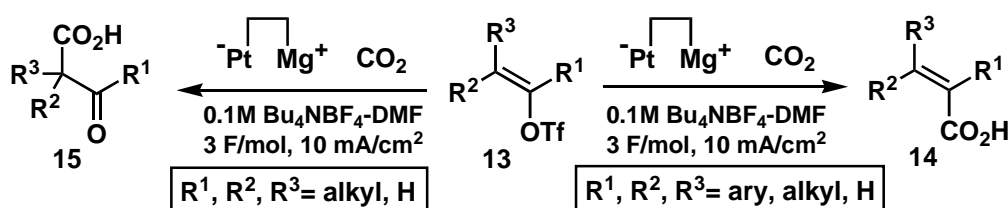


Scheme 6 Probable Reaction pathways of an efficient electrochemical fixation of carbon dioxide using a sacrificial anode

2.4 Electrochemical carboxylation of vinyl triflates

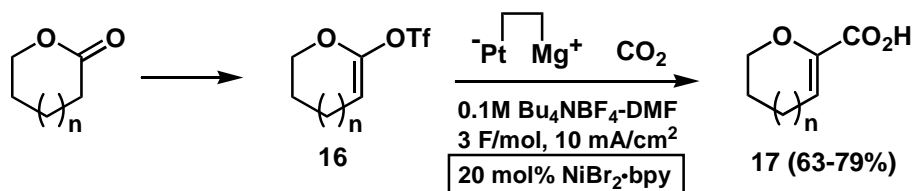
Electrochemical carboxylation of vinyl triflates, instead of vinyl halides, was also examined since triflyl function (-OTf = -OSO₂CH₃) works as a good leaving group in organic reactions. In the electrochemical carboxylation of vinyl triflates **13**, two types of reactions occurred to

give completely different products, α,β -unsaturated carboxylic acids (**14**) or β -keto carboxylic acids (**15**) (Scheme 7).¹²⁻¹⁴ Electrolysis of phenyl-substituted vinyl triflates in the presence of an atmospheric pressure of carbon dioxide gave acids **14** in good yields, whereas similar electrochemical carboxylation of alkyl-substituted vinyl triflates gave carboxylic acids **15** exclusively. These divergent electrochemical carboxylations are resulted from chemoselective cleavage of O-S or C-O bond of vinyl triflates. In the case of phenyl-substituted vinyl triflates, a preferential reduction of vinyl triflates occurs to give vinyl carbanions, which are trapped by carbon dioxide to give **14**. On the other hand, in the case of alkyl-substituted vinyl triflates, carbon dioxide is more readily reduced to give its anion radical, which would attack on sulfur atom of vinyl triflates followed by O-S bond cleavage to give the corresponding enolate anions. The enolates would be captured by carbon dioxide to give **15** exclusively.



Scheme 7 Divergent electrochemical carboxylation of vinyl triflates (13)

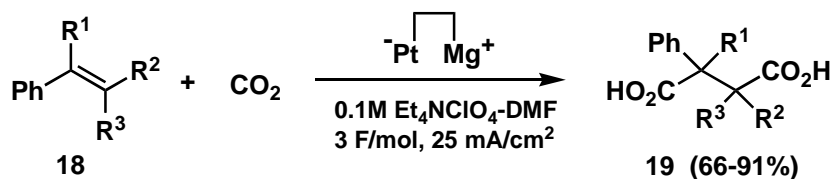
Carboxylation pathway of **13** to give **15** can completely be changed to another one giving **14** by the use of Ni(II) catalyst in the electrolysis. Such electrochemical carboxylation of lactone enol triflates (**16**) in the presence of 20 mol% of NiBr₂(bpy) gave the corresponding cyclic α -alkoxyl- α,β -unsaturated carboxylic acids **17**, captodative cycloalkenes, in 63-79% yields (Scheme 8).¹⁵⁾



Scheme 8 Electrochemical carboxylation of lactone enol triflates (16)

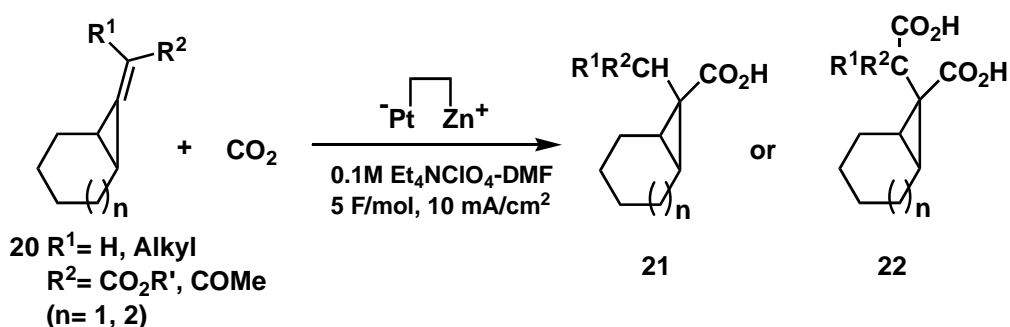
2.5 Electrochemical carboxylation of alkenes

Fixation of two molecule of carbon dioxides can take place when the electrolysis of phenyl-substituted alkenes was carried out in the presence of an atmospheric pressure of carbon dioxide with a platinum cathode and a magnesium anode. Various phenylsuccinic acids (**19**) were obtained in 66-91% isolated yields by the electrochemical dicarboxylation of alkenes **18** (Scheme 9).¹⁶⁾ Dicarboxylation probably occurs *via* the pathways **A** of Scheme 1 in the case of stilbene (**18**; R¹=R³=H, R²=Ph) and *via* the pathways **B** in the case of styrene (**18**; R¹=R²=R³=H).



Scheme 9 Electrochemical dicarboxylation of phenyl-substituted alkenes (18)

Electrochemical fixation of carbon dioxide to alkenes having more complex structure readily occurs to give the corresponding carboxylic acids in good yields. Electrochemical carboxylation of ring-fused alkylidenecyclopropanes **20** in the presence of an atmospheric pressure of carbon dioxide afforded either mono- (**21**) or dicarboxylic acid (**22**) in 44-74% yields (Scheme 10).¹⁷⁾



Scheme 10 Electrochemical carboxylation of bicyclo[n.1.0]alkylidene derivatives (20)

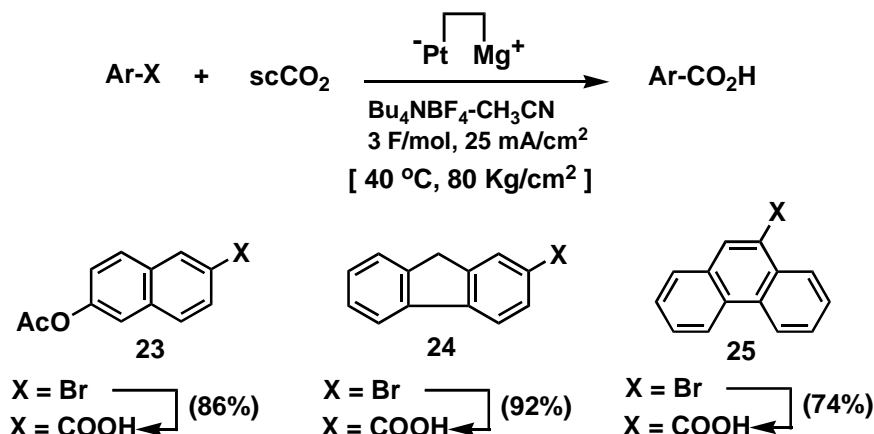
2.6 Use of supercritical carbon dioxide in the electrochemical carboxylation

Supercritical carbon dioxide (scCO₂) can readily be attained under relatively moderate conditions (T_c = 31 °C, P_c = 7.5 Mpa). It has significant potential as an environmentally benign solvent to replace hazardous organic solvents since it is nontoxic and inexpensive, and can be recovered and reused after the reaction. We developed a new method for electrochemical carboxylation in scCO₂ by using a small amount of acetonitrile (5-10 ml to 155 ml of scCO₂) as a co-solvent.¹⁸⁾ No current flows in pure supercritical carbon dioxide due to its poor conductivity.

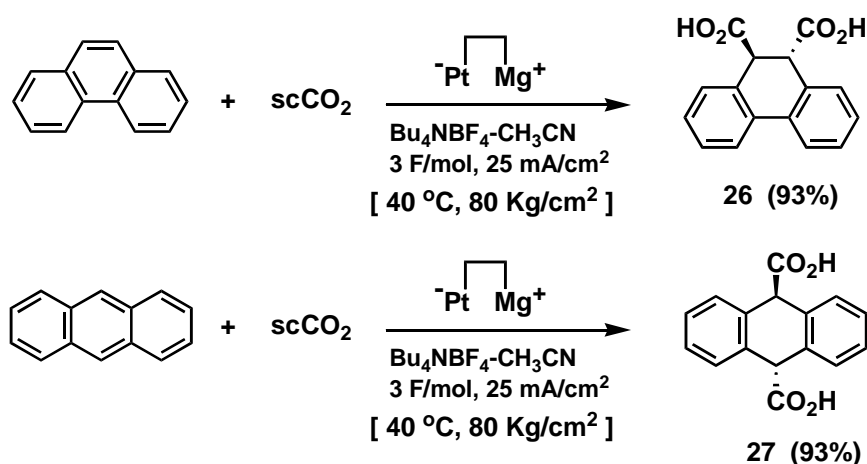
Fixation of carbon dioxide to aromatic compounds successfully occurred in scCO₂. Electrolysis of aryl halides (Ar-X) in scCO₂ containing a small amount of acetonitrile with a platinum cathode and a magnesium anode gave aryl carboxylic acids (Ar-CO₂H) such as **23**, **24** and **25** in high yields (Scheme 11).^{19, 20)} Electrochemical dicarboxylation of phenanthrene and anthracene also proceeded efficiently in scCO₂ to give acids **26** and **27** in high yields (Scheme 12).²⁰⁾ Similar electrochemical carboxylation of anthracene in acetonitrile solution in the presence of an atmospheric pressure of carbon dioxide gave **27** only in 32% yield. Most of the electrochemical carboxylations in scCO₂ gave higher yields of carboxylated products than those using an atmospheric pressure of carbon dioxide. This is probably due to higher diffusion rate of species RCOO⁻ and Mg²⁺ in scCO₂ to form stable (RCOO)₂Mg or RCOOMgX, compared with slow diffusion rate in DMF solution containing an atmospheric pressure of carbon dioxide (Scheme 6, equations (4) and (5)).

Electrochemical carboxylation of arylmethyl halides, 1-aryl-1-bromoethenes and aryl methyl

ketones in scCO₂ also proceeded efficiently to give the corresponding carboxylic acids in high yields.²⁰⁾



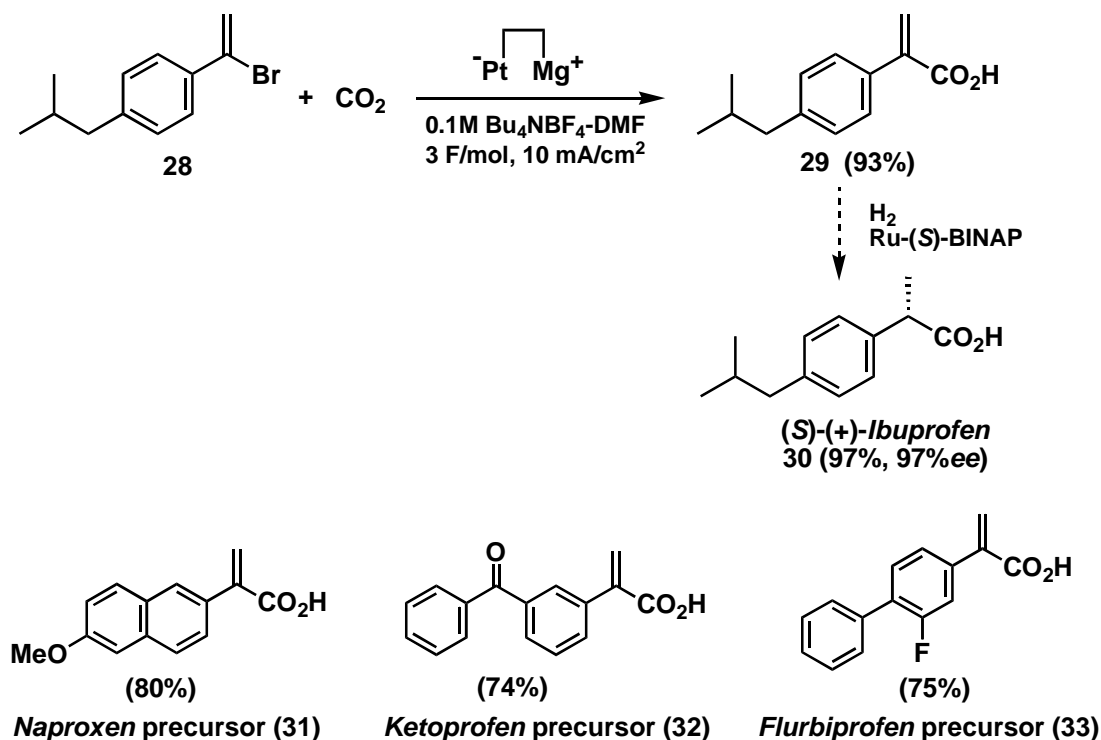
Scheme 11 Electrochemical carboxylation of aryl halides in supercritical carbon dioxide



Scheme 12 Electrochemical dicarboxylation of arenes in supercritical carbon dioxide

2.7 Application to a synthesis of the precursor of anti-inflammatory agents

Efficient electrochemical carboxylation of vinyl bromide using an atmospheric pressure of carbon dioxide was successfully applied to a synthesis of the precursor of anti-inflammatory agents. For example, the electrochemical carboxylation of vinyl bromide **28** gave the desired α,β -unsaturated carboxylic acid **29** in 93% yield,⁸⁾ which can readily be transformed into (*S*)-ibuprofen by enantioselective hydrogenation^{21, 22)} (Scheme 13). The precursors of naproxen (**31**), ketoprofen (**32**) and flurbiprofen (**33**) were produced in good yields by similar electrochemical carboxylation (Scheme 13).

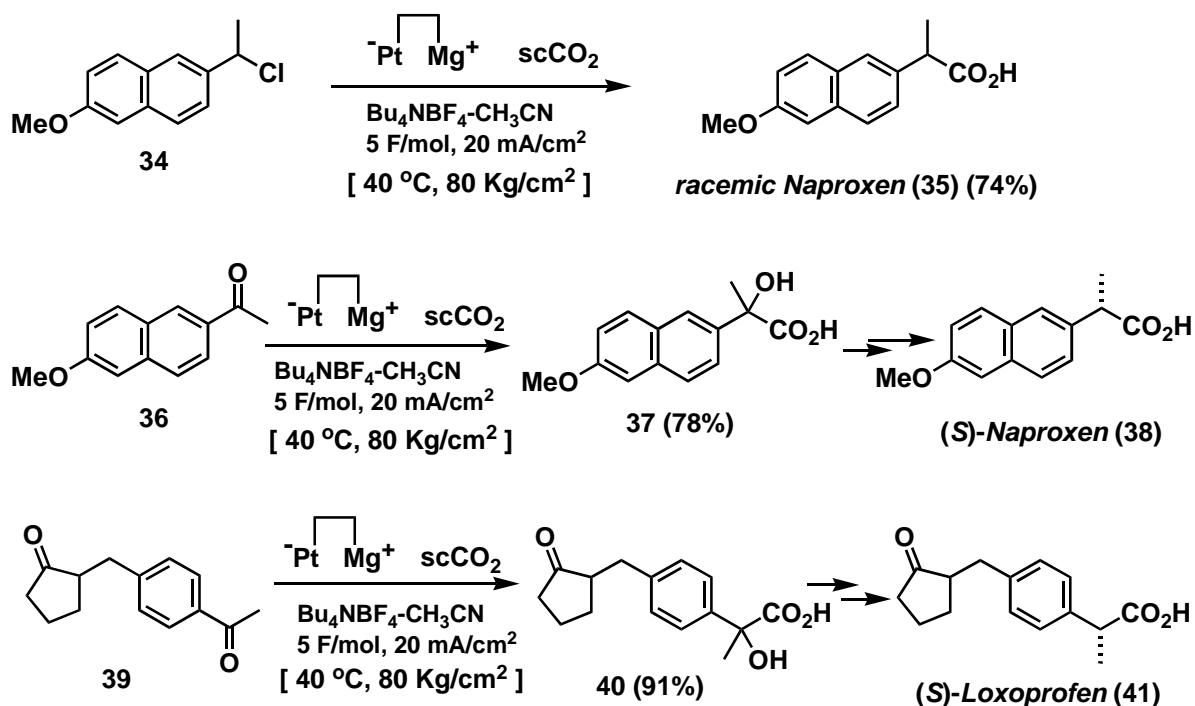


Scheme 13 Synthesis of several precursors of anti-inflammatory agents by electrochemical carboxylation of vinyl bromides

The electrochemical carboxylation in scCO₂ was successfully applied to a synthesis of anti-inflammatory agents. Electrolysis of benzylic chloride **34** in scCO₂ gave *racemic* naproxen (**35**) in 74% yield (Scheme 14).^{19, 20} Electrochemical carboxylation of aryl methyl ketone **36** in scCO₂ took place to give α -hydroxycarboxylic acid **37** in 78% yield, which can afford (*S*)-naproxen (**38**) by dehydration and enantioselective hydrogenation. Synthesis of (*S*)-loxoprofen (**41**) is of synthetic and electrochemical interest since usual chemical reaction can not control the reactivity of two carbonyl groups in **39**. In the electrochemical reactions, however, aryl methyl ketone is more readily reduced than cyclopentanone and the electro-chemical carboxylation of **39** gave the desired α -hydroxypropanoic acid (**40**) in 91% yield (Scheme 14). The product **40** can be transformed into (*S*)-loxoprofen (**41**).²⁰

Similar electrochemical carboxylation of vinylic bromides in scCO₂ also gave the precursor of anti-inflammatory agents **29**, **31** and **33** in almost the same yields as those using atmospheric carbon dioxide.²⁰

The precursors of various anti-inflammatory agents such as **29**, **31**, **32** and **33** as well as those of cicloprofen, indoprofen, suprofen and loxoprofen were also prepared by cross-coupling reaction of the corresponding aryl iodides with organozinc bromides obtained by the reaction of ethyl 2-bromoacrylate with the electrogenerated highly reactive zinc.²³⁻²⁵



Scheme 14 Synthesis of anti-inflammatory agents by electrochemical carboxylation in supercritical carbon dioxide

3.0 Conclusion

The present electrochemical method for an efficient fixation of an atmospheric pressure of carbon dioxide to a variety of organic compounds has several advantages: use of a simple one-compartment cell by the use of a platinum cathode and a magnesium anode, simple electrolysis at a constant-current, high yields in a synthesis of useful carboxylic acids and easy application to a synthesis of the precursor of non-steroidal anti-inflammatory agents. This procedure might be used for an industrial production of high value-added substances such as pharmaceuticals. Use of supercritical carbon dioxide in the electrochemical fixation of carbon dioxide would be useful in the future since an environmental problem will become more important for us.

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