Sequential Radical Cyclization – Fixation of Carbon Dioxide by Electrochemical Reduction of Aryl and Vinyl Bromides

A Dissertation for the Degree of Doctor of Philosophy
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Contents

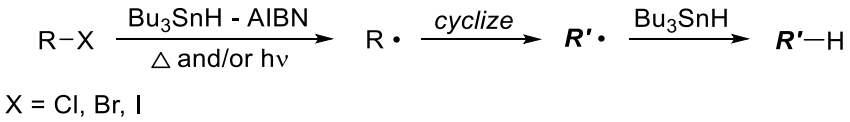
Chapter 1

Introduction

1-1 Organic radical reaction: generation, cyclization, and termination

In organic synthesis, radical cyclization is a powerful, straightforward, and efficient tool for synthesis of cyclic compounds. Results of many studies on and successful applications of radical cyclization for the synthesis of various carbocycles and heterocycles have been reported, and they have also been summarized as reviews in many books and journals.[1,2]

A radical reaction can be classified three different steps: initiation, propagation and termination. As well as hydrogen abstraction and several radical-induced cleavage reactions, cyclization is one of the propagation reactions and is the most widely used radical reaction in organic synthesis. Most of the carbon-centered radicals used for radical cyclization have been generated from organic halides by reaction with organotin reagents, such as tributyltin hydride (Bu_3SnH), and radical initiators, such as azobisisobutyronitrile (AIBN), under thermal or photolysis conditions (Scheme 1).

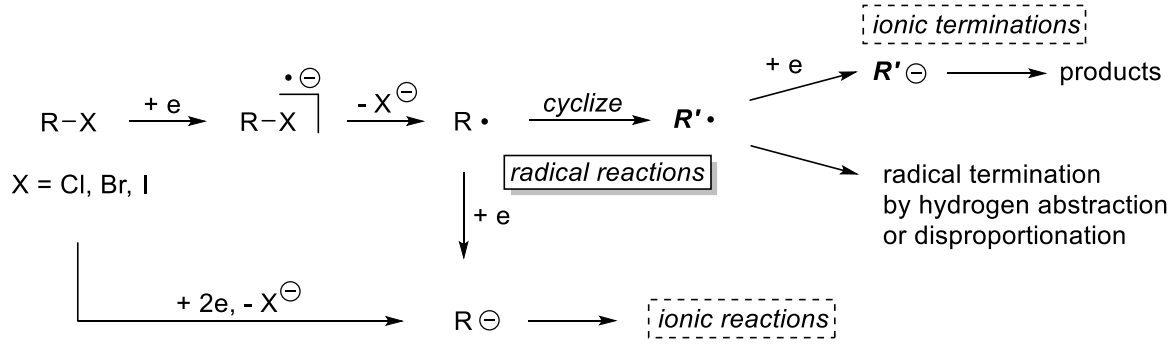


Scheme 1

However, as is well known, organotin reagents are unfriendly for nature because of their toxicity. From the viewpoint of green and sustainable chemistry and environmentally benign organic synthesis, the use of such organotin reagents is unfavorable and should be avoided. Therefore, the development of alternatives for efficient and environmentally benign generation of carbon-centered radicals from organic halides has been highly desirable. Moreover, when Bu_3SnH is used as a radical mediator, the termination reaction always involves hydrogen abstraction of the resulting cyclized radical from Bu_3SnH, and further functionalization is generally impossible. This point might be one drawback in a radical reaction using Bu_3SnH from the viewpoint of organic synthesis.

One of the effective methods for generation of a carbon-centered radical from organic halides is the use of a redox reaction with electron transfer. One-electron reduction of organic

halides generates the corresponding radical anion. Spontaneous elimination of a halide ion from the radical anion can generate the corresponding carbon-centered radical. However, if further one-electron reduction of the generated radical takes place rapidly under the reaction conditions with electron transfer, the corresponding anion species are unexpectedly generated, resulting in ionic reactions. Two-electron reduction of organic halides also generates the corresponding anion species, not the corresponding carbon-centered radical, with elimination of a halide ion. Therefore, selective one-electron reduction of organic halides is critical for efficient generation of a carbon-centered radical from organic halides, and after generation of the radical, control of the redox system under the condition of electron transfer during the radical reaction is also essential for efficient progress of radical reaction/cyclization (Scheme 2).

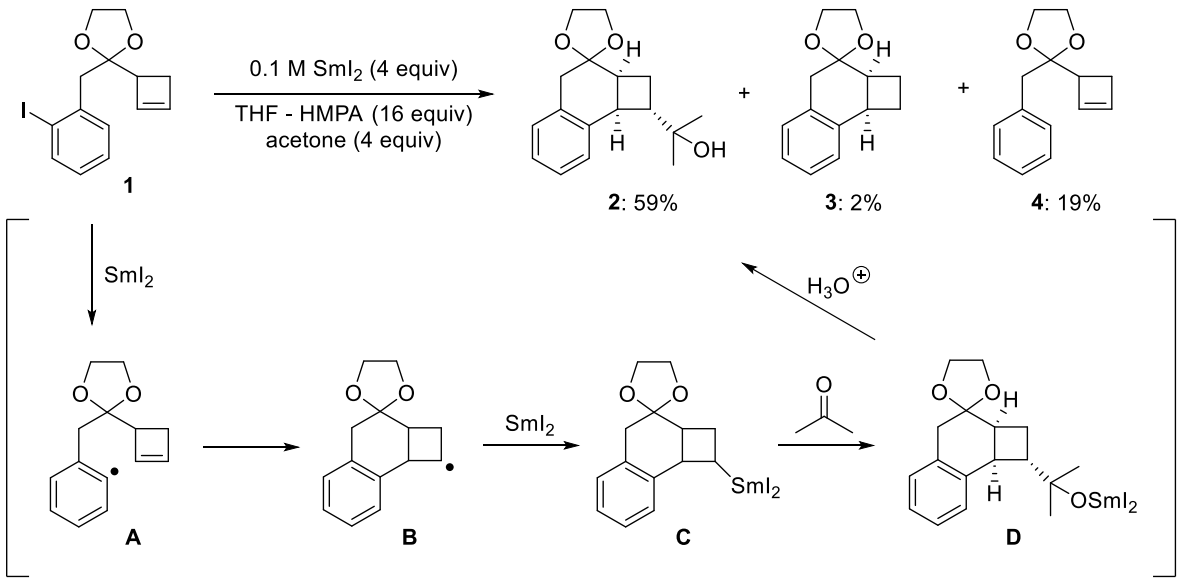


Scheme 2

One of representative reagents to overcome these complicated problems is samarium(II) iodide (SmI_2).[3] The corresponding carbon-centered radical can be efficiently generated from organic halides under mild conditions using SmI_2, and following radical cyclization also proceeds efficiently to give the cyclized products. For these reasons, many papers on radical cyclization using SmI_2 have been published and reviewed.[3,4] However, samarium is one of heavy metals in the lanthanide series, and to achieve efficient yields and selectivity of the products, the reaction of SmI_2 sometimes needs hexamethylphosphoric triamide (HMPA), which is also known to be an unfavorable reagent and its use should also be avoided if possible.

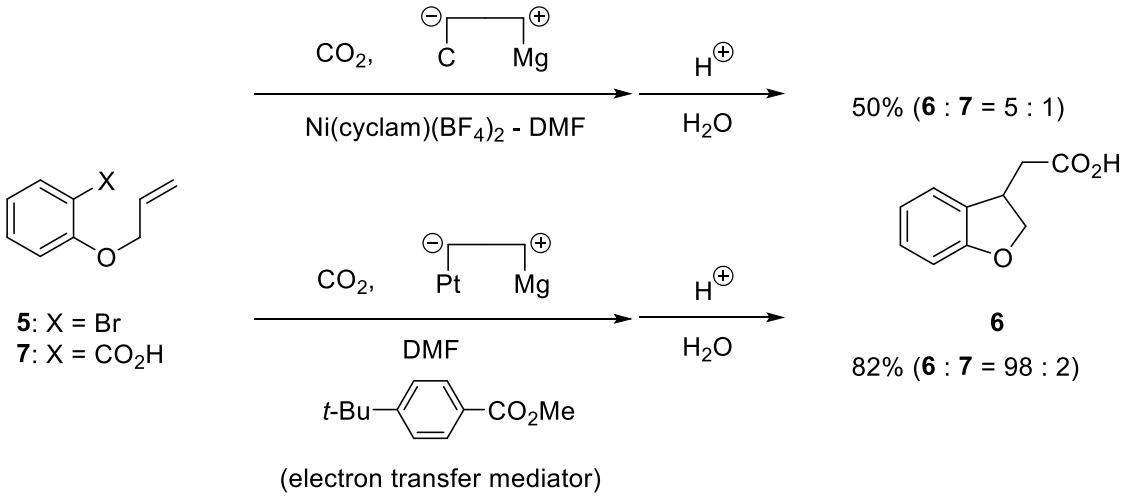
In radical generation using a redox system as shown in Scheme 2, the termination

reaction has the possibility of being used as further transformation reactions. When a carbon-centered radical is generated under reductive conditions with electron transfer, the termination reaction usually proceeds by the reaction of anion species, which are produced by further one-electron reduction of the resulting cyclized radical. This is a useful advantage from the viewpoint of organic synthesis, because anion species can induce several organic transformations such as functionalization and especially carbon-carbon bond forming reaction. However, most of the termination step of radical cyclization reactions of organic halides under reductive conditions is merely protonation of the resulting carbo anion, and there are only a few examples using the resulting anion species for further reaction with an electrophile, such as CO_2, to achieve a carbon-carbon bond forming reaction in the termination step.[5,6] One successful example is shown in Scheme 3. Aryl radical **A** was successfully generated by the reaction of aryl iodide **1** with SmI_2. Thus-generated **A** cyclized with an alkene in a 6-*exo* manner and then further reduction of cyclized radical **B** with SmI_2 gave anionic species **C**, which reacted with an electrophile, acetone, to give sequential radical – anion reaction product **2** in good yield, although excess amounts of SmI_2 and HMPA were unfortunately used.[6a]



Scheme 3

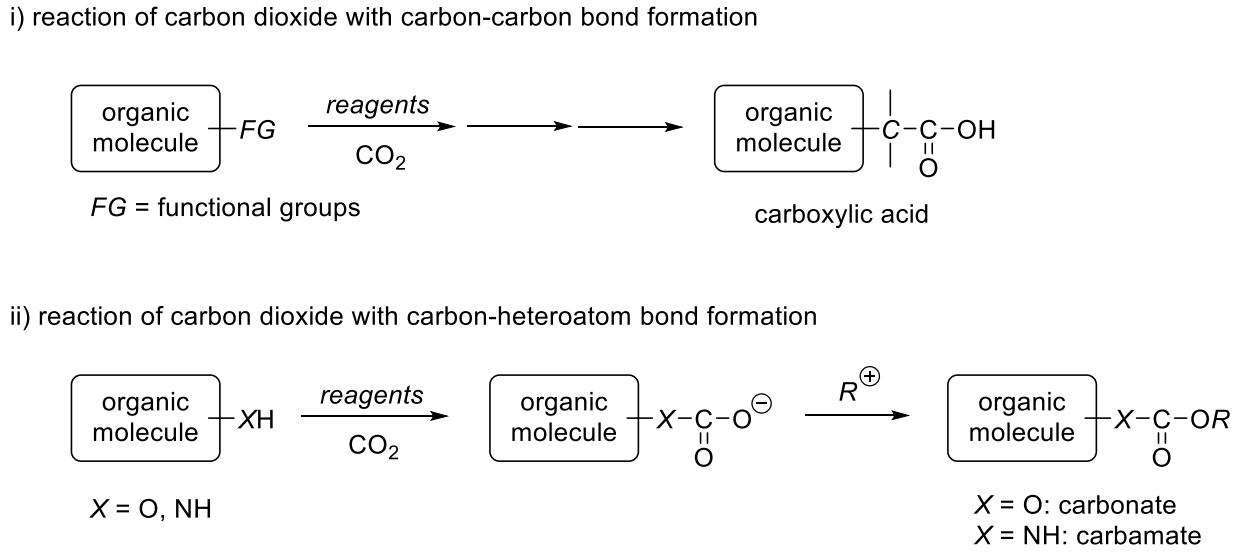
Electrochemical reduction[7] is also an effective alternative for generation of a carbon-centered radical from organic halides using a redox system. Electron transfer from the cathode to the substrate generates the corresponding anion radical, and spontaneous elimination of a leaving group such as a halide ion produces radical species by the mechanism shown in Scheme 2. Actually, carbon-centered radicals were successfully generated by direct,[8,9] metal complex-catalyzed,[10-13] or mediated[14-18] electrochemical reduction of organic halides and diazonium salts, and they were successfully applied to radical cyclization to construct carbo- and heterocycles. As mentioned earlier, under electrochemical reduction conditions, the termination reaction also includes the reaction of anion species, not a radical reaction such as hydrogen abstraction or disproportionation. However, all of the reported electrochemical radical cyclizations were terminated by protonation, and there is no reports on the use of the resulting anion species for further transformations such as carbon-carbon bond forming reactions. To the best of our knowledge, Ni-catalyzed cyclization followed by fixation of carbon dioxide of unsaturated haloaryl ethers **5** reported by Duñach and co-workers[19] is the only example of 'radical-like' cyclization followed by carbon-carbon bond formation with carbon dioxide as a termination step to yield **6** in moderate yields (Scheme 4). Recently, efficient and environmentally benign generation of aryl radicals from 2-allyloxybromobenzenes **5** by electrochemical reduction using methyl 4-*tert*-butylbenzoate as an electron transfer mediator was reported by Senboku and co-workers,[20] and thus-generated aryl radicals were also found to undergo radical cyclization with alkene followed by fixation of carbon dioxide without a nickel-catalyst to give **6** in high yields as shown in Scheme 4. This is the first example of radical cyclization followed by anionic termination under electrochemical reduction conditions without a metal catalyst and reagents. However, further investigation of this attractive and promising reaction system has not been carried out, and application and extension are desirable both as a new cascade radical/anion reaction and for utilization of carbon dioxide as a carbon source from the viewpoint of environmentally-benign organic transformations.


CO2,
C
Mg
H⊕
Ni(cyclam)(BF4)2 - DMF
H2O
50% (6 : 7 = 5 : 1)
X
O
CO2H
O
5: X = Br
7: X = CO2H
CO2,
Pt
Mg
H⊕
DMF
H2O
6
82% (6 : 7 = 98 : 2)
t-Bu
CO2Me
(electron transfer mediator)

Scheme 4

1-2 Carbon dioxide

It is well known that carbon dioxide is a useful C1 source in organic synthesis from the viewpoint of economy, safety, and green and sustainable chemistry.[21] Fixation of carbon dioxide with organic molecules can be categorized two classes: i) reaction with carbon-carbon bond formation to produce carboxylic acids and ii) reaction with carbon-heteroatom bond formation such as reaction with an oxygen or nitrogen atom to produce carbonates or carbamates as shown in Scheme 5.



Scheme 5

The former is generally called “carboxylation” reaction and is one of the best ways to synthesize carboxylic acid. However, carbon dioxide is also known as a stable and unreactive molecule. Therefore, reaction of carbon dioxide with organic compounds often needs severe reaction conditions including high temperature, high pressure, and highly basic conditions such as reaction with a Grignard reagent,[22] Kolbe-Schmidt reaction,[23] and synthesis of carboxylic acids or esters via metallacycles.[24] Some of the pioneering studies on fixation of carbon dioxide to organic compounds under neutral and mild conditions were carried out in the field of electrochemistry, and an electrochemical method contributed greatly to the development of a carboxylation reaction in the past. Several successful results for

electrochemical fixation of carbon dioxide are introduced in the next section, section 1-3. Recently, several conventional methods for carboxylation, especially transition metal-catalyzed reactions, under mild reaction conditions have been developed and reviewed.[25] Fixation of carbon dioxide proceeds efficiently using a transition metal catalyst under mild conditions to give carboxylic acid in good to excellent yield. However, some of the transition metals used for fixation of carbon dioxide are rare metals and cannot always be supplied stably. Transition metal catalysts and some phosphine ligands are expensive, though only catalytic amounts are used in the reaction. Therefore, electrochemical fixation of carbon dioxide has an important role as a complementary method to fixation of carbon dioxide using a transition metal catalyst, and its development is still desirable as an alternative method for transition metal-catalyzed fixation of carbon dioxide.

On the other hand, a cyanide ion, such as KCN or NaCN, and carbon monoxide (CO) are also effective C1 carbon sources as well as carbon dioxide in conventional methods for synthesis of a nitrile and ester, which are the precursors of carboxylic acid and are readily converted to carboxylic acid by hydrolysis. However, these C1 reagents are unfortunately toxic, and from the viewpoint of green and sustainable chemistry, the use of these reagents is unfavorable.

Finally, abundant, economical, non-toxic and environmentally benign carbon dioxide is the best C1 chemical reagent for organic synthesis from the viewpoint of green and sustainable chemistry and reuse of a carbon source. Consequently, research and development of its use and application in organic synthesis, especially an efficient fixation method, as a carbon source is still desirable.

1-3 Electroorganic synthesis and electrochemical fixation of carbon dioxide

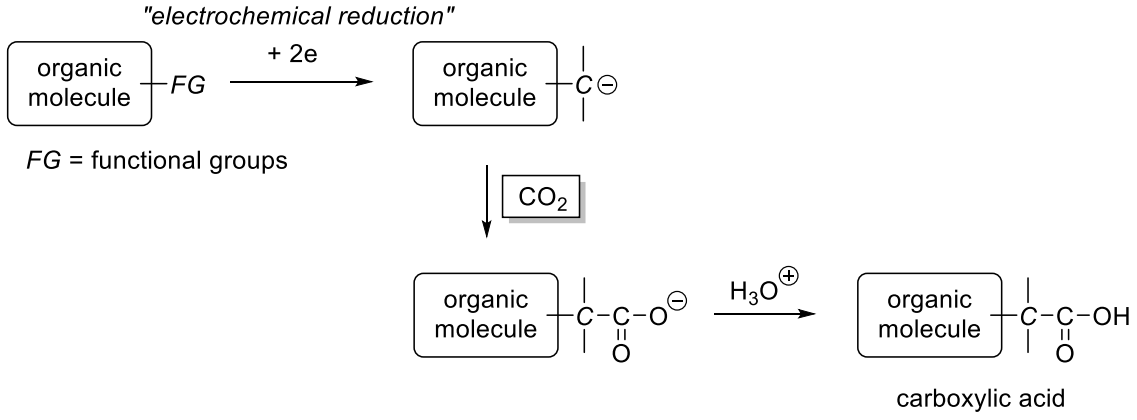
Electrochemical transformation of organic compounds using both anodic (oxidation) and/or cathodic (reduction) reactions has a long history. In 1834, Kolbe reported oxidative decarboxylative dimerization of carboxylic acids with carbon-carbon bond forming reaction, so-called Kolbe reaction.[26] Several electrochemical oxidation and/or reduction techniques were developed in industry from 1920 to 1940. For instance, electrochemical hydrodimerization of acrylonitrile to produce adiponitrile, which is well known as an important chemical in industry, was found by Manuel M. Baizer in 1964. Since then, more attention has been paid by many organic chemists to organic transformations using electrochemical techniques, and many electrochemical transformations of organic compounds have been developed.[7,27]

The features and advantages of electrochemical organic reaction in synthetic chemistry are as follows.

1) Various activated species such as radicals, anions, cations, and ion radicals can be generated by direct/indirect electron transfer between the electrode and the substrate.
2) A target activated species can be generated selectively by choosing the potential of the electrode.
3) Progress of the reaction can be easily controlled by changing the amount of current and quantity of electricity.
4) Reaction proceeds efficiently even under almost neutral and mild conditions.
5) Control of the initiation, interruption, and termination of the reaction is easy.
6) Analysis of the reaction mechanism depending on the electrochemical technique is easy.
7) Scale-up is easy because the reaction proceeds at room temperature and atmospheric pressure.
8) Oxidation or reduction reaction can be achieved without oxidants such as heavy metal reagents or reducing agents such as metal hydrides.

As mentioned above, electrochemical transformation of organic compounds has these features and advantages and proceeds efficiently even under neutral and mild conditions as a clean process. Therefore, it is a very useful and powerful method and is of great interest as a transformation method for organic synthesis.

When electrochemical reduction of organic molecules is carried out in the presence of carbon dioxide, fixation of carbon dioxide to organic molecules would proceed. As described in the previous section, electrochemical fixation of carbon dioxide can be classified into two categories. One category is fixation with a carbon-carbon bond formation between carbon dioxide and organic molecules to yield carboxylic acid. Most of the reports on electrochemical fixation of carbon dioxide are involve in this category and consequently, electrochemical fixation of carbon dioxide yielding carboxylic acid is often called "electrochemical carboxylation" or "electrocarboxylation" (Scheme 6). The other category is fixation of carbon dioxide with a carbon-heteroatom bond formation between a carbon of CO_2 and a heteroatom, such as an oxygen or nitrogen atom, in organic molecules. As heteroatom sources, alcohol and amine are used for this type of fixation to form carbonate and carbamate ions (-X-CO_2^-), respectively. Since the resulting carbonic acid and carbamic acid cannot generally be isolated due to their rapid decarboxylation, they are obtained and isolated as their esters, carbonate and carbamate, respectively, by reaction of the forming carbonate or carbamate ions with appropriate electrophiles, such as alkyl halides, *in situ* after the fixation of carbon dioxide.



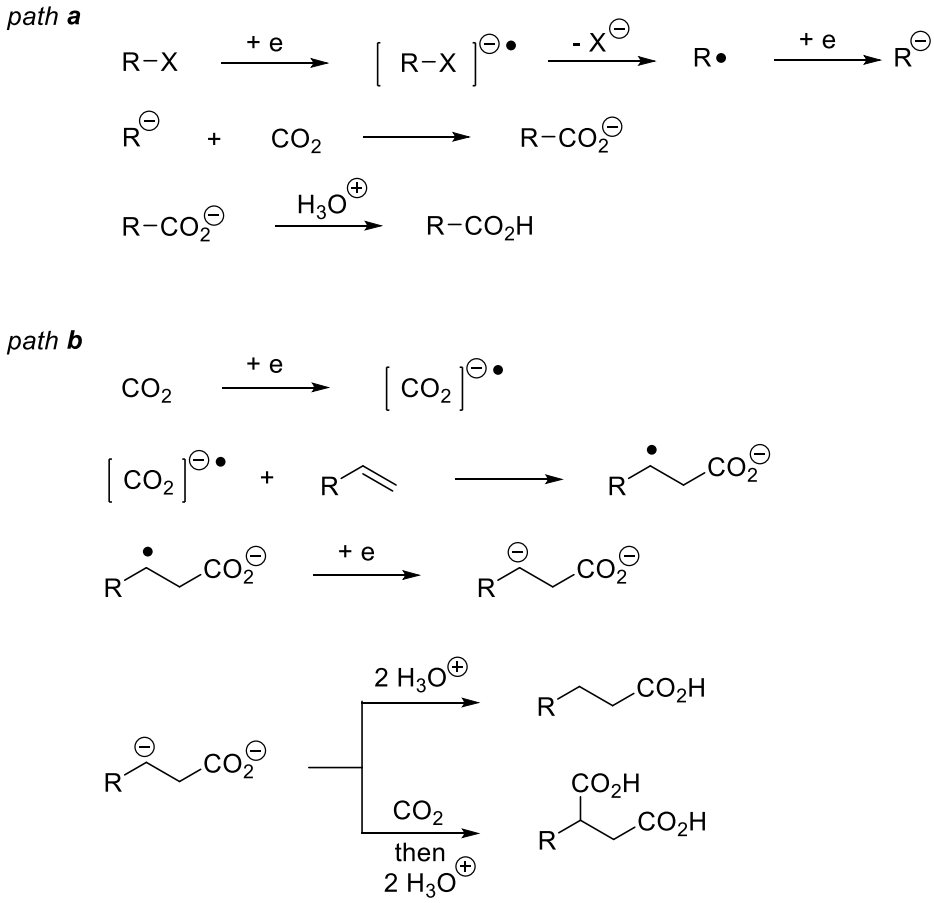
Scheme 6

Carbon dioxide used as a source of a carboxyl group is not only abundant and economical but also non-toxic and attractive as an environmentally benign C1 chemical reagent for organic synthesis, as previously described. By using an electrochemical method, efficient fixation of carbon dioxide in appropriate organic molecules can be achieved even under an atmospheric pressure of carbon dioxide under quite mild and almost neutral conditions. Electrochemical reduction of organic molecules in the presence of carbon dioxide using magnesium or aluminum as a sacrificial anode in a one-compartment electrochemical cell has been found to be the most convenient, useful and effective method for efficient fixation of carbon dioxide to yield carboxylic acid in high yields.[28,29] Carbon dioxide is also used for synthesizing carboxylic acid by conventional methods as mentioned in the previous section. For example, reaction of a Grignard reagent or organolithium reagent with carbon dioxide in a flammable organic solvent, such as ether or tetrahydrofuran, gives carboxylic acid. The reaction, however, proceeds under highly basic conditions, and there should be a limitation of usable functional groups in the reagents themselves because of the highly reactive reagents, and special caution in their handling is needed.

An electrochemical method is an environmentally benign method, and there is no need to use toxic reagents and flammable solvents with special caution in electrochemical fixation of carbon dioxide to yield carboxylic acid in high yields. Although, as mentioned earlier, transition metal-catalyzed fixation of carbon dioxide in organic and organometallic compounds has recently been developed,[25] an electrochemical method can achieve efficient fixation of carbon dioxide without such expensive and air-sensitive rare-metal catalysts by using electrons as an essential reagent, and electrochemical carboxylation stands as a complementary method to transition metal-catalyzed fixation of carbon dioxide.

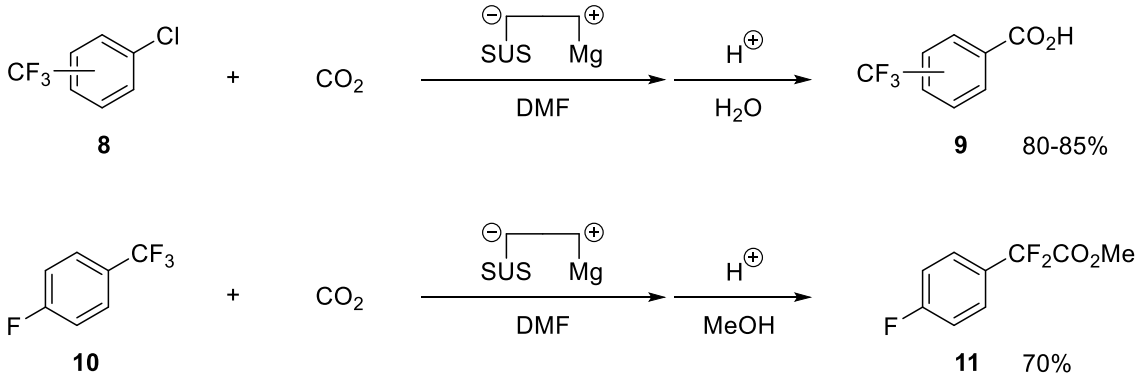
Carbon-carbon bond formation between carbon dioxide and organic molecules in electrochemical reduction is thought to proceed via two different pathways. When the reduction potential of an organic substrate is more positive than that of carbon dioxide, electrochemical reduction of the organic substrate predominantly occurs to generate anionic species. Nucleophilic attack of the resulting anionic species on carbon dioxide yields carboxylic acid (path ***a*** in Scheme 7). On the other hand, when the reduction potential of the organic substrate is more negative than that of carbon dioxide, one-electron reduction of carbon dioxide predominantly occurs to generate the radical anion of carbon dioxide, which

reacts with organic substrates, such as alkenes, to yield the corresponding mono- and/or dicarboxylic acids (path ***b*** in Scheme 7).



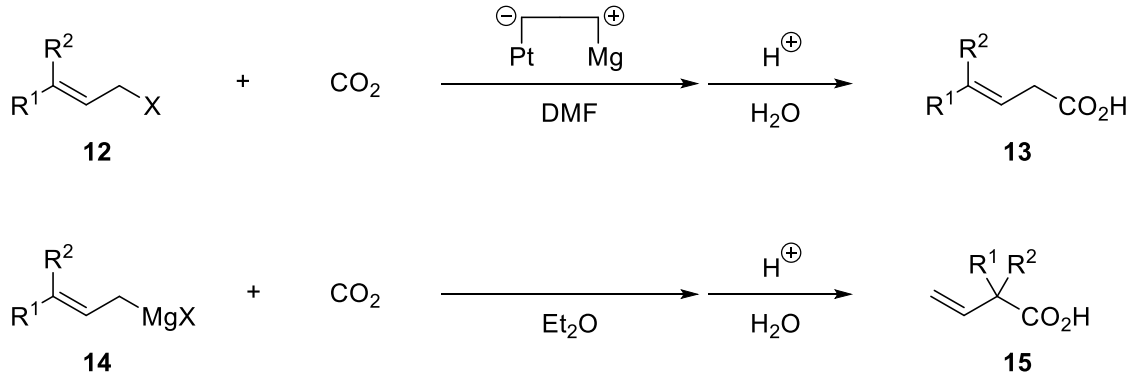
Scheme 7

By using an electrochemical method, efficient fixation of carbon dioxide in various kinds of organic molecules has been successfully carried out with carbon-carbon bond formation to give carboxylic acids. For instance, halides **8** and **10** could selectively be carboxylated by an electrochemical method to give fluorine-containing carboxylic acids **9** and ester **11**, respectively, in high yields (Scheme 8).[30,31] Generally, synthesis of these carboxylic acids is difficult by a conventional method using organometallic reagents. Therefore, it is obvious that an electrochemical method is very useful for synthesis of these carboxylic acids.



Scheme 8

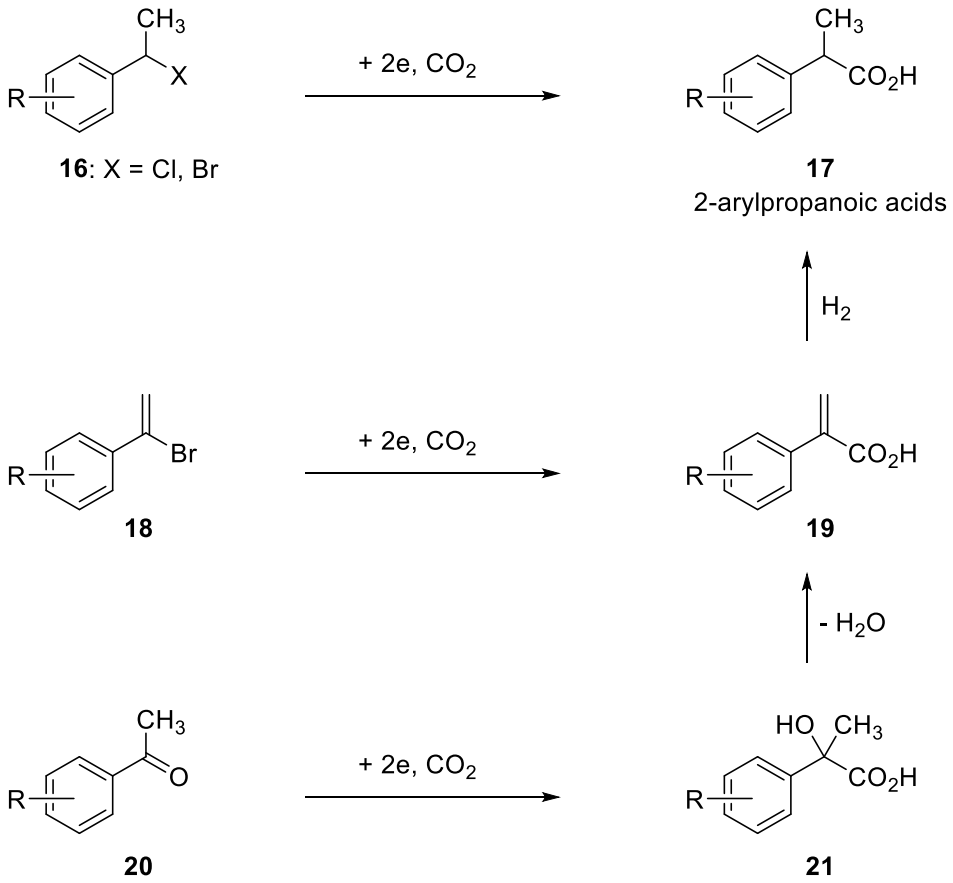
Substituted allylic halide **12** was reported to be carboxylated at the α-position regioselectively by electrochemical reduction of carbon dioxide to give unsaturated carboxylic acid **13**, while regioisomer **15** was obtained as a sole product by conventional reaction of the corresponding Grignard reagent **14**, derived from halide **12**, with carbon dioxide at the γ-position via a six-membered transition state (Scheme 9).[32]



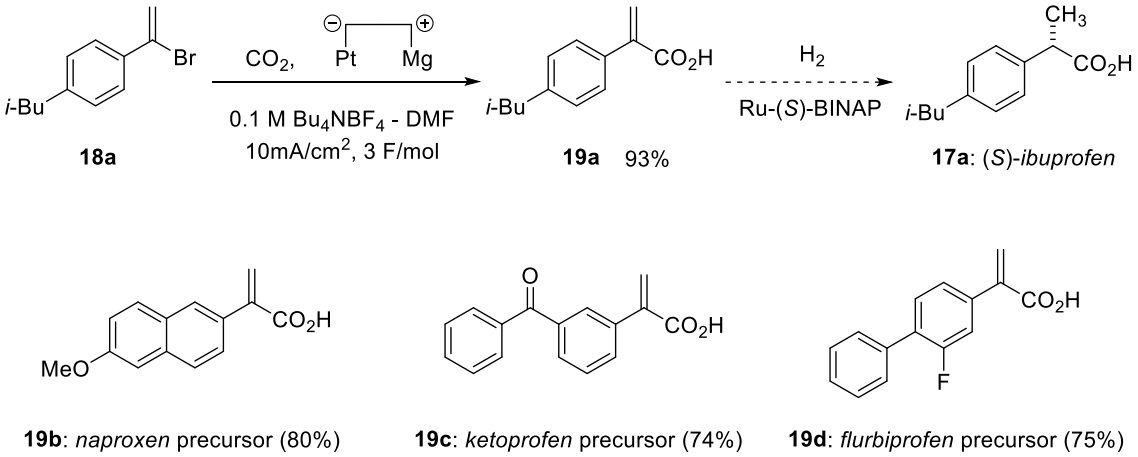
Scheme 9

One notable synthetic application of electrochemical fixation of carbon dioxide is synthesis of 2-arylpropanoic acids, non-steroidal anti-inflammatory drugs (NSAIDs), and their useful precursors (Scheme 10). Electrochemical carboxylations of benzyl halide **16** give 2-arylpropanoic acid **17**. Many successful syntheses of NSAIDs, such as ibuprofen and naproxen, by this type of reaction have been reported[28a,29a,33-44]. On the other hand, chiral 2-

arylpropanoic acid **17** can be readily synthesized by electrochemical carboxylation of vinyl bromide **18**[42,45] followed by enantioselective hydrogenation. For example, electrochemical carboxylation of vinyl bromide **18a** yields α,β-unsaturated carboxylic acid **19a** in 93% yield,[45] which can be readily transformed into (*S*)-ibuprofen **17a** by enantioselective hydrogenation[46] (Scheme 11). The precursors of naproxen (**19b**), ketoprofen (**19c**), and flurbiprofen (**19c**) are also synthesized in high yields by similar electrochemical carboxylation. Consequently, synthesis of chiral NSAIDs can be readily achieved from vinyl bromides **18** and carbon dioxide only in two steps by an electrochemical method (Scheme 11). α,β-Unsaturated carboxylic acid **19** can also be obtained from aryl methyl ketone **20** by electrochemical carboxylation followed by dehydration of the resulting α-hydroxycarboxylic acid **21**. Successful syntheses of **21** as precursors of chiral NSAIDs have been reported by using this type of reaction[42-44,47-48] (Scheme 10).



Scheme 10

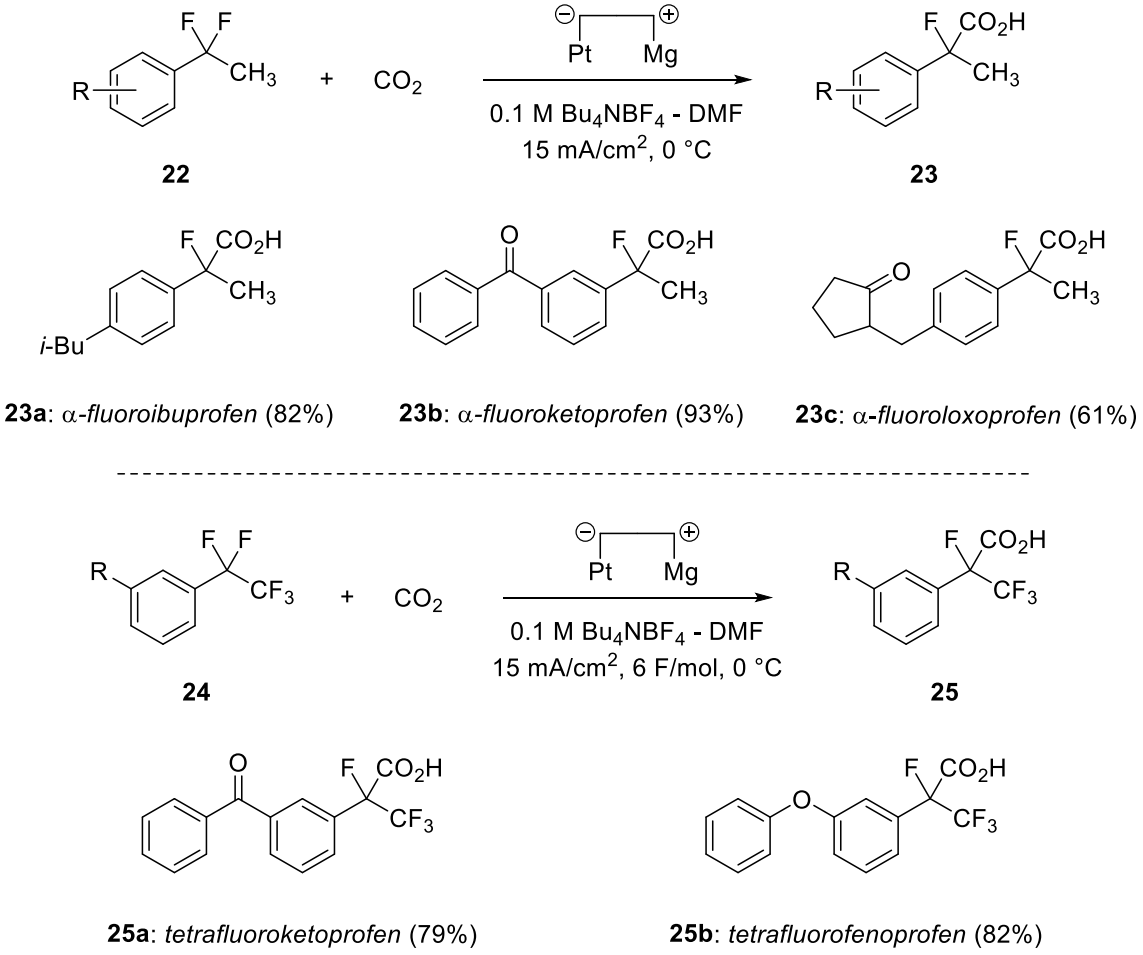


18a **19a** 93% **17a**: (*S*)-*ibuprofen*

19b: *naproxen* precursor (80%) **19c**: *ketoprofen* precursor (74%) **19d**: *flurbiprofen* precursor (75%)

Scheme 11

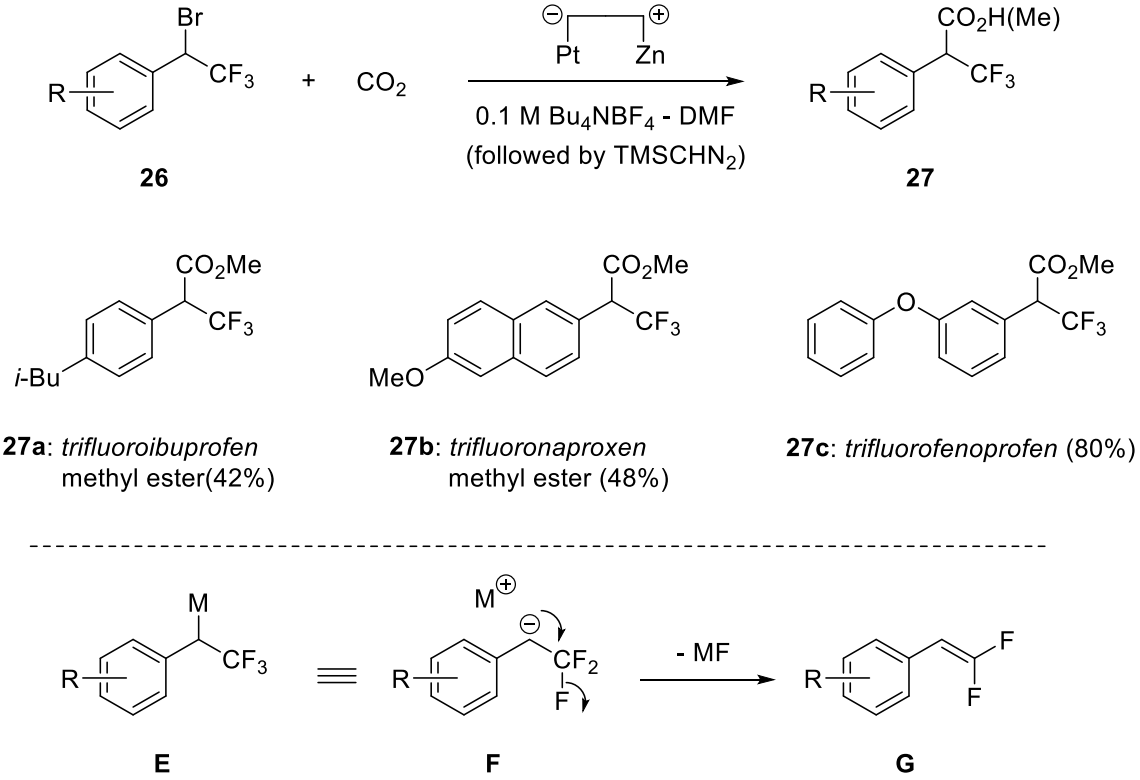
It is noteworthy that syntheses of fluorinated analogues of NSAIDs can also be achieved by electrochemical fixation of carbon dioxide.[41] For example, electrochemical reduction of α,α-difluoroethylarenes **22** in the presence of carbon dioxide by using a Pt cathode and an Mg anode resulted in the reductive cleavage of one C–F bond followed by fixation of carbon dioxide at the benzylic position to give 2-fluoro-2-arylpropanoic acids, α-fluorinated NSAIDs, **23** in good yields (Scheme 12). α-Fluoroibuprofen (**23a**), α-fluoroketoprofen (**23b**), α-fluoroloxoprofen (**23c**), and other α-fluorinated NSAIDs are successfully synthesized in high yields by similar electrochemical carboxylation.[41a] Synthesis of tetrafluorinated ketoprofen (**25a**) and fenoprofen (**25b**) is also accomplished using pentafluoroethylarenes **24** as starting materials by similar electrochemical carboxylation[41b] (Scheme 12).



Scheme 12

Electrochemical fixation of carbon dioxide is also an effective and powerful tool for synthesis of β,β,β-trifluoro-derivatives of ibuprofen, naproxen and related NSAIDs.[41c] Electrochemical reduction of benzyl bromide **26**, having a trifluoromethyl group at the benzylic position, in the presence of carbon dioxide by using zinc, instead of magnesium, as an anode results in efficient fixation of carbon dioxide to give the corresponding carboxylated product **27** in good yields. Trifluoroibuprofen methyl ester (**27a**), trifluoronaproxen methyl ester (**27b**) and trifluorofenoprofen (**27c**) are successfully synthesized in moderate to good yields by the present electrochemical method (Scheme 13). Synthesis of **E** is quite difficult by conventional chemical fixation of carbon dioxide using organometallic reagents. Since β,β,β-trifluoroethyl anions such as **F** are mostly known to release a fluoride ion spontaneously to give difluoroalkenes such as **G**,[41c,49] it is difficult to prepare corresponding

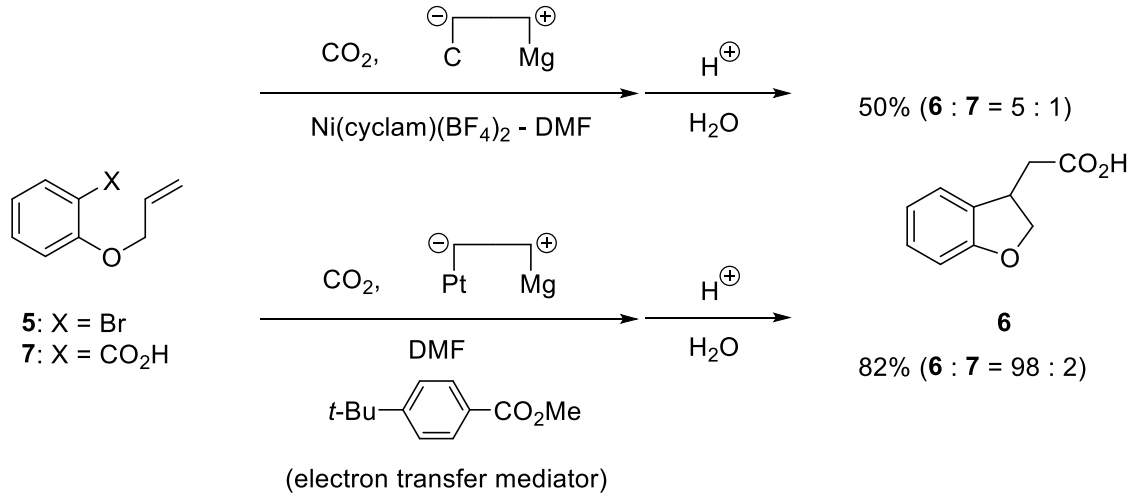
organometallic reagents such as **E** by conventional chemical methods.



Scheme 13

These successful syntheses of fluorinated NSAIDs **23**, **25**, and **27** strongly indicate the usefulness, significance, advantage and convenience of an electrochemical fixation of carbon dioxide for synthesis of carboxylic acids.

As described in Chapter 1-1, carboxylation can also take place with other electrochemically induced chemical reactions such as radical cyclization.[19-20,50] For example, electrochemical carboxylation of 2-allyloxybromobenzene (**5**) in the presence of a nickel catalyst or electron transfer mediator results in cyclization followed by fixation of carbon dioxide to give carboxylic acid **6** in high selectivity toward direct-carboxylation product **7** (See Scheme 2, reproduced below as Scheme 14).[19-20] However, only a few examples of sequential electrochemical reaction, especially radical cyclization, – carboxylation have been reported.



Scheme 14 (identical to Scheme 2)

1-4 This study

In this dissertation, the author describes the new development of sequential radical cyclization – fixation of carbon dioxide reaction by electrochemical reduction of aryl and vinyl bromides.

This dissertation consists of five chapters.

A general introduction of the dissertation is presented in Chapter 1.

In Chapter 2, the results of electrochemical reduction of aryl bromides having terminal alkyne as a radical acceptor in the presence of carbon dioxide are described. Constant current electrolysis of 2-(2-propynyloxy)bromobenzenes in DMF using an undivided cell equipped with a Pt cathode and an Mg anode in the presence of carbon dioxide and an electron transfer mediator, methyl 4-*tert*-butylbenzoate, resulted in aryl radical cyclization with a carbon-carbon triple bond followed by fixation of two molecules of carbon dioxide to give 2,2-ring-fused succinic acid derivatives in moderate to good yields. Dihydrobenzofuran, indoline, dihydrobenzothiophene, and indane as well as tetrahydropyran skeletons were successfully constructed by aryl radical cyclization, and unique tandem carboxylation successively occurred to produce succinic acids. One of the resulting succinic acid derivatives, 3-carboxy-2,3-dihydrobenzofuran-3-ylacetic acid, was successfully applied to the synthesis of a novel spiro compound consisting of 2,3-dihydrobenzofuran and γ-butyrolactone at each C3 position in two steps in high yield.

In Chapter 3, results for efficient generation of a vinyl radical and its radical cyclization followed by fixation of carbon dioxide are described. Constant current electrolysis of vinyl bromide in DMF containing 0.1 M Bu_4NBF_4 using an undivided cell equipped with a platinum plate cathode and a magnesium rod anode in the presence of an electron transfer mediator, methyl 4-*tert*-butylbenzoate, and carbon dioxide resulted in selective generation of a vinyl radical, for which cyclization followed by fixation of carbon dioxide with a carbon-carbon bond formation gave γ,δ-unsaturated carbo- and heterocycle carboxylic acids in moderate to good yields. A vinyl radical could be selectively generated under the electrolysis conditions, and the following reaction of anion species, generated by one-electron reduction of the resulting cyclized radical, with carbon dioxide took place efficiently. These results and cyclic voltammetry indicate that methyl 4-*tert*-butylbenzoate plays an important role in the

generation of vinyl radicals from vinyl bromides. The resulting cyclized γ,δ-unsaturated carboxylic acid was successfully applied to stepwise and direct iodo-lactonization to give the corresponding bicycle γ-lactones in good yields.

In Chapter 4, electrochemical studies on the generation of aryl and vinyl radicals by electrochemical reduction of the corresponding bromides in the presence of methyl 4-*tert*-butylbenzoate and the reaction mechanism of sequential radical cyclization – fixation of carbon dioxide are described. Cyclic voltammetry of methyl 4-*tert*-butylbenzoate in the absence and presence of aryl and vinyl bromides was carried out, and methyl 4-*tert*-butylbenzoate was found to act as an electron-transfer mediator in the electrochemical reduction and to be essential for efficient generation of aryl and vinyl radicals from the corresponding bromides. From these results, the reaction mechanism of sequential radical cyclization – fixation of carbon dioxide described in Chapters 2 and 3 is proposed.

The conclusion of this dissertation is given in Chapter 5.

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Chapter 2

Aryl Radical Cyclization to Terminal Alkynes Followed by Fixation of Two Molecules of Carbon Dioxide by Methyl 4-*tert*-Butylbenzoate-mediated Electrochemical Reduction of 2-(2-Propynyloxy)bromobenzenes in the Presence of Carbon Dioxide

2-1 Introduction

As described in Chapter 1, radical cyclization is a powerful tool for synthesis of carbocycles and heterocycles.[1] The combination of organic halides and Bu_3SnH with AIBN has promoted many radical cyclizations.[2] On the other hand, one-electron reduction of organic halides or related substrates can generate carbon-centered radicals and has also been used for radical cyclization as an attractive alternative to hazardous organotin reagents from the viewpoint of green chemistry. As well as the use of organic[3] or metal[4] reductants, electrochemical reduction[5-16] can be used as a reducing method for generation of carbon-centered radicals. Direct,[6,7] metal complex-catalyzed[8-11] or mediated[12-16] electrochemical reduction of organic halides and diazonium salts can generate carbon-centered radicals without any tin reagents, and thus-generated carbon-centered radicals have been successfully applied to cyclization reactions yielding carbo- and heterocycles. Under reductive electron transfer conditions, a termination step involves one-electron reduction of the resulting cyclized radical, and a reaction of anion species is dominant as a termination reaction providing final products. Although anion species are known to induce various organic transformations, protonation of the resulting anion species yielding protonated cyclized products is the sole reaction in most of the termination steps in these reductive radical reactions with electron transfer. Several examples of the use of the resulting anion for further carbon-carbon bond-forming reaction under reductive electron transfer conditions have been reported.[17,18] There are, however, few reports on sequential radical cyclization-anionic carbon-carbon bond formation in electroreductive generation of carbon radicals. Senboku and co-workers recently succeeded in efficient generation of aryl radicals from 2-allyloxybromobenzenes by electrochemical reduction using methyl 4-*tert*-butylbenzoate as an electron transfer mediator. Thus-generated aryl radicals were also found to undergo radical cyclization with alkene, and after further one-electron reduction of the resulting cyclized radical, the generated anion species efficiently reacted with carbon dioxide to give 2,3-dihydrobenzofuran-3-ylacetic acids as sequential aryl radical cyclization-anionic carbon-carbon bond-forming reaction products in high selectivities and good yields.[19] In the course of efforts of the group to apply electrochemistry to organic synthesis,[20] a unique electrochemical reaction in aryl radical cyclization using a carbon-carbon triple bond as an

aryl radical acceptor could recently be found. When 2-(2-propynyloxy)bromobenzene was similarly electrolyzed using methyl 4-*tert*-butylbenzoate as an electron transfer mediator in the presence of carbon dioxide, aryl radical cyclization followed by fixation of two molecules of carbon dioxide took place efficiently to give a cyclized dicarboxylic acid, 3-carboxy-2,3-dihydrobenzofuran-3-ylacetic acid. This unique reaction involves three carbon-carbon bond-forming reactions, aryl radical cyclization and fixation of two molecules of carbon dioxide, in one step, and succinic acid derivatives could be obtained in up to 71% isolated yield. Although nickel-catalyzed electroreductive cyclization followed by carboxylation of 2-(2-propynyloxy)bromobenzene providing the same succinic acid as a mixture of three cyclized carboxylic acids was also reported by Olivero and Duñach,[21] only one example was shown and no detailed investigation has been reported. In chapter, the results of electrochemical aryl radical cyclization followed by tandem carboxylation involving fixation of two molecules of carbon dioxide to obtain succinic acid derivatives and one synthetic application of the resulting succinic acid to a novel spirolactone in two steps in high yields are described.

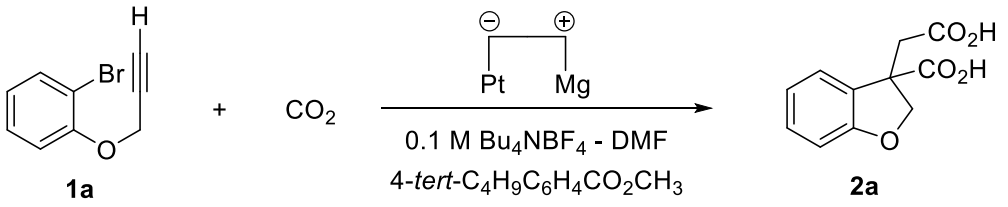
2-2 Results and discussion of aryl radical cyclization followed by fixation of two molecules of carbon dioxide

2-2-1 Screening of reaction conditions

Screening of reaction conditions using 2-(2-propynyloxy)bromobenzene (**1a**) as a substrate was carried out, and the results are shown in Table 1. Constant current electrolysis (current density of 20 mA/cm^2) of a DMF solution of **1a** containing 0.1 M Bu_4NBF_4 was carried out at 0 °C by using a one-compartment cell equipped with a platinum plate cathode (2 x 2 cm^2) and a magnesium rod anode (3 mmϕ) in the presence of 0.5 equiv. of methyl 4-*tert*-butylbenzoate as an electron transfer mediator[19] with bubbling of carbon dioxide through the solution. After supplying 4 F/mol of electricity, conversion of **1a** reached 79% by ^{1}H NMR, and 3-carboxy-2,3-dihydro-3-benzofuranacetic acid (**2a**) was obtained in 45% ^{1}H NMR yield (Entry 1). In Entries 2-4, effects of temperature were examined, and electrolysis at –10 °C gave a better yield, 51% (Entry 3). Effects of current density were also investigated in Entries 3, 5 and 6. While the yield of **2a** slightly decreased to 48% with electrolysis at a current density of 15 mA/cm^2, a similar yield based on reacted **1a** was obtained and unidentified byproducts decreased in ^{1}H NMR analysis of the crude product under the conditions in Entry 5. When 6 F/mol of electricity was supplied in electrolysis at 15 mA/cm^2 and at –10 °C, the yield of **2a** increased to 55% (Entry 7). However, an efficient current could not be obtained when further electricity was supplied under these conditions. A decrease of current density to 5 mA/cm^2 in electrolysis at –10 °C solved the problem and resulted in an increase in the yield of **2a** to 62% with 6 F/mol of electricity (Entry 8). Finally, in electrolysis at 5 mA/cm^2 with 10 F/mol of electricity at –10 °C, dicarboxylic acid **2a** was obtained in 71% ^{1}H NMR yield and in 62% isolated yield after purification by silica gel column chromatography (Entry 9). Electrolysis in the absence of methyl 4-*tert*-butylbenzoate, on the other hand, gave **2a** in 32% yield along with benzoic acid derivative in 32% ^{1}H NMR yield (Entry 10). Use of acetonitrile, instead of DMF, decreased the ^{1}H NMR yield of **2a** to 40% and unidentified byproducts were detected in ^{1}H NMR (Entry 11). When a zinc plate (ca. 1.5 x 2 cm^2) was used, instead of a magnesium rod, as an anode, only 8 F/mol of electricity could be passed to provide a complex mixture (Entry 12). In the absence of carbon dioxide, similar electrolysis under the conditions in Entry 9 only gave a complex mixture (Entry 13). It was

thought that **2a** was produced by the expected radical cyclization followed by fixation of two molecules of carbon dioxide. However, **2a** was also obtained as a major product even when 2 F/mol of electricity was supplied.

Table 1



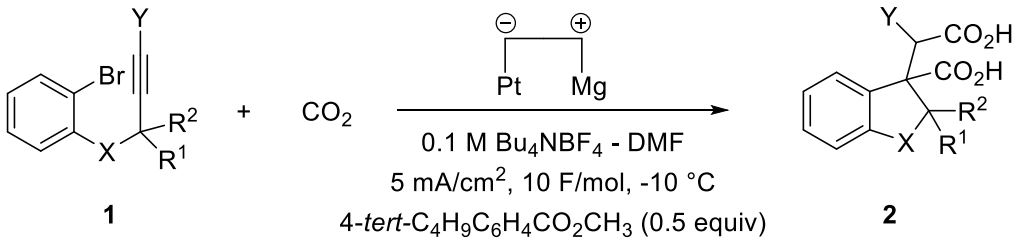
Entry	Current density [mA/cm^{2}]	Temperature [°C]	Electricity [F/mol]	Conversion of **1a** [%][a)]	Yield of **2a** [%][b)]
1	20	0	4	79	45 (57)
2	20	20	4	82	42 (51)
3	20	-10	4	80	51 (64)
4	20	-20	4	70	42 (60)
5	15	-10	4	75	48 (65)
6	10	-10	4	73	46 (63)
7	15	-10	6	80	55 (69)
8	5	-10	6	81	62 (77)
9	5	-10	10	91	71 (78) [62]
10[c)]	5	-10	6	89	32 (36)[d)]
11[e)]	5	-10	10	96	40 (42)
12[f)]	5	-10	8	---	---
13[g)]	5	-10	10	---	---

a) Conversion of **1a** was determined by ^{1}H NMR using 1,4-dinitrobenzene as an internal standard.
b) Yield of **2a** was determined by ^{1}H NMR using 1,4-dinitrobenzene as an internal standard.
The yield based on reacted **1a** and isolated yield are shown in parenthesis and bracket, respectively.
c) Electrolysis was carried out in the absence of 4-*tert*-$C_4H_9C_6H_4CO_2CH_3$.
d) Direct carboxylation product, 2-(2-propynyloxy)benzoic acid, was obtained in 32% ^{1}H NMR yield.
e) Instead of DMF, acetonitrile was used as a solvent.
f) A zinc plate (ca. 1.5 x 2 cm^{2}), instead of a magnesium rod, was used as an anode.
g) Electrolysis was carried out in the absence of carbon dioxide under nitrogen atmosphere.

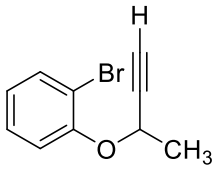
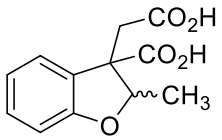
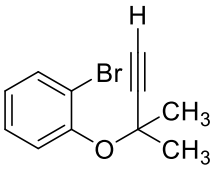
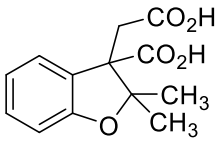
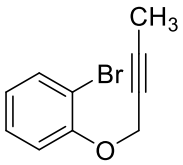
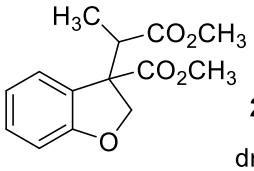
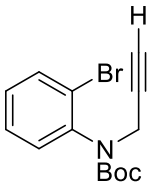
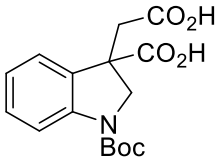
2-2-2 Substrate scope for aryl radical cyclization followed by fixation of two molecules of carbon dioxide

Substrate scope was investigated under the optimized conditions shown in Entry 9 in Table 1, and the results are shown in Table 2. When substrates **1b** and **1c**, having methyl groups at the α-position of the oxygen atom, were subjected to the present reaction, the corresponding cyclized dicarboxylic acids **2b** and **2c** were obtained in 62% and 55% isolated yields, respectively (Entries 1 and 2). Dicarboxylic acid **2b** was obtained as a 63:37 mixture of diastereoisomers, while the stereochemistry of them could not be determined (Entry 1). Electrolysis of 2-(2-butynyloxy)bromobenzene (**1d**) having an internal alkyne under the same conditions provided the expected dicarboxylic acid in lower yield, and the product was isolated as its dimethyl ester by treatment of the crude product with trimethylsilyldiazomethane-CH_3OH in benzene. After column chromatography on silica gel, the corresponding dimethyl ester **2d** was obtained in 39% isolated yield as a 56:44 mixture of diastereoisomers (Entry 3). Indoline, indane and dihydrobenzothiophene skeletons could also be constructed by the present radical cyclization-dicarboxylation sequence. Constant current electrolysis of N-Boc-N-(2-propynyl)-2-bromoaniline (**1e**) at 5 mA/cm^2 in the presence of 0.5 equiv. of methyl 4-*tert*-butylbenzoate with bubbling of carbon dioxide through the solution at –10 °C provided indoline dicarboxylic acid **2e** in 71% isolated yield after 10 F/mol of electricity was supplied (Entry 4). Similar electrolysis of 2-(3-butynyl)bromobenzene (**1f**) gave 1-carboxy-2,3-dihydro-1H-inden-1-acetic acid (**2f**) in 30% isolated yield (Entry 5). 3-Carboxy-2,3-dihydrobenzo[b]thiophen-3-ylacetic acid (**2g**) was also obtained by electrolysis of **1g** in 38% yield (Entry 6). Construction of a six-membered ring followed by fixation of two molecules of carbon dioxide was also achieved when 2-(3-butynyloxy)bromobenzene (**1h**) was used as a substrate. 4-Carboxy-3,4-dihydro-2H-1-benzopyran-4-acetic acid (**2h**) was afforded in 51% isolated yield (Entry 7).

Table 2



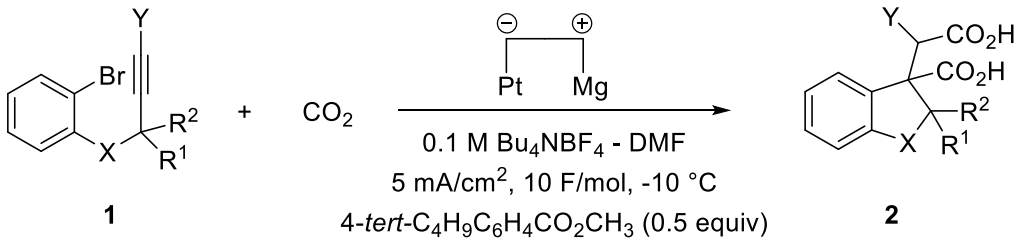
1 **2**

Entry	Substrate and conversion	Product and isolated yield
1	 **1b**: 87%	 **2b**: 62% dr[a] = 63 : 37
2	 **1c**: 87%	 **2c**: 55%
3[b]	 **1d**: 93%	 **2d**: 39% dr[a] = 56 : 44
4	 **1e**: 87%	 **2e**: 71%

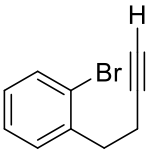
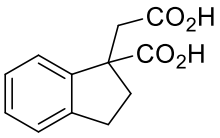
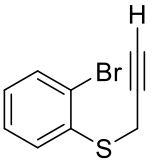
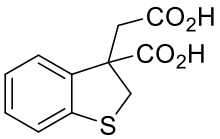
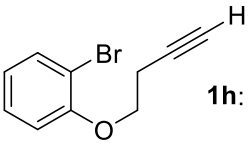
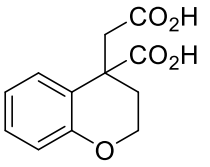
a) Diastereomeric ratio is shown as dr, which was determined by ^{1}H NMR.

b) Diester was isolated after treatment of the crude diacid with $TMSCHN_2$-CH_3OH in benzene.

Table 2 (continued)



1 **2**

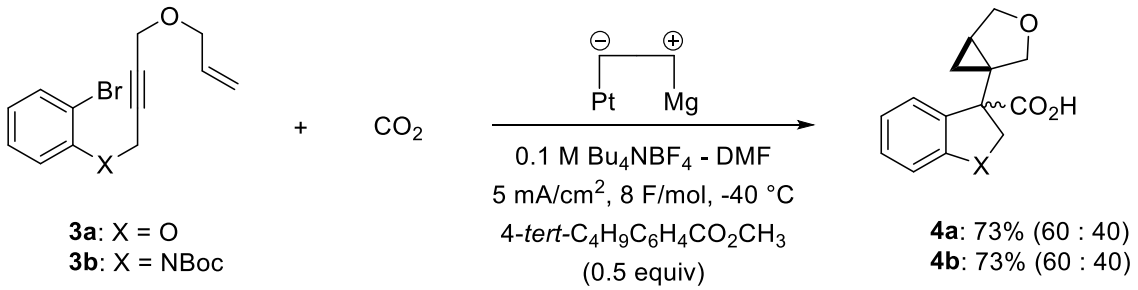
Entry	Substrate and conversion	Product and isolated yield
5	 **1f**: 84%	 **2f**: 30%
6	 **1g**: 78%	 **2g**: 38%
7[b)]	 **1h**: 91%	 **2h**: 51%

a) Diastereomeric ratio is shown as dr, which was determined by ^{1}H NMR.
b) Diester was isolated after treatment of the crude diacid with $TMSCHN_2$-CH_3OH in benzene.

2-2-3 Aryl radical cyclization with internal alkyne

In relation to the results of electrolysis of **1d** having internal alkyne as a radical acceptor (Entry 3 in Table 2), we tried electrolysis of **3** having an ene-yne unit to obtain some information about reaction pathways. When electrolysis of **3a** was carried out under the optimized conditions shown in Table 2, monocarboxylic acid **4a** was obtained in 55% isolated yield as a 59/41 mixture of diastereoisomers. After several attempts to improve the yield, **4a** could be obtained from **3a** in 73% isolated yield as a 60/40 mixture of diastereoisomers under the conditions shown in Scheme 1. Although diastereoisomers, **4a**-major and **4a**-minor, could fortunately be separated by recrystallization, stereochemistry of the isomers could

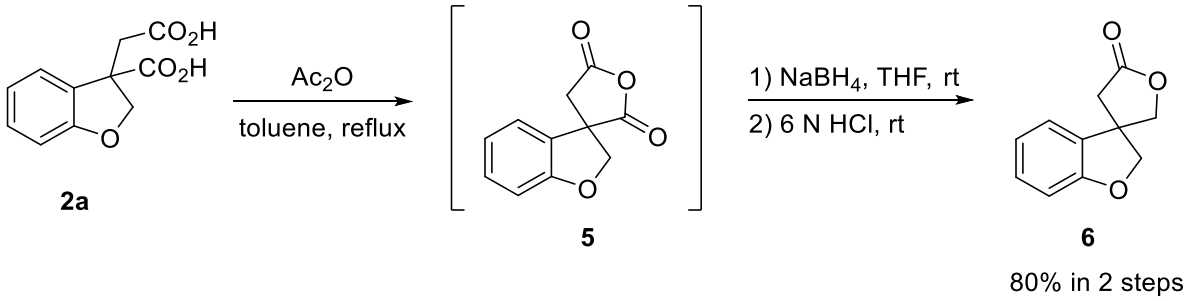
unfortunately not be determined by spectroscopic analyses using the NOESY technique. Indoline derivative **4b** was also obtained in 73% isolated yield as a 60/40 mixture of diastereoisomers by similar electrolysis of **3b** (Scheme 1). Monocarboxylic acid **4** would be produced through 5-exo cyclization of the electrochemically-generated aryl radical with alkyne and sequential 5-exo and 3-exo tandem cyclization followed by one-electron reduction of the radical to the corresponding anion and fixation of carbon dioxide at the benzylic position. It is noteworthy that a four carbon-carbon bond-forming reaction took place in one step, and the high yield of the product **4**, 73%, indicates that all of these processes proceeded efficiently, especially aryl radical cyclization with internal alkyne as the first step. These results indicate that the aryl radical cyclization process for internal alkyne also proceeded efficiently even in the case of 1d (Entry 3 in Table 2), and low yield of **2d** would result from processes following aryl radical cyclization.



Scheme 1

2-3 Synthetic application of the resulting succinic acid

One synthetic application of the obtained succinic acids was successfully performed and the result is shown in Scheme 2. Treatment of succinic acid **2a** with acetic anhydride in toluene under reflux gave the corresponding spiro succinic anhydride **5**. Sequential treatment of **5** with $NaBH_4$ in THF followed by 6 M HCl gave a novel spirolactone, spiro[benzofuran-3(2H),3'(2'H)-furan]-5'(4'H)-one (**6**), in two steps in 80% yield (Scheme 2). These results indicate that succinic acid derivatives **2** can be good precursors and that the present process is promising as an efficient and easy way to access a novel spirolactone skeleton such as **6**.



Scheme 2

2-4 Conclusion

In conclusion, this chapter includes a unique tandem carboxylation following aryl radical cyclization with alkyne by electrolysis of 2-(2-propynyloxy)bromobenzene derivatives **1** in the presence of carbon dioxide using methyl 4-*tert*-butylbenzoate as an electron transfer mediator. By aryl radical cyclization, dihydrobenzofuran, indoline, dihydrobenzothiophene, and indane as well as tetrahydropyran skeletons could be constructed efficiently, and subsequent tandem carboxylation afforded the corresponding 2,2-ring-fused succinic acid derivatives **2** in moderate to good yields. As one synthetic application, transformation of the resulting succinic acid derivative **2a** into a novel spirolactone skeleton was successfully performed in high yield.

2-5 Experimental

General

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a JASCO FT/IR-410 spectrometer in neat form unless otherwise stated. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in indicated solvents with a JEOL ECX400P or ECS400 FT NMR spectrometer. The chemical shifts, δ, are given in ppm with tetramethylsilane for ^{1}H and solvents for ^{13}C as references. *J* values are in Hz. Peak multiplicities were given as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. MS spectra and elemental analyses were carried out using a JEOL JMS-T100GCv or Thermo Scientific Exactive and Exacter Analytical CE440 or J-Science Lab JM10, respectively, at Instrumental Analysis Division, Equipment Management Center Creative Research Institution, Hokkaido University. Electrochemical reactions were carried out using a Constant Current Power Supply (model 5944), Metronix Corp., Tokyo. Column chromatography was carried out using Kanto Kagaku Silica gel 60N. Reagents and solvents were commercially available and were used as received without further purification.

*2-5-1 Starting materials **1** and **3***

*2-(2-Propynyloxy)bromobenzene (**1a**).*[19, 22] To a solution of 2-bromophenol (3.46 g, 20 mmol) in DMF (10 mL) were added K_2CO_3 (8.29 g, 60 mmol) and propargyl bromide (8.29 g, 24 mmol) at 0 °C, and then the mixture was stirred at rt overnight. After addition of H_2O (20 mL), the reaction mixture was extracted with ether (30 mL×3). The combined ethereal solution was washed with H_2O (30 mL×3) and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give 2-(2-propynyloxy)bromobenzene (**1a**, 4.11 g, 97%). Oil. ^{1}H NMR ($CDCl_3$): δ 7.56 (1H, dd, *J* = 7.9 and 1.6 Hz), 7.31–7.26 (1H, m), 7.07 (1H, dd, *J* = 8.3 and 1.5 Hz), 6.89 (1H, dt, *J* = 7.9 and 1.5 Hz), 4.78 (2H, d, *J* = 2.4 Hz), 2.54 (1H, t, *J* = 2.4 Hz). ^{13}C NMR ($CDCl_3$): δ 153.7, 133.3, 128.2, 122.6, 113.9, 112.1, 77.8, 76.1, 56.6.

*2-(1-Methyl-2-propynyloxy)bromobenzene (**1b**).* To a solution of DMAP (37 mg, 0.3 mmol) in CH_2Cl_2 (3 mL) were successively added aqueous 3-butyn-2-ol (7.5 M, 1.5 mL, 11.3 mmol),

aqueous NaOH (25%, 2 mL) and tosyl chloride (1.90 g, 10 mmol) at 0 °C, and then the mixture was stirred at rt for 2 h. After addition of H_2O (30 mL), the reaction mixture was extracted with CH_2Cl_2 (30 mL×3). Combined organic layer was washed with H_2O (50 mL×3) and then dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the corresponding 3-butyn-2-yl tosylate (1.97 g, 88%), which was used for next step without further purification. In a similar manner to preparation of **1a**, reaction of 2-bromophenol (1.21 g, 7 mmol) with K_2CO_3 (1.16 g, 8.4 mmol) and the prepared 3-butyn-2-yl tosylate (1.88 g, 8.4 mmol) in DMF (15 mL) gave 2-(1-methyl-2-propynyloxy)bromobenzene (**1b**, 1.30 g, 82%) after a similar work-up followed by column chromatography on silica gel (hexane/ethyl acetate = 20/1). Oil. ^{1}H NMR ($CDCl_3$): δ 7.55 (1H, dd, *J* = 7.8 and 1.8 Hz), 7.29–7.25 (1H, m), 7.14 (1H, dd, *J* = 8.2 and 1.4 Hz), 6.89 (1H, dt, *J* = 7.8 and 1.4 Hz), 4.78 (2H, dq, *J* = 6.8 and 1.8 Hz), 2.50 (1H, d, *J* = 1.8 Hz), 1.74 (3H, d, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 153.8, 133.3, 128.2, 122.8, 116.0, 113.0, 82.3, 74.4, 65.0, 22.0. IR: 3294, 2116, 1588, 1476, 1278, 1242, 1090, 1032, 942, 748 cm^{-1}. HRMS (EI): *m/z* 223.9834 (M^+). Calcd for $C_{10}H_9{}^{79}BrO$ 223.9837.

2-(1,1-Dimethyl-2-propynyloxy)bromobenzene ***(1c)****.* 2-(1,1-Dimethyl-2-propynyloxy)bromobenzene (**1c**) was prepared according to the reported procedure.[23] 2-Methyl-3-butyn-2-ol (1.00 g, 12 mmol) was dissolved in anhydrous CH_3CN (6 mL) and to this solution were successively added DBU (2.44 g, 16 mmol) and trifluoroacetic anhydride (2.52 g, 12 mmol) at 0 °C, and then the mixture was stirred at the same temperature for 30 min. To a solution of 2-bromophenol (1.73 g, 10 mmol) in anhydrous CH_3CN (6 mL) were successively added DBU (1.83 g, 12 mmol) and $CuCl_2 \cdot H_2O$ (1.7 mg, 0.01 mmol) at 0 °C. To this solution was dropwise added the prepared solution of 2-methyl-3-butyn-2-ol in CH_3CN for 30 min, and then the mixture was stirred at the same temperature for 5 h. After addition of 1 M hydrochloric acid (50 mL), the mixture was extracted with ethyl acetate (50 mL×3). Combined organic layer was washed with 1 M hydrochloric acid (50 mL×2) and H_2O (100 mL) successively and dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by column chromatography on silica gel (hexane/ethyl acetate = 10/1) gave 2-(1,1-dimethyl-2-propynyloxy)bromobenzene (**1c**, 1.66 g, 69%) and recovered 2-bromophenol (301 mg, 17%). Oil. ^{1}H NMR ($CDCl_3$): δ 7.62 (1H, dd, *J* = 8.2 and 1.4 Hz), 7.54 (1H, dd, *J* = 7.8 and 1.8 Hz), 7.26–7.21 (1H, m), 6.92 (1H, dt, *J* = 7.8 and 1.4 Hz), 2.60 (1H, s), 1.71 (6H, s). ^{13}C NMR

($CDCl_3$): δ 153.0, 133.4, 127.9, 124.1, 121.5, 117.1, 86.1, 74.2, 74.1, 29.6. IR: 3293, 2113, 1584, 1472, 1239, 1138, 1047, 1029, 951, 901, 753 cm^{-1}. MS (EI): *m/z* 240 [$(M+2)^+$, 3], 238 (M^+, 3), 174 (94), 172 (100). HRMS (EI): *m/z* 237.9992 (M^+). Calcd for $C_{11}H_{11}{}^{79}BrO$ 237.9993.

*2-(2-Butynyloxy)bromobenzene (**1d**).*[24] To a solution of 2-(2-propynyloxy)bromobenzene (**1a**, 2.11 g, 10 mmol) in anhydrous THF (20 mL) was added dropwise 1 M solution of NaHMDS in THF (12 mL, 12 mmol) under nitrogen atmosphere at 0 °C. After stirring for 30 min at the same temperature, iodomethane (7.10 g, 50 mmol) was added to the solution and the reaction mixture was stirred at rt overnight. Saturated aqueous NH_4Cl solution (50 mL) was added to the reaction mixture and the mixture was then extracted with ether (30 mL×3). The combined ethereal solution was washed with 100 mL of 1 M hydrochloric acid and H_2O (100 mL×3) successively and then dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by column chromatography on silica gel (hexane/ethyl acetate = 20/1) gave 2-(2-butynyloxy)bromobenzene (**1d**, 2.13 g, 97%). Oil. ^1H NMR ($CDCl_3$): δ 7.55 (1H, dd, *J* = 7.8 and 1.4 Hz), 7.30–7.26 (1H, m), 7.06 (1H, dd, *J* = 8.3 and 1.4 Hz), 6.87 (1H, dt, *J* = 7.8 and 1.4 Hz), 4.74 (2H, q, *J* = 2.3 Hz), 1.86 (3H, t, *J* = 2.3 Hz). ^{13}C NMR ($CDCl_3$): δ 154.0, 133.2, 128.2, 122.2, 113.8, 112.0, 84.2, 73.4, 57.2, 3.6.

*tert-Butyl N-(2-bromophenyl)-N-(2-propynyl)carbamate (**1e**).*[25] To a solution of 2-bromoaniline (3.43 g, 20 mmol) in THF (40 mL) was added di-*tert*-butyl dicarbonate (10.90 g, 50 mmol) and then the mixture was stirred under reflux for 3 days. To the reaction mixture was added ether (50 mL) and the organic layer was washed with saturated brine (50 mL×3) and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a crude product, which was subjected to column chromatography on silica gel (hexane/ethyl acetate = 20/1) to give *tert*-butyl *N*-(2-bromophenyl)carbamate (4.73 g, 87%). Spectral data were in good accordance with reported data.[25,26] To a suspension of NaH (722 mg, 60% oil dispersion, 18 mmol, washed with hexane before use) in anhydrous THF (60 ml) was added dropwise *tert*-butyl *N*-(2-bromophenyl)carbamate (4.08 g, 15 mmol) at 0 °C. After stirring for 30 min at rt, propargyl bromide (2.14 g, 1.2 equiv) was added and the mixture was stirred at 30 °C overnight. 60 mL of H_2O was added to the reaction mixture, which was then extracted with

ethyl acetate (50 mL×3). The combined organic layer was washed with H_2O (50 mL×3) and dried over anhydrous $MgSO_4$. After evaporation of the solvent, column chromatography on silica gel (hexane/ethyl acetate = 10/1) gave *tert*-butyl *N*-(2-bromophenyl)-*N*-(2-propynyl)carbamate (**1e**, 3.88 g, 83%). Solid, mp: 55–58°C. ^{1}H NMR ($CDCl_3$): δ 7.62 (1H, d, *J* = 7.8 Hz), 7.47–7.31 (2H, m), 7.20–7.16 (1H, m), 4.78 (0.7H, dd, *J* = 17.6 and 2.4 Hz), 4.64 (0.3H, br d, *J* = 17.8 Hz), 4.04–3.86 (1H, m), 2.23 (0.3H, br s), 2.20 (0.7H, br t, *J* = 2.4 Hz) 1.55 (2.7H, s), 1.35 (6.3H, s).^{13}C NMR ($CDCl_3$): δ 153.5 (153.3), (140.2), 139.9, (133.1), 132.8, (130.9), 130.6, (129.1), 128.9, (128.1), 127.8, 123.4, (81.3), 80.7, (79.2), 79.1, 72.3, (72.0), (39.3), 37.9, (28.2), 27.9. Chemical shifts of observed signals of a minor rotamer are shown in parentheses.

*2-(3-Butynyl)bromobenzene (**1f**)*.[27] In a round-bottom flask flushed with N_2 was placed Mg turning (1.22 g, 50 mmol) and then anhydrous ether (10 mL), a tip of iodine and a drop of 1,2-dibromoethane was successively added. After leaving the mixture at 0 °C for 30 min, a solution of allyl bromide (2.43 g, 20 mmol) in dry ether (20 mL) was added dropwise to the mixture to prepare a solution of a Grignard reagent. To a solution of 2-bromobenzyl bromide (2.49 g, 10 mmol) in anhydrous THF (20 mL) was added dropwise a prepared solution of a Grignard reagent at rt and the reaction mixture was stirred at rt overnight. 100 mL of H_2O was added to the mixture, which was then extracted with ether (50 mL×3). The combined ethereal solution was washed with H_2O (100 mL×3) and dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by column chromatography on silica gel (hexane) gave 2-(3-butenyl)bromobenzene (1.82 g, 87%). Spectral data were in good accordance with reported data.[19,22] To a solution of 2-(3-butenyl)bromobenzene (633 mg, 3 mmol) in CH_2Cl_2 (10 mL) was added dropwise bromine (480 mg, 3 mmol) at 0 °C and then the mixture was stirred at rt for 1 h. The solvent was evaporated to give a crude 2-(3,4-dibromobutyl)bromobenzene, which was dissolve in DMSO (5 mL). To this solution was slowly added a solution of *t*-BuOK (740 mg, 6.6 mmol) in DMSO (15 mL) at rt for 1h. After stirring at rt for 3 h followed by addition of 1 M hydrochloric acid (30 mL), the mixture was extracted with ether (50 mL×3). The combined ethereal solution was washed with H_2O (50 mL×3) and then dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by column chromatography on silica gel (hexane) gave 2-(3-butynyl)bromobenzene (**1f**, 438 mg,

70%). Oil. ^{1}H NMR ($CDCl_3$): δ 7.54 (1H, dd, *J* = 7.6 and 1.1 Hz), 7.29 (1H, dd, *J* = 7.6 and 2.0 Hz), 7.25 (1H, dt, *J* = 7.6 and 1.1 Hz), 7.09 (1H, dt, *J* = 7.6 and 2.0 Hz), 2.98 (2H, t, *J* = 7.5 Hz), 2.52 (2H, dt, *J* = 7.5 and 2.6 Hz), 1.99 (1H, t, *J* = 2.6 Hz). ^{13}C NMR ($CDCl_3$): δ 139.3, 132.7, 130.6, 128.0, 127.3, 124.2, 83.2, 69.2, 35.0, 18.7.

*2-(2-Propynylthio)bromobenzene (**1g**)*. In a similar manner to preparation of **1a**, reaction of 2-bromothiophenol (3.78 g, 20 mmol) with K_2CO_3 (3.32 g, 24 mmol) and propargyl bromide (2.86 g, 24 mmol) in DMF (20 mL) gave 2-(2-propynylthio)bromobenzene (**1g**, 4.01 g, 88%) after a similar work-up followed by column chromatography on silica gel (hexane/ethyl acetate = 20/1). Oil. ^{1}H NMR ($CDCl_3$): δ 7.57 (1H, dd, *J* = 7.8 and 1.4 Hz), 7.44 (1H, dd, *J* = 7.8 and 1.4 Hz), 7.32 (1H, dt, *J* = 7.8 and 1.4 Hz), 7.09 (1H, dt, *J* = 7.8 and 1.4 Hz), 3.67 (2H, d, *J* = 2.8 Hz), 2.24 (1H, t, *J* = 2.8 Hz). ^{13}C NMR ($CDCl_3$): δ 136.2, 132.8, 128.6, 127.7, 127.2, 123.4, 78.8, 71.8, 21.2. IR: 3296, 2244, 1576, 1450, 1428, 1233, 1109, 1020, 908, 742 cm^{-1}. HRMS (EI): *m/z* 225.9448 (M^+). Calcd for $C_9H_7{}^{79}Br{}^{32}S$ 225.9452.

*2-(3-Butynyloxy)bromobenzene (**1h**)*. To a solution of 3-butyn-1-ol (351 mg, 5 mmol) in anhydrous THF (20 mL) was successively added 2-bromophenol (1.04 g, 6 mmol), PPh_3 (1.57 g, 6 mmol) and diisopropyl azodicarboxylate (1.21 g, 6 mmol) at 0 °C. After stirring at rt overnight, the solvent was evaporated to give a residue, to which was added a 4/1 mixture of hexane/ether (50 mL) and the mixture was stirred at rt for 30 min. Precipitated solid, triphenylphosphine oxide, was removed by filtration and the resulting solution was evaporated to give a crude product, which was subjected to column chromatography on silica gel (hexane/ethyl acetate = 10/1 to 5/1) to give 2-(3-butynyloxy)bromobenzene (**1h**, 769 mg, 68%). Oil. ^{1}H NMR ($CDCl_3$): δ 7.54 (1H, dd, *J* = 7.8 and 2.0 Hz), 7.28–7.24 (1H, m), 6.91 (1H, dd, *J* = 8.3 and 1.4 Hz), 6.86 (1H, dt, *J* = 7.8 and 1.4 Hz), 4.16 (2H, t, *J* = 7.3 Hz), 2.75 (2H, dt, *J* = 7.3 and 2.8 Hz), 2.06 (1H, t, *J* = 2.8 Hz). ^{13}C NMR ($CDCl_3$): δ 154.7, 133.4, 128.4, 122.3, 113.6, 112.3, 79.9, 70.1, 67.1, 19.4. IR: 3297, 2123, 1587, 1480, 1279, 1248, 1054, 1031, 900, 748 cm^{-1}. MS (EI): *m/z* 226 [$(M+2)^+$, 31], 224 (M^+, 33), 187 (7), 185 (8), 174 (98), 172 (100), 145 (37), 117 (28), 53 (29). HRMS (EI): *m/z* 223.9832 (M^+). Calcd for $C_{10}H_9{}^{79}BrO$ 223.9837.

*2-[(4-Allyloxy-2-butynyl)oxy]bromobenzene (**3a**)*. To a suspension of NaH (480 mg, 60% oil dispersion, 12 mmol, washed with hexane before use) in anhydrous DMF (10 mL) was dropwise added a solution of 2-butyn-1,4-diol (1.73 g, 20 mmol) in DMF (10 mL) at 0 °C and then the mixture was stirred at 80 °C for 1 h. To this solution was dropwise added a solution of allyl bromide (1.20 g, 10 mmol) in DMF (10 mL) and then the mixture was stirred at the same temperature for 4 h. After cooling to rt, 50 mL of 1 M hydrochloric acid was added and the resulting aqueous solution was extracted with ether (50 mL×3). The combined ethereal solution was washed with saturated brine (100 mL×2) and then dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by column chromatography on silica gel (hexane/ethyl acetate = 2/1) gave 4-allyloxy-2-butyn-1-ol (705 mg, 56%). Spectral data were in good accordance with reported data.[28] To a solution of 4-allyloxy-2-butyn-1-ol (630 mg, 5 mmol) in anhydrous THF (20 mL) was successively added 2-bromophenol (1.04 g, 6 mmol), PPh_3 (1.57 g, 6 mmol) and diisopropyl azodicarboxylate (1.21 g, 6 mmol) at 0 °C. After stirring at rt overnight, the solvent was evaporated to give a residue, to which was added a 4/1 mixture of hexane/ether (50 mL) and the mixture was stirred for 30 min. Precipitated solid was removed by filtration and the resulting solution was evaporated to give a crude product, which was subjected to column chromatography on silica gel (hexane/ethyl acetate = 10/1 to 5/1) to give 2-[(4-allyloxy-2-butynyl)oxy]bromobenzene (**3a**, 1.16 g, 83%). Oil. ^{1}H NMR ($CDCl_3$): δ 7.55 (1H, dd, *J* = 7.9 and 1.6 Hz), 7.28 (1H, ddd, *J* = 8.2, 7.4 and 1.6 Hz), 7.06 (1H, dd, *J* = 8.2 and 1.4 Hz), 6.88 (1H, ddd, *J* = 7.9, 7.4 and 1.4 Hz), 5.88 (1H, ddt, *J* = 17.2, 10.4 and 5.8 Hz), 5.27 (1H, dq, *J* = 17.2 and 1.6 Hz), 5.20 (1H, ddt, *J* = 10.4, 1.6 and 1.4 Hz), 4.83 (2H, t, *J* = 1.8 Hz), 4.19 (2H, t, *J* = 1.8 Hz), 4.02 (2H, dt, *J* = 5.8 and 1.4 Hz). ^{13}C NMR ($CDCl_3$): δ 153.6, 133.5, 133.1, 128.0, 122.3, 117.5, 113.7, 111.9, 83.8, 80.4, 70.2, 56.9, 56.6. IR: 2853, 1586, 1575, 1477, 1444, 1354, 1279, 1229, 1126, 1082, 1052, 1032, 1005, 930, 749, 660 cm^{-1}. HRMS (ESI): *m/z* 302.9992 [$(M+Na)^+$]. Calcd for $C_{13}H_{13}{}^{79}BrNaO_2$ 302.9991.

*tert-Butyl N-(2-bromophenyl)-N-(4-allyloxy-2-butynyl)carbamate (**3b**)*. To a solution of 4-(allyloxy)-2-butyn-1-ol (1.88 g, 15 mmol) and Et_3N (1.88 g, 18 mmol) in CH_2Cl_2 (30 mL) was added methanesulfonyl chloride (2.06 g, 18 mmol) at 0 °C. After stirring for 2 h at the same temperature, 50 mL of H_2O was added and organic layer was separated. The resulting

aqueous solution was extracted with CH_2Cl_2 (30 mL×2) and the combined organic layer was washed with H_2O (100 mL×3). After drying over anhydrous $MgSO_4$ and evaporation of the solvent, column chromatography on silica gel (hexane/ether = 1/1) gave 4-allyloxy-2-butyn-1-ly methanesulfonate (2.45 g, 12 mmol, 83%). Spectral data were in good accordance with reported data.[29] To a suspension of NaH (480 mg, 60% oil dispersion, 12 mmol, washed with hexane before use) in anhydrous THF (20 mL) was dropwise added *tert*-butyl *N*-(2-bromophenyl)carbamate (2.72 g, 10 mmol) at 0 °C under nitrogen atmosphere and then the reaction mixture was stirred at rt for 30 min. To this solution was dropwise added 4-allyloxy-2-butynyl methanesulfonate (2.45 g, 12 mmol) and the resulting mixture was stirred at rt overnight. After addition of H_2O (100 mL), the reaction mixture was extracted with ethyl acetate (50 mL×3). The combined organic layer was washed with H_2O (100 mL×3) and then dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by column chromatography on silica gel (hexane/ethyl acetate = 4/1) gave *tert*-butyl *N*-(2-bromophenyl)-*N*-(4-allyloxy-2-butynyl)carbamate (**3b**, 3.38 g, 9 mmol, 89%). Oil. ^{1}H NMR ($CDCl_3$): δ 7.64–7.60 (1H, m), 7.46–7.30 (2H, m), 7.19–7.15 (1H, m), 5.91–5.81 (1H, m), 5.28–5.18 (2H, m), 4.78 (0.8H, br.d, *J* = 17.4 Hz), 4.66 (0.2H, br.d, *J* = 17.1 Hz), 4.16–3.92 (5H, m), 1.55 (1.8H, s), 1.35 (7.2H, s). ^{13}C NMR ($CDCl_3$): δ 153.3, (153.2), (140.1), 139.8, 133.7, (133.0), 132.7, (130.8), 130.5, (128.9), 128.7, (127.9), 127.6, 123.4, 117.3, (81.6), 81.5, (81.0), 80.4, 79.9, (79.7), 70.0, 57.0, (39.4), 38.0, (28.0), 27.8. Chemical shifts of the observed signals of a minor rotamer are shown in parentheses. IR: 1708, 1477, 1382, 1304, 1253, 1167, 1116, 1067, 1017, 935, 862, 758 cm^{-1}. MS (ESI): *m/z* 402.0675 [(M+Na)$^+$]. Calcd for $C_{18}H_{22}O_3{}^{79}BrNNa$ 402.0675.

*2-5-2 General procedure for electrochemical reaction of **1** or **3***

A solution of aryl bromide **1** or **3** (1 mmol) in anhydrous DMF (10 mL) containing Bu_4NBF_4 (0.1 M) was electrolyzed at –10 °C for **1** (at –40 °C for **3**) with a constant current (5 mA/cm^2) in the presence of methyl 4-*tert*-butylbenzoate (96 mg, 0.5 mmol) under atmospheric pressure of bubbling carbon dioxide. A test tube-like (ca. 25 mmϕ) undivided cell equipped with a Pt plate cathode (2×2 cm^2), an Mg rod anode (3 mmϕ, ca. 25 mm) and a Teflon® tube (ϕ 1 mm) for supplying carbon dioxide was used for the electrolysis. After an appropriate amount of electricity had been passed (shown in the tables and schemes), 1 M hydrochloric acid (100

mL) was added to the electrolyzed solution and then the mixture was extracted with ethyl acetate (30 mL×5). The combined organic layer was washed with saturated $NaHCO_3$ (40 mL×3) and the resulting aqueous solution was acidified with 3 M hydrochloric acid and then extracted with ethyl acetate (30 mL×5). The combined ethyl acetate solution was washed with H_2O (100 mL×3) and dried over $MgSO_4$. Evaporation of the solvent gave a crude product. i) In the reaction of **1** and **3** except **1d**; a crude product was purified by column chromatography on silica gel (hexane/ethyl acetate/acetic acid = 20/10/3 for the reaction of **1**, hexane/ethyl acetate/acetic acid = 8/2/1 for the reaction of **3**) to give pure dicarboxylic acid **2** or tandem-cyclized carboxylic acid **4**. ii) In the reaction of **1d**; a crude product was dissolved in benzene (7 mL) and CH_3OH (3 mL). To this solution was added trimethylsilyldiazomethane (0.6 M solution in hexane, 3.5 mL) at rt and the mixture was stirred at rt for 2h. Evaporation of the solvent followed by column chromatography on silica gel (hexane/ethyl acetate = 4/1) gave diester **2d** (101 mg, 39%).

*3-Carboxy-2,3-dihydrobenzo[b]furan-3-ylacetic acid (**2a**).*[19] Yield: 62%. Solid, mp: 186–187 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6): δ 7.27 (1H, dd, *J* = 7.5 and 0.8 Hz), 7.19–7.15 (1H, m), 6.89–6.83 (1H, dd, *J* = 7.5 and 0.9 Hz), 6.79 (1H, br.d, *J* = 8.1 Hz), 5.31 (1H, dd, *J* = 9.7 and 0.8 Hz), 4.46 (1H, d, *J* = 9.7 Hz), 3.39 (1H, dd, *J* = 17.4 and 0.8 Hz), 2.69 (1H, d, *J* = 17.4 Hz). ^{13}C NMR (DMSO-d_6): δ 173.8, 172.7, 159.4, 129.8, 128.7, 124.1, 120.6, 109.9, 79.2, 53.3, 42.3.

*3-Carboxy-2,3-dihydro-2-methylbenzo[b]furan-3-ylacetic acid (**2b**)*. Yield: 62% (a 60/40 mixture of isomers). Solid, mp: 176–178 °C. ^{1}H NMR (DMSO-d_6): δ 7.36 (0.6H, br.d, *J* = 7.6 Hz), 7.28 (0.4H, br.d, *J* = 7.6 Hz), 7.18–7.11 (1H, m), 6.86–6.81 (1H, m), 6.764 (0.4H, d, *J* = 7.6 Hz), 6.755 (0.6H, d, *J* = 7.6 Hz), 5.35 (0.4H, q, *J* = 6.4 Hz), 4.73 (0.6H, q, *J* = 6.4 Hz), 3.16 (0.4H, d, *J* = 18.0 Hz), 2.99 (0.6H, d, *J* = 17.2 Hz), 2.78 (0.4H, d, *J* = 18.0 Hz), 2.75 (0.6H, d, *J* = 17.2 Hz), 1.36 (1.8H, d, *J* = 6.4 Hz), 1.23 (1.2H, d, *J* = 6.4 Hz). ^{13}C NMR (DMSO-d_6): δ (173.6), (172.6), 172.4, 172.0, 159.1, (157.9), 130.3, (129.6), 128.9, (128.5), 126.1, (124.9), 120.3 (may be overlapped), (109.6), 109.4, 85.7, (83.7), 56.7, (55.3), 41.8, (37.4), 16.4, (16.3). Chemical shifts of the signals probably derived from a minor isomer are shown in parentheses. IR (KBr): 3500–2300, 1704, 1596, 1481, 1436, 1280, 1241, 1071, 751 cm^{-1}. Anal: Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 60.93; H, 5.04.

*3-Carboxy-2,3-dihydro-2,2-dimethylbenzo[b]furan-3-ylacetic acid (**2c**)*. Yield: 55%. Solid, mp: 173–175 °C. ^{1}H NMR (DMSO-d_6): δ 7.33 (1H, dd, *J* = 7.6 and 1.2 Hz), 7.09 (1H, dt, *J* = 7.6 and 1.2 Hz), 6.79 (1H, dt, *J* = 7.6 and 1.2 Hz), 6.71 (1H, d, *J* = 7.6 Hz), 3.04 (1H, d, *J* = 17.2 Hz), 2.38 (1H, d, *J* = 17.2 Hz), 1.42 (3H, s), 1.19 (3H, s). ^{13}C NMR (DMSO-d_6): δ 172.5, 171.8, 157.6, 130.0, 128.8, 127.8, 120.1, 109.7, 89.5, 58.7, 40.0, 24.1, 22.2. IR (KBr): 3500–2500, 1701, 1475, 1460, 1248, 940, 849, 749 cm^{-1}. Anal: Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.02; H, 5.36.

*Methyl 2-(3-methoxycarbonyl-2,3-dihydrobenzo[b]furan-3-yl)propanoate (**2d**)*. Yield: 39% (a 55/45 mixture of isomers). Oil. ^{1}H NMR ($CDCl_3$): δ 7.39 (0.55H, dd, *J* = 7.6 and 1.2 Hz), 7.22‑7.15 (1.45H, m), 6.90‑6.86 (2H, m), 6.82 (0.45H, d, *J* = 7.8 Hz), 6.79 (0.55H, d, *J* = 8.2 Hz), 5.28 (0.45H, d, *J* = 10.5 Hz), 4.97 (0.55H, d, *J* = 9.6 Hz), 4.74 (0.55H, d, *J* = 9.6 Hz), 4.64 (0.45H, d, *J* = 10.5 Hz), 3.76 (1.65H, s), 3.73, (1.35H, s), 3.71, (1.35H, s), 3.55 (0.45H, q, *J* = 7.3 Hz), 3.53 (1.65H, s), 3.35 (0.55H, q, *J* = 7.3 Hz), 1.18 (1.65H, d, *J* = 7.3 Hz), 1.02 (1.35H, d, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 175.0, 173.6, 173.0, 172.3, 160.2, 160.1, 130.0, 129.9, 126.3, 126.0, 125.5, 123.6, 120.7, 120.5, 110.1, 110.0, 75.9, 74.9, 58.7, 58.2, 52.94, 52.85, 52.1, 51.8, 45.4, 44.8, 13.0, 12.0. IR: 2953, 1734, 1597, 1483, 1460, 1435, 1226, 1119, 1077, 981, 838, 753 cm^{-1}. HRMS (EI): *m/z* 264.0994 $(M)^+$. Calcd for $C_{14}H_{16}O_5$ 264.0998.

*1-tert-Butoxycarbonyl-3-carboxy-2,3-dihydro-1H-indol-3-ylacetic acid (**2e**)*. Yield: 71%. Solid, mp: 188–189 °C. ^{1}H NMR (DMSO-d_6): δ 7.72 (0.7H, br. s), 7.39 (0.3H, br. s), 7.32–7.22 (2H, m), 6.95 (1H, m), 4.60 (1H, d, *J* = 11.5 Hz), 3.82 (1H, d, *J* = 11.5 Hz), 3.23 (1H, d, *J* = 17.4 Hz), 2.80 (1H, d, *J* = 7.4 Hz), 1.52 (9H, s). ^{13}C NMR (DMSO-d_6): δ 173.9, 172.6, 151.5, 142.3, (141.3), (132.7), 131.8, 129.2, 123.9, 122.4, 114.4, (81.31), 80.4, 56.7, 50.9, (50.1), 42.6, 28.1. Chemical shifts of the observed signals of a minor rotamer are shown in parentheses. IR (KBr): 3600–2400, 1710, 1489, 1402, 1351, 1247, 1146, 1049, 753 cm^{-1}. Anal: Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.55; H, 5.87; N, 4.31.

*1-Carboxy-2,3-dihydro-1H-indene-1-ylacetic acid (**2f**)*. Yield: 30%. Solid, mp: 175–177 °C.

^{1}H NMR (DMSO-d_6): δ 12.3 (2H, br.s), 7.28–7.14 (4H, m), 3.15 (1H, d, *J* = 17.6 Hz), 3.04–2.96 (1H, m), 2.92–2.84 (1H, m), 2.81–2.74 (1H, m), 2.50 (1H, d, *J* = 17.6 Hz), 2.13–1.95 (1H, m). ^{13}C NMR (DMSO-d_6): δ 175.5, 172.6, 144.3, 143.8, 127.8, 126.5, 124.8, 123.7, 55.5, 42.6, 34.8, 30.7. IR (KBr): 3500–2300, 1710, 1419, 1297, 1249, 1210, 928, 768 cm^{-1}. Anal: Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.35; H, 5.28.

*3-Carboxy-2,3-dihydro-1H-benzo[b]thiophen-3-ylacetic acid (**2g**).* Yield: 30%. Solid, mp: 174–176 °C. ^{1}H NMR (CD_3OD): δ 7.30 (1H, d, *J* = 7.8 Hz), 7.15–7.18 (2H, m), 7.03–7.08 (1H, m), 4.15 (1H, d, *J* = 11.9 Hz), 3.47 (1H, d, *J* = 11.9 Hz), 3.03 (1H, d, *J* = 17.4 Hz), 2.87 (1H, d, *J* = 17.4 Hz). ^{13}C NMR (CD_3OD): δ 175.6, 174.4, 142.7, 141.7, 130.0, 125.7, 125.4, 123.4, 60.2, 41.4, 40.4. IR (KBr): 3500–2500, 1721, 1460, 1426, 1355, 1300, 1250, 1228, 1200, 1070, 941, 853, 795, 744 cm^{-1}. Anal: Calcd for $C_{11}H_{10}O_4S$: C, 55.45; H, 4.23; S, 13.46. Found: C, 55.31; H, 4.23, S, 13.46.

*4-Carboxy-3,4-dihydro-2H-benzo[b]pyran-4-ylacetic acid (**2h**).* Yield: 51%. Solid, mp: 197–199 °C. ^{1}H NMR (DMSO-d_6): δ 7.50 (1H, dd, *J* = 8.4 and 1.6 Hz), 7.14–7.10 (1H, m), 6.88–6.84 (1H, m), 6.76 (1H, dd, *J* = 8.4 and 1.6 Hz), 4.26–4.20 (1H, m), 4.19–4.13 (1H, m), 3.13 (1H, d, *J* = 16.8 Hz), 2.63 (1H, d, *J* = 16.8 Hz), 2.60–2.54 (1H, m), 2.12–2.06 (1H, m). ^{13}C NMR (DMSO-d_6): δ 175.2, 172.2, 154.4, 128.5, 128.2, 123.1, 120.5, 117.3, 63.0, 43.9, 42.7, 29.7. IR (KBr): 3500–2300, 1700, 1490, 1450, 1431, 1299, 1227, 1059, 939, 753 cm^{-1}. Anal: Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 60.73; H, 5.01.

*(±)-3-(3-oxabicyclo[3.1.0]hexan-1-yl)-2,3-dihydrobenzofuran-3-carboxylic acid (**4a-major**).* Solid, mp: 108–109 °C. ^{1}H NMR ($CDCl_3$): δ 7.39 (1H, d, *J* = 7.6 Hz), 7.25–7.21 (1H, m), 6.92 (1H, br. t, *J* = 7.6 Hz), 6.83 (1H, br. d, *J* = 8.1 Hz), 4.99 (1H, d, *J* = 9.5 Hz), 4.59 (1H, d, *J* = 9.5 Hz), 3.86 (1H, d, *J* = 8.4 Hz), 3.78 (2H, s), 3.57 (1H, d, *J* = 8.4 Hz), 1.44–1.37 (1H, m), 0.94–0.87 (1H, m), 0.70 (1H, d, *J* = 8.4 Hz). ^{13}C NMR ($CDCl_3$): δ 177.3, 159.9, 130.1, 126.2, 125.0, 120.7, 110.3, 77.2, 70.6, 70.0, 56.4, 33.7, 20.8, 11.0. IR (KBr): 3500–2500, 1713, 1476, 1457, 1297, 1259, 1234, 1021, 835, 750 cm^{-1}. Anal.: Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.31; H, 5.81.

*(±)-3-(3-oxabicyclo[3.1.0]hexan-1-yl)-2,3-dihydrobenzofuran-3-carboxylic acid (**4a-minor**).* Solid, mp: 166–168 °C. ^{1}H NMR ($CDCl_3$): δ 7.35 (1H, dd, *J* = 7.6 and 1.0 Hz), 7.26–7.21 (1H, m), 6.89 (1H, dt, *J* = 7.6 and 1.0 Hz), 6.84 (1H, br. d, *J* = 8.1 Hz), 5.04 (1H, d, *J* = 9.2 Hz), 4.50 (1H, d, *J* = 9.2 Hz), 3.84–3.80 (3H, m), 3.69 (1H, dd, *J* = 8.1 and 1.2 Hz), 1.80–1.76 (1H, m), 0.55 (1H, t, *J* = 4.9 Hz), 0.40–0.35 (1H, m). ^{13}C NMR ($CDCl_3$): δ 177.4, 159.9, 130.3, 125.2, 124.8, 120.7, 110.4, 77.2, 70.4, 69.9, 56.2, 33.8, 21.9, 9.2. IR (KBr): 3500–2400, 1724, 1481, 1459, 1234, 894, 761 cm^{-1}. Anal.: Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.14; H, 5.83.

*(±)-3-(3-oxabicyclo[3.1.0]hexan-1-yl)-1-(tert-butoxycarbonyl)indoline-3-carboxylic acid (**4b**) (a 60/40 mixture of diastereoisomers).* Yield: 73 %. Solid, mp: 86–87 °C. ^{1}H-NMR ($CDCl_3$): δ 7.88 (0.6H, br. s), 7.48 (0.4H, br. s), 7.41–7.39 (0.6H, m), 7.36 (0.4H, d, *J* = 7.8 Hz), 7.29–7.25 (1H, m), 7.02–6.93 (1H, m), 4.57 (0.4H, d, *J* = 11.9 Hz), 4.52 (0.6H, d, *J* = 11.9 Hz), 4.02 (1H, br. s), 3.89–3.74 (3H, m), 3.68 (1H, d, *J* = 8.0 Hz), 1.79–1.74 (0.4H, m), 1.57 (9H, br. s), 1.49–1.46 (0.6H, m), 0.87–0.83 (0.6H, m), 0.67 (0.6H, t, *J* = 5.0 Hz), 0.50 (0.4H, t, *J* = 4.8 Hz), 0.29 (0.4H, dd, *J* = 8.0 and 5.0 Hz). ^{13}C-NMR ($CDCl_3$): δ 174.6, 174.5, 151.7, 142.2, 141.2, 129.3, 129.1, 128.4, 127.9, 125.7, 124.5, 122.0, 121.9, 114.6, 82.1, 80.9, 70.2, 69.5, 55.2, 53.5, 53.3, 34.2, 33.8, 27.9, 21.3, 20.4, 10.6, 8.6. IR (KBr): 3415, 1737, 1707, 1487, 1393, 1148, 754 cm^{-1}. Anal.: Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.89; H, 6.86; N, 3.94.

*2-5-3 Transformation of diacid **2a** into spirolactone **6**.*

A mixture of **2a** (111.1 mg, 0.5 mmol) and acetic anhydride (61 mg, 0.6 mmol) in toluene (5 mL) was heated under reflux for 4 h. Evaporation gave a crude anhydride **5**, which was used for a next reaction without further purification. To a solution of anhydride **5** in THF (5 mL) was added $NaBH_4$ (37.8 mg, 1.0 mmol) at rt. After stirring at rt for 2 h, 6 M HCl (10 mL) was added to the mixture and stirring was continued at rt for 12 h. The mixture was extracted with ethyl acetate (30 mL×3) and combined organic layer was washed with H_2O (30 mL×3). Dryness over $MgSO_4$ and evaporation of the solvent gave a crude product, which was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1) to give spirolactone **6** (76 mg, 80%).

*Spiro[benzofuran-3(2H),3'(4'H)-furan]-2',5'-dione (**5**)(not isolated)*. ^{1}H NMR ($CDCl_3$): δ 7.29 (1H, dt, *J* = 7.5 and 1.4 Hz), 7.15 (1H, dd, *J* = 7.5 and 0.9 Hz), 6.99 (1H, dt, *J* = 7.5 and 0.9 Hz), 6.93 (1H, d, *J* = 8.2 Hz), 5.07 (1H, d, *J* = 9.6 Hz), 4.58 (1H, d, *J* = 9.6 Hz), 3.32 (1H, d, *J* = 19.2 Hz), 3.27 (1H, d, *J* = 19.2 Hz). ^{13}C NMR ($CDCl_3$): δ 172.8, 168.0, 159.5, 131.1, 126.7, 122.1, 122.0, 110.9, 78.6, 54.8, 42.3.

*Spiro[benzofuran-3(2H),3'(2'H)-furan]-5'(4'H)-one (**6**)*. Solid, mp: 68–70 °C. ^{1}H NMR ($CDCl_3$): δ 7.22–7.27 (2H, m), 6.98 (1H, dt, *J* = 7.6 and 0.8 Hz), 6.87 (1H, d, *J* = 7.6 Hz), 4.60 (1H, d, *J* = 9.2 Hz), 4.48 (1H, d, *J* = 9.2 Hz), 4.44 (1H, d, *J* = 9.2 Hz), 4.40 (1H, d, *J* = 9.2 Hz), 2.96 (1H, d, *J* = 17.6 Hz), 2.76 (1H, d, *J* = 17.6 Hz). ^{13}C NMR ($CDCl_3$): δ 174.8, 159.6, 129.9, 128.2, 122.4, 121.5, 110.3, 81.2, 77.5, 49.8, 40.5. IR (KBr): 1774, 1601, 1482, 1459, 1409, 1242, 1182, 1039, 1010, 977, 840, 753 cm^{-1}. Anal.: Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.54; H, 5.31.

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Chapter 3

Sequential Vinyl Radical Cyclization/Fixation of Carbon Dioxide through Methyl 4-*tert*-Butylbenzoate-mediated Electrochemical Reduction of Vinyl Bromides in the presence of Carbon Dioxide

3-1 Introduction

A vinyl radical is a useful intermediate for various purposes in organic synthesis. As well as other radical species, it can perform simple radical cyclization to produce unsaturated carbo- and heterocycles.[1,2] Radical translocation by 1,5-hydrogen abstraction and the following cyclization are also characteristic reactions of vinyl radicals.[3-7] One representative and frequently used way to generate such a vinyl radical involves reaction of alkynes with Bu_3SnH-AIBN,[8] and many successful applications of thus-generated vinyl radicals to cyclization affording carbo- and heterocycles have been reported.[8-16] Regioselectivity in the generation of vinyl radicals from internal alkynes was, however, sometimes troublesome and problematic.[17] On the other hand, vinyl bromide and iodide are good and straightforward precursors of vinyl radicals. Reaction with Bu_3SnH-AIBN generates a vinyl radical at the carbon having a bromine or iodine atom, which can also undergo efficient radical cyclization to afford unsaturated carbo- and heterocycles.[3-7,18-20] Since organotin reagents such as Bu_3SnH are known to be hazardous, an environmentally-benign alternative method for generation of a vinyl radical without the use of hazardous reagents is desirable. Samarium(II) iodide is a useful reducing agent for generation of a vinyl radical by one-electron reduction of vinyl bromide.[21] However, the use of a heavy metal, samarium, and hazardous HMPA, in some cases, is also to be avoided from the viewpoint of green chemistry. On the other hand, direct electrochemical reduction of vinyl iodide[22] and bromide[23] is also known to generate a vinyl radical. However, only a few successful applications to radical cyclization by electrochemical reduction of vinyl bromide catalyzed by nickel complexes[24,25] and β-carbonyl enol phosphate[26] have been reported. Moreover, all of these reported vinyl radical cyclizations involved only protonation as a termination step, and there is no report on use of the resulting anion species generated after vinyl radical cyclization for further organic transformation, especially carbon-carbon bond formation. We previously reported that methyl 4-*tert*-butylbenzoate is an effective electron transfer mediator for efficient generation of aryl radicals from aryl bromides in electrochemical reduction even in the presence of carbon dioxide. Thus-generated aryl radicals were found to undergo aryl radical cyclization with a carbon-carbon double bond, and one-electron reduction of the resulting cyclized radicals followed by reaction of the generated anion species with carbon dioxide took place

efficiently to give cyclized carboxylic acid in good yields and good selectivity.[27] Recently, we also found unique electrochemical fixation of two molecules of carbon dioxide in aryl radical cyclization using a carbon-carbon triple bond as an aryl radical acceptor.[28] In the course of our studies on electroorganic synthesis,[29] electrochemical reduction of vinyl bromide using methyl 4-*tert*-butylbenzoate as an electron transfer mediator was found to generate a vinyl radical with high selectivity even in the presence of carbon dioxide. Moreover, the thus-generated vinyl radical underwent radical cyclization followed by fixation of carbon dioxide with a carbon-carbon bond formation. To the best of my knowledge, this is the first example of electrochemical vinyl radical cyclization generated from vinyl bromides without a transition metal catalyst and the sequential fixation of carbon dioxide with a carbon-carbon bond formation as a termination step. In this chapter, sequential vinyl radical cyclization/fixation of carbon dioxide by electrochemical reduction of vinyl bromide in the presence of an electron transfer mediator is described.

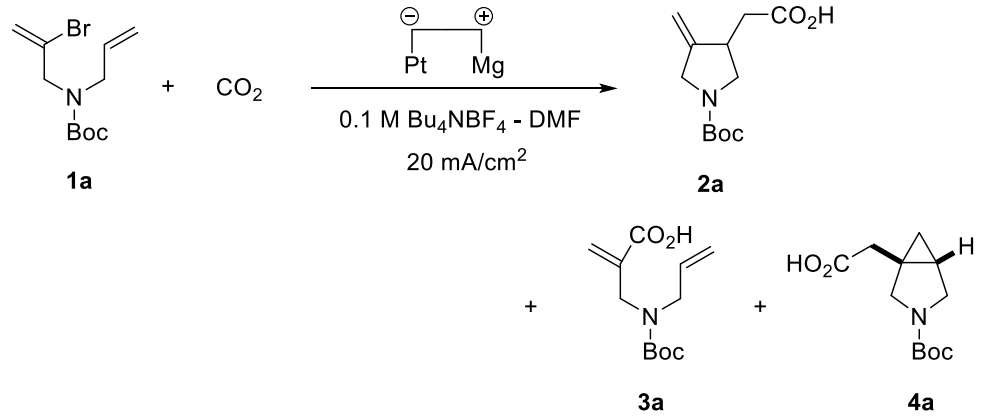
3-2 Results and discussion of sequential vinyl radical cyclization-fixation of carbon dioxide through methyl-4-*tert*-butylbenzoate-mediated electrochemical reduction of vinyl bromides in the presence of carbon dioxide

3-2-1 Screening of reaction conditions

Screening of reaction conditions was carried out using known *tert*-butyl *N*-(2-allyl)-*N*-(2-bromoallyl)carbamate (**1a**)[30] as a substrate, and the results are summarized in Table 1. Constant current electrolysis of a DMF (10 mL) solution of **1a** (1 mmol) containing 0.1 M Bu_4NBF_4 was carried out using a test-tube like undivided cell equipped with a platinum plate cathode (2 x 2 cm^2) and a magnesium rod anode (3 mmϕ) in the absence or presence of 0.5 equiv of methyl 4-*tert*-butylbenzoate as an electron transfer mediator with bubbling of carbon dioxide through the solution. When 3 F/mol of electricity was supplied by 20 mA/cm^2 constant current in the absence of an electron transfer mediator, the expected sequential reaction, vinyl radical cyclization – fixation of carbon dioxide, proceeded to give cyclized carboxylic acid **2a** along with direct carboxylated product **3a** in passable selectivity (entry 1). Finally, supplying 7 F/mol of electricity provided desired **2a** and undesired direct carboxylated product **3a** in 66% total yield with a ratio of 84/16 (entry 2). We previously reported electrochemical carboxylation of vinyl bromides under similar reaction conditions, and we mentioned the possibility that a vinyl radical would be involved in the reaction mechanism as an intermediate.[31] The fact that vinyl radical cyclization products were actually obtained by the present electrochemical carboxylation of vinyl bromide having an appropriate radical acceptor under similar conditions is clear evidence of our previous assertion. On the other hand, similar electrolysis of **1a** in the presence of 0.5 equiv of methyl 4-*tert*-butylbenzoate as an electron transfer mediator[27,28] gave **2a** with higher selectivity, 92% (entry 3). In this case, a small amount of bicyclic carboxylic acid **4a**, which would have been produced by tandem radical cyclization followed by fixation of carbon dioxide, was also detected by ^1H NMR. Both **2a** and **4a** would have been produced by the reaction of vinyl radical, while **3a** would have been formed by the reaction of vinyl anion. Based on these points, the ratio of vinyl radical reaction/vinyl anion reaction can be determined as 97/3. These results indicate that electrolysis of vinyl bromide **1a** in the presence of methyl 4-*tert*-butylbenzoate generates a vinyl radical with high selectivity and that methyl 4-*tert*-

butylbenzoate would play an important role in the generation of a vinyl radical from vinyl bromide **1a** by the present electrolysis. When a similar reaction was carried out at –20 °C or 20 °C, the yields of **2a** decreased (entries 4 and 5). A slight decrease in the selectivity of **2a** and a slight increase in the selectivity of **4a** were observed in electrolysis at –20 °C (entry 4), although the exact reason is not clear at present. Under the reaction conditions in entry 3, an increase in the supply of electricity to 7 F/mol resulted in improvements of the conversion of **1a** and the yield of **2a** (entry 6). Finally, after supplying 10 F/mol of electricity, *N*-Boc-4-methylenepyrrolidine-3-ylacetic acid (**2a**) was obtained in 71% yield with 92% selectivity (entry 7).

Table 1



Entry	Additive (0.5 equiv)	Temperature [°C]	Electricity [F/mol]	Conversion of **1a** [%][a]	Yield of acids and ratio [%][b] (**2a** / **3a** / **4a**)[a]
1	none	0	3	79	53 [67] (88 / 12 / 0)
2	none	0	7	90	66 [73] (84 / 16 / 0)
3	4-*tert*-$C_4H_9C_6H_4CO_2CH_3$	0	3	66	49 [74] (92 / 3 / 5)
4	4-*tert*-$C_4H_9C_6H_4CO_2CH_3$	-20	3	44	37 [84] (88 / 4 / 8)
5	4-*tert*-$C_4H_9C_6H_4CO_2CH_3$	20	3	59	39 [66] (92 / 3 / 5)
6	4-*tert*-$C_4H_9C_6H_4CO_2CH_3$	0	7	84	63 [75] (92 / 3 / 5)
7	4-*tert*-$C_4H_9C_6H_4CO_2CH_3$	0	10	92	71 [77] (92 / 3 / 5)

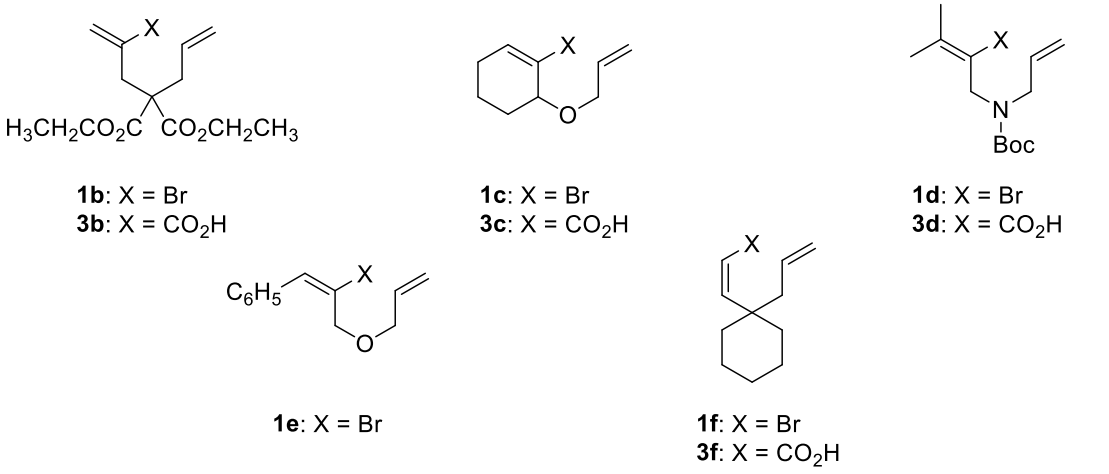
[a] Conversion and isomer ratio were determined by ^{1}H NMR. In conversion, *p*-dinitrobenzene was used as an internal standard. [b] Combined isolated yields of **2**, **3**, and **4**. The combined yields based on reacted **1** are shown in brackets.

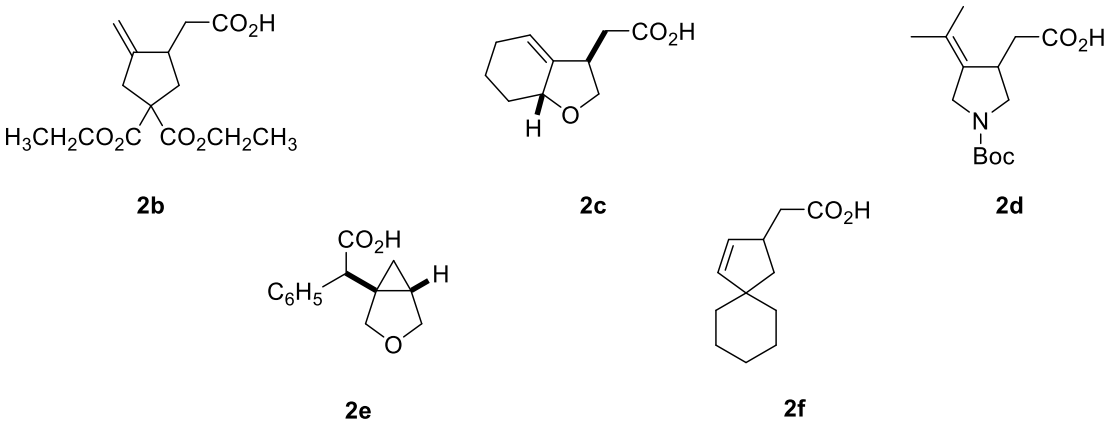
3-2-2 Substrate scope

We next investigated the scope of the present vinyl radical cyclization – fixation of carbon dioxide cascade reaction using several vinyl bromides, which are shown in Scheme 1 along with the corresponding cascade products **2** and directly carboxylated products **3**. The results of electrochemical sequential vinyl radical cyclization – fixation of carbon dioxide using these vinyl bromides as substrates are shown in Table 2. When 2-bromo-1,6-diene **1b** having two ester groups at the C4 carbon was subjected to the present electrolysis at 20 mA/cm^2 of current density with 3 F/mol of electricity, vinyl radical cyclization followed by fixation of carbon dioxide took place efficiently and selectively even in the absence of an electron transfer mediator to give 2-methylenecyclopenten-1-ylacetic acid **2b** in 50% yield with 99% selectivity (entry 1). Highly selective formation of vinyl cyclization product **2b** might be due to an increase of the cyclization rate by the *gem*-disubstituent effect,[32] though there is no evidence and the exact reason is not clear at present. Finally, supplying 7 F/mol of electricity afforded **2b** in 65% yield and 97% selectivity (entry 2). In similar electrolysis of 2-bromo-4-oxa-1,6-diene **1c** having an alkyl group at the C1 carbon, the absence of an electron transfer mediator, methyl 4-*tert*-butylbenzoate, in electrolysis resulted in a major decrease in selectivity of radical cyclization product **2c** to 76% (entry 3). In the presence of 0.5 equiv of methyl 4-*tert*-butylbenzoate, selectivity of radical cyclization product **2c** was greatly improved, while conversion of **1c** decreased (entry 4). Although an efficient current could not be obtained for further supply of electricity over 7 F/mol, electrolysis of **1c** in the presence of methyl 4-*tert*-butylbenzoate with 7 F/mol of electricity finally gave hexahydrobenzofuran-3-ylacetic acid **2c** in 42% yield with 96% selectivity (entry 5). It is noteworthy that **2c** was obtained as a single isomer, and its stereochemical outcome as shown in Scheme 1 was determined by ^{1}H NMR using C-H COSY and NOESY techniques. These results indicate that the cyclization of vinyl radical generated from **1c** proceeded with high stereoselectivity, although the exact reason for the involvement of a transition state is unclear at present. A slight decrease of the selectivity was also observed in electrolysis of 2-bromo-4-aza-1,6-diene **1d** having dimethyl groups at the C1 carbon in the absence of an electron transfer mediator. When electrolysis of **1d** was carried out in the absence of methyl 4-*tert*-butylbenzoate, radical cyclization product **2d** was obtained in 48% yield along with directly carboxylated product **3d** in a ratio of 87/13 (entry 6). On the other hand, vinyl radical

cyclization followed by fixation of carbon dioxide selectively occurred in the presence of methyl 4-*tert*-butylbenzoate to give **2d** in 98% selectivity, while conversion of **1d** and the combined yield of carboxylic acids **2d** and **3d** decreased (entry 7). The cascade reaction product **2d** was finally obtained in 44% yield with 98% selectivity when electrolysis of **1d** was carried out in the presence of methyl 4-*tert*-butylbenzoate with 7 F/mol of electricity (entry 8). 2-Bromo-4-oxa-1,6-diene **1e** having a phenyl group at the C1 carbon was also subjected to the present sequential reaction. When phenyl-substituted vinyl bromide **1e** was electrolyzed in the absence of an electron transfer mediator, only a complex mixture was obtained (entry 9). It is likely that several side reactions and over reduction of the resulting products proceeded due to the existence of a phenyl group on the C-C double bond. On the other hand, electrolysis of **1e** in the presence of methyl 4-*tert*-butylbenzoate under similar conditions resulted in tandem radical cyclization of the generated vinyl radical followed by fixation of carbon dioxide to give 2-(3-oxabicyclo[3.1.0]hexan-1-yl)-2-phenylacetic acid (**2e**) as a 56/44 mixture of stereoisomers in 40% yield, and no other carboxylic acid was detected by ^{1}H NMR (entry 10). Although similar tandem radical cyclization of a vinyl radical producing a bicyclo[3.1.0]hexane skeleton by an electrochemical method has been reported,[25,26] this is the first example of tandem cyclization of a vinyl radical producing a bicyclo[3.1.0]hexane skeleton that was terminated not by protonation but by carbon-carbon bond-forming reaction with carbon dioxide. After 7 F/mol of electricity was passed, bicycle-carboxylic acid **2e** was obtained in 53% yield, 65% based on reacted **1e**, with high selectivity (entry 11). 1-Bromo-1,5-diene **1f** was also subjected to the present sequential vinyl radical cyclization followed by fixation of carbon dioxide. Electrolysis of 1-bromo-1,5-diene **1f** with carbon dioxide in the absence of an electron transfer mediator resulted in generation of the corresponding vinyl radical, and its sequential cyclization – fixation of carbon dioxide reaction also took place to give cascade reaction product **2f** in 52% yield along with **3f** in a ratio of 94/6 (entry 12). Passable selectivity of cascade reaction product **2f** even in the absence of an electron transfer mediator would be due to the *gem*-disubstituted effect,[32] similar to the electrolysis of **1b** producing **2b**. When electrolysis of **1f** was carried out in the presence of methyl 4-*tert*-butylbenzoate, a slight increase in selectivity and major decreases in the yield and conversion were observed (entry 13). These results indicate that an electron transfer mediator, methyl 4-*tert*-butylbenzoate, is not necessary for efficient formation of a

vinyl radical cyclization product with highly selectivity in electrolysis of **1f**. Finally, spiro[4.5]dec-1-en-3ylacetic acid (**2f**) was obtained in 67% yield, 76% based on reacted **1f**, with 96% selectivity by electrolysis of **1f** in the absence of an electron transfer mediator with 7 F/mol of electricity (entry 14). In all cases, a vinyl radical could be generated with high selectivity from vinyl bromides **1** by electrochemical reduction, and cyclization of the resulting radical followed by fixation of carbon dioxide also took place successfully to give radical – anion cascade reaction product **2** in moderate to good yields with high product selectivity.





Scheme 1

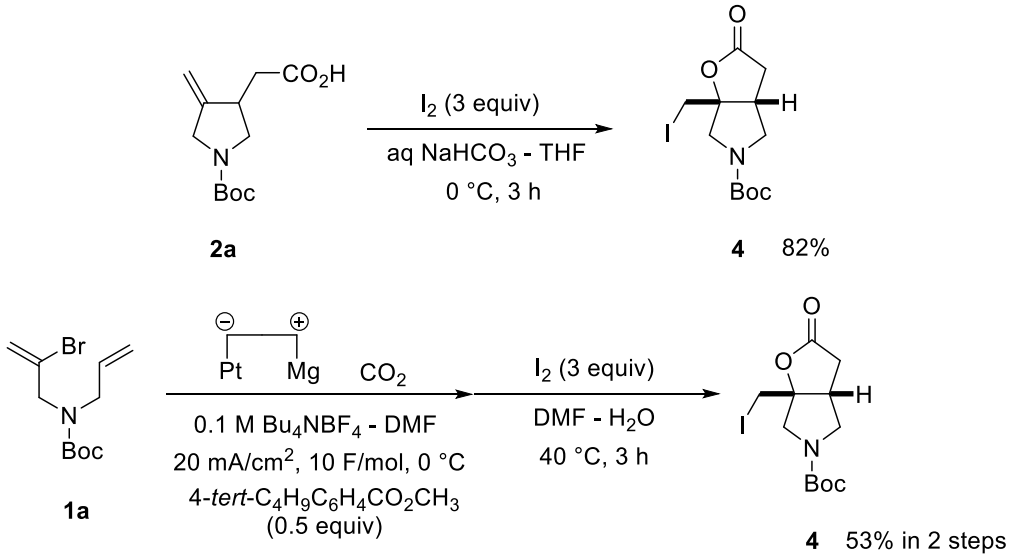
Table 2

Entry	Substrate	Products	4-*tert*-$C_6H_4C_6H_4CO_2CH_3$ (0.5 equiv)	Conversion of **1** [%][a]	Yield of acids and ratio [%][b] (**2** / **3**)[a]
1	**1b**	**2b**	absence	69	50 [72] (99 / 1)
2 [c]	**1b**	**2b**	absence	86	65 [76] (97 / 3)
3	**1c**	**2c**	absence	77	49 [64] (76 / 24)
4	**1c**	**2c**	***presence***	47	32 [68] (97 / 3)
5 [c]	**1c**	**2c**	***presence***	65	42 [65] (96 / 4)
6	**1d**	**2d**	absence	72	48 [67] (87 / 13)
7	**1d**	**2d**	***presence***	44	26 [59] (98 / 2)
8 [c]	**1d**	**2d**	***presence***	69	44 [64] (98 / 2)
9	**1e**	**2e**	absence	76	complex mixture
10	**1e**	**2e**	***presence***	62	40 [65] (>99 / 1)
11 [c]	**1e**	**2e**	***presence***	82	53 [65] (>99 / 1)
12	**1f**	**2f**	absence	75	52 [69] (94 / 6)
13	**1f**	**2f**	***presence***	40	22 [55] (98 / 2)
14 [c]	**1f**	**2f**	absence	88	67 [76] (96 / 4)

[a] Conversion and isomer ratio were determined by ^{1}H NMR. In conversion determination, *p*-dinitrobenzene was used as an internal standard. [b] Combined isolated yields of **2** and **3**. The combined yields based on reacted **1** is shown in brackets. [c] 7 F/mol of electricity was passed.

3-3 Synthetic application

Finally, one application of the resulting unsaturated carboxylic acid to iodo-lactonization was demonstrated. Treatment of *N*-Boc-4-methylenepyrrolidin-3-ylacetic acid (**2a**), synthesized from vinyl bromide **1a** using the present method, with iodine (3 equiv) and aqueous $NaHCO_3$ in THF at 0 °C for 3 h provided bicyclic γ-lactone **4** in 82% isolated yield as shown in Scheme 3. Direct one-pot conversion of vinyl bromide **1a** to bicyclic γ-lactone **4** was also performed by the present electrolysis – iodo-lactonization sequence. Electrolysis of vinyl bromide **1a** was carried out under the conditions shown in entry 7 in Table 1, and then the resulting electrolyzed mixture was directly treated with three equiv of iodine in DMF and water at 40 °C for 6 h. Usual work-up followed by column chromatography on silica gel gave bicyclic γ-lactone **4** in 53% isolated yield in two steps (Scheme 3).



Scheme 3

3-4 Conclusion

In conclusion, a vinyl radical could be selectively generated by electrochemical reduction of vinyl bromide even in the presence of carbon dioxide using methyl 4-*tert*-butylbenzoate as an electron transfer mediator. The resulting vinyl radical successfully underwent sequential radical cyclization – fixation of carbon dioxide reaction to provide cyclized γ,δ-unsaturated carboxylic acid in moderate to good yields. The obtained γ,δ-unsaturated carboxylic acid was successfully applied to iodo-lactonizetion reaction to give bicyclic γ-lactone by stepwise and direct one-pot reactions in high yields.

3-5 Experimental

General

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a JASCO FT/IR-410 spectrometer in neat form unless otherwise stated. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in indicated solvents with a JEOL ECX400P or ECS400 FT NMR spectrometer. The chemical shifts, δ, are given in ppm with tetramethylsilane for ^{1}H and solvents for ^{13}C as references. *J* values are in Hz. Peak multiplicities were given as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. MS spectra and elemental analyses were carried out using a JEOL JMS-T100GCv or Thermo Scientific Exactive and Exacter Analytical CE440 or J-Science Lab JM10, respectively, at Instrumental Analysis Division, Equipment Management Center Creative Research Institution, Hokkaido University. Column chromatography was carried out using Kanto Kagaku Silica gel 60N. Reagents and solvents were commercially available and were used as received without further purification.

*3-5-1 Starting materials **1***

1a[30] and **1b**[33] are known compounds and were prepared according to the literatures.

*tert-Butyl N-allyl-N-(2-bromoallyl)carbamate (**1a**)*. Colorless oil. ^{1}H NMR ($CDCl_3$): 2 rotamers: δ 1.47 &1.53 (9H, s), 3.83-3.89 (2H, m), 4.01-4.07 (2H, m), 5.10-5.17 (2H, m), 5.56 (1H, br s), 5.70-5.78 (2H, m). ^{13}C NMR ($CDCl_3$): 2 rotamers: δ 27.9, 48.1, 48.7, 53.1, 53.2, 79.7. 116.3, 116.8, 116.9, 129.2, 129.4, 133.0, 154.4, 154.7. IR: 2978, 1702, 1641, 1455, 1404, 1366, 1248, 1172, 926, 874 cm^{-1}. The analytical data were consistent with the reported one.[30]

*Diethyl 2-allyl-2-(2-bromoallyl)malonate (**1b**)*: Colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.26 (6H, t, *J* = 7.2 Hz), 2.78 (2H, dt, *J* = 1.2 and 7.4 Hz), 3.15 (2H, d, *J* = 1.5 Hz), 4.14-4.26 (4H, m), 5.11-5.16 (2H, m), 5.60 (1H, d, *J* = 1.6 Hz), 5.61-5.72 (2H, m). ^{13}C NMR ($CDCl_3$): δ 13.6, 35.6, 42.5, 56.3, 61.0, 119.0. 121.5, 126.9, 131.8, 169.4. The analytical data were consistent with the reported one.[33]

*6-Allyloxy-1-bromocyclohex-1-ene (**1c**)*. To a suspension of NaH (960 mg, 60% oil dispersion, 24 mmol, washed with hexane before use) in anhydrous THF (70 mL) was dropwise added 2-bromo-2-cyclohexen-1-ol[34] (2.4 g, 14 mmol) at rt and then the mixture was heated under reflux for 2 h. To this solution, after cooling to rt, was dropwise added allyl bromide (2.54 g, 21 mmol) and then the mixture was heated again under reflux for 2 h. After cooling to rt, 100 mL of 1 M hydrochloric acid was added and the resulting aqueous solution was extracted with ethyl acetate (50 mL × 3). The combined organic solution was washed with saturated brine (100 mL × 2) and then dried over anhydrous $MgSO_4$. Evaporation of the solvent followed by column chromatography on silica gel (hexane/ethyl acetate = 20/1) gave **1c** (2.56 g, 87%). **1c**: Colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.58-1.64 (1H, m), 1.68-1.80 (2H, m), 1.95-2.07 (2H, m), 2.10-2.18 (1H. m), 3.90 (1H, br s), 4.07-4.19 (2H, m), 5.17-5.21 (1H, m), 5.30-5.35 (1H, m), 5.93-6.03 (1H, m), 6.24 (1H, dd, *J* = 3.3 and 4.8 Hz). ^{13}C NMR ($CDCl_3$): δ 16.5, 27.3, 28.8, 70.2, 75.9, 116.3, 122.4, 132.8, 134.6. IR: 1644, 1425, 1331, 1163, 1082, 1062, 993, 920, 806, 749 cm^{-1}. HRMS (EI): *m/z* 216.0143 (M^+). Calcd for $C_9H_{13}{}^{79}BrO$ 216.0150.

*tert-Butyl N-allyl-N-(2-bromo-3-methylbut-2-en-1-yl)carbamate (**1d**)*. To a solution of allyl amine (1.14 g, 20 mmol) in DMF (20 ml) was added K_2CO_3 (8.3 g, 60 mmol) at 0 °C, and then the mixture was stirred for 30 min at rt. 1,2-Dibromo-3-methyl-2-butene (2.28 g, 10 mmol), prepared from 3-methyl-2-buten-1-ol in two steps by the reported procedures,[35] was dropwise added to this mixture at 0 °C. After stirring at rt for additional 3 h, water (100 mL) was added to the reaction mixture. Then, the mixture was extracted with ether (50 mL × 3) and the combined ethereal solution was washed with water (50 mL × 3). Dryness over anhydrous $MgSO_4$ followed by evaporation of the solvent gave a crude amine, which was used for further reaction as it is. The resulting amine and Boc_2O (1.53 g 7 mmol) in THF (20 mL) was heated under reflux for 4h under nitrogen atmosphere. After cooling to rt, ether (50 mL) was added and the mixture was washed successively with 1 M HCl (50 mL × 3) and water (50 mL × 3). Dryness over anhydrous $MgSO_4$ followed by evaporation of the solvent gave a crude product, which was purified by column chromatography on silica gel (CH_2Cl_2) to afford vinyl bromide **1d** (2.37 g, 2 steps 78%). **1d**: Colorless oil. ^{1}H NMR ($CDCl_3$): 2

rotamers: δ 1.47 (9H, s), 1.83 (3H, br s), 1.91 (3H, s), 3.78-3.84 (2H, br m), 4.20-4.26 (2H, br m), 5.07-5.14 (2H, br m), 5.77 (1H, br m), 7.17 (3H, br m), 7.25-7.35 (2H, m). ^{13}C NMR ($CDCl_3$): 2 rotamers: δ 20.5, 25.4, 28.2, 47.3, 47.8, 48.8, 79.6, 79.7, 115.9, 116.3, 117.8, 118.3, 133.8, 134.0, 134.9, 155.1, 155.3. IR: 1810, 1758, 1698, 1454, 1408, 1367, 1248, 1173, 1146, 1119, 1071, 923, 873, 774, 738 cm^{-1}. HRMS (ESI): *m/z* 326.0726 (M^+). Calcd for $C_{13}H_{22}{}^{79}BrNNaO_2$ 326.0726.

*(E)- 3-Allyloxy-2-bromo-1-phenylprop-1-ene (**1e**).* Vinyl bromide **1e** was prepared from *E*-α-bromocinnamyl alcohol in 90% yield in a similar manner to preparation of **1c**. **1e**: Colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.02 (2H, dt, *J* = 1.4 and 5.5 Hz), 4.32 (2H, s), 5.15-5.18 (1H, m), 5.21-5.26 (1H, m), 5.91 (1H, ddt, *J* = 5.9, 10.1, and 17.1 Hz), 7.24-7.25 (2H, m), 7.30-7.39 (3H, m). ^{13}C NMR ($CDCl_3$): δ 70.1, 71.1, 117.8, 124.7, 127.9, 128.4, 128.5, 134.1, 135.6, 136.7. IR: 1625, 1495, 1446, 14210, 1359, 1249, 1080, 991, 926, 756, 701 cm^{-1}. HRMS (EI): *m/z* 252.0149 (M^+). Calcd for $C_{12}H_{13}{}^{79}BrO$ 252.0150.

*(Z)-1-Allyl-1-(2-bromoethenyl)cyclohexane (**1f**).* To a mixture of potassium *tert*-butoxide (2.02 g, 18 mmol) in THF (20 mL) was added bromomethyltriphenylphosphonium bromide (7.85 g, 18 mmol), prepared from methylene dibromide and triphenylphosphine[36] in toluene at -78 °C and the mixture was stirred at the same temperature for 30 min. To this mixture was added 1-allylcyclohexanacarbardehyde (2.28 g, 15 mmol), prepared by the reported procedure,[37] and then the mixture was stirred at the same temperature for additional 30 min. After warming-up to rt and stirring for 12 h, 1 M HCl (50 mL) was added to the mixture and then the mixture was extracted with ethyl acetate (50 mL × 3). The combined organic solution was washed with water (50 mL × 3) and then dried over anhydrous $MgSO_4$. After evaporation of the solvent, a 3/1 mixture of hexane and ether (200 mL) was added to the mixture and solidified phosphine oxide was filtered off. Evaporation of the filtrate followed by column chromatography on silica gel (hexane/ether = 20/1) gave vinyl bromide **1f** (2.16 g, 62%). **1f**: Colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.16-1.1.28 (3H, m), 1.31-1.41 (2H, m), 1.52-1.60 (3H, m), 2.04 (2H, br d, *J* = 12.8 Hz), 2.35 (2H, d, *J* = 7.3 Hz), 5.17-5.21 (1H, m), 5.78 (1H, ddt, *J* = 7.3, 10.5, and 17.0 Hz), 5.99 (1H, d, *J* = 7.8 Hz), 6.18 (1H, d, *J* = 7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 22.6, 25.9, 36.2, 41.1, 44.1, 105.2, 116.9, 134.8, 139.9. IR: 1638, 1615, 1451,

1328, 1287, 996, 913, 712 cm^{-1}. HRMS (EI): *m/z* 228.0512 (M^+). Calcd for $C_{11}H_{17}{}^{79}Br$ 228.0514.

*3-5-2 Electrochemical reduction of vinyl bromide **1** in the presence of carbon dioxide and methyl 4-tert-butyl benzoate.*

A solution of vinyl bromide **1** (1 mmol) in anhydrous DMF (10 mL) containing Bu_4NBF_4 (0.1 M) was electrolyzed at 0 °C for **1** with a constant current (20 mA/cm^2) in the presence of methyl 4-*tert*-butylbenzoate (96 mg, 0.5 mmol) under atmospheric pressure of bubbling carbon dioxide. A test tube-like (ca. 25 mmϕ) undivided cell equipped with a Pt plate cathode (2 × 2 cm^2), an Mg rod anode (3 mmϕ, ca. 25 mm) and a Teflon® tube (ϕ 1 mm) for supplying carbon dioxide was used for the electrolysis. An appropriate amount of electricity shown in the tables was passed. i) For isolation of carboxylic acid: 1 M hydrochloric acid (100 mL) was added to the electrolyzed solution and then the mixture was extracted with ethyl acetate (30 mL × 5). The combined organic layer was washed with saturated $NaHCO_3$ (40 mL × 3), and the resulting aqueous solution was acidified with 3 M hydrochloric acid and then extracted with ethyl acetate (30 mL × 5). The combined ethyl acetate solution was washed with H_2O (100 mL × 3) and dried over $MgSO_4$. Evaporation of the solvent gave cyclized carboxylic acid **2**, which was analyzed by ^1H NMR.

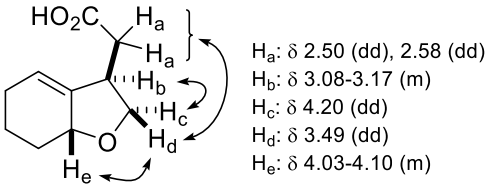
*3-5-3 Cyclized carboxylic acid **2***

*2-(N-tert-Butyloxycarbonyl-4-methylenepyrrolidin-3-yl)acetic acid (**2a**).* White solid. mp: 122-123 °C. ^1H NMR ($CDCl_3$): 2 rotamers: δ 1.47 (9H, s), 2.43 (1H, dd, *J* = 8.5 and 16.1 Hz), 2.68 (1H, br d, *J* = 16.1 Hz), 3.13 (2H, br d, *J* = 7.5 Hz), 3.82 (1H, br m), 3.99 (2H, br m), 4.96 (1H, br s), 5.03 (1H, br d, *J* = 12.2 Hz). ^{13}C NMR ($CDCl_3$): 2 rotamers: δ 28.3, 36.4, 36.6, 38.2, 38.8, 50.1, 50.5, 50.9, 51.4, 80.0, 106.56, 106.63, 147.0, 147.8, 154.6, 176.0, 176.4. IR: 3500-2800, 1741, 1654, 1426, 1167, 1126, 893, 770 cm^{-1}. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.53; H, 7.94; N, 5.75.

*2-(4,4-Bis(ethoxycarbonyl)-2-methylenecyclopentyl)acetic acid (**2b**).* Colorless oil. ^1H NMR ($CDCl_3$): δ 1.249 (3H, t, *J* = 7.3 Hz), 1.252 (3H, t, *J* = 7.3 Hz), 1.95 (1H, dd, *J* = 10.1 and 13.1 Hz), 2.40 (1H, dd, *J* = 9.2 and 16.1 Hz), 2.66-2.72 (2H, m), 2.96-3.07 (3H, m), 4.16-

4.23 (4H, m), 4.83-4.86 (1H, m), 4.99-5.00 (1H, m). ^{13}C NMR ($CDCl_3$): δ 13.9 (× 2), 38.2, 38.3, 40.0, 40.5, 58.2, 61.5 (× 2), 106.8, 150.3, 171.4 (× 2), 178.6. The analytical data were consistent with the reported one.[33c]

*(±)-2-(3R,7aR-2,3,5,6,7,7a-hexahydrobenzofuran-3-yl)acetic acid (**2c**).* White solid. mp: 82-84 °C. ^{1}H NMR ($CDCl_3$): δ 1.20-1.29 (1H, m), 1.41-1.53 (1H, m), 1.81-1.86 (1H, m), 2.03-2.07 (2H, m), 2.15-2.21 (1H, m), 2.50 (1H, dd, *J* = 8.7 and 16.6 Hz), 2.58 (1H, dd, *J* = 6.6 and 16.6 Hz), 3.08-3.17 (1H, m), 3.49 (1H, dd, *J* = 6.0 and 9.1 Hz), 4.03-4.10 (1H, m), 4.20 (1H, dd, *J* = 7.4 and 9.1 Hz), 5.59 (1H, s). ^{13}C NMR ($CDCl_3$): δ 19.4, 24.9, 28.2, 38.5 (× 2), 72.0, 75.9, 120.2, 141.7, 177.8. IR: 3500-2500, 1702, 1426, 1411, 1346, 1263, 1240, 1055, 991, 941, 918, 803, 649 cm^{-1}. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.85; H, 7.75. Results of NOESY experiment of **2c** are shown below.



*2-(1-tert-Butyloxycarbonyl-4-(propan-2-ylidene)pyrrolidin-3-yl)acetic acid (**2d**).* White solid. mp: 126-128 °C. ^{1}H NMR ($CDCl_3$): 2 rotamers: δ 1.47 (9H, s), 1.62 (3H, s), 1.70 (3H, s), 2.39-2.41 (2H, m), 3.22-3.27 (1H, m), 3.39-3.60 (2H, m), 3.84-4.00 (2H, m), 11.36 (1H, br s). ^{13}C NMR ($CDCl_3$): 2 rotamers: δ 20.3, 20.9, 28.4, 36.5, 37.3, 37.9, 38.0, 47.9, 48.1, 50.9, 51.3, 79.7, 79.9, 124.9, 125.1, 131.0, 131.8, 155.2, 176.5, 177.4. IR: 3500-2500, 2979, 1731, 1655, 1434, 1249, 1166, 1125, 887, 757 cm^{-1}. Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.30; H, 8.62; N, 5.18.

*(±)-2-((1R,5S)-3-Oxabicyclo[3.1.0]hexan-1-yl)-2-phenylacetic acid (**2e**).* Colorless oil. ^{1}H NMR ($CDCl_3$): a 56/44 mixture of diastereoisomers: δ 0.65-0.72 (1.4H, m), 0.82 (0.6H, dd, *J* = 5.0 and 8.2 Hz), 1.45-1.49 (0.4H, m), 1.60-1.64 (0.6H, m), 3.61 (0.6H, d, *J* = 8.2 Hz), 3.71 (0.6H, dd, *J* = 2.7 and 8.2 Hz), 3.79-3.85 (3.8H,m), 3.09-3.18, 1H, m), 7.24-7.35 (5H, m). ^{13}C NMR ($CDCl_3$): a 56/44 mixture of diastereoisomers: δ 11.7, 12.0, 21.9, 22.3, 30.4,

30.5, 52.3, 52.6, 69.6, 69.7, 71.3, 71.5, 127.6, 127.7, 128.4, 128.55, 128.60, 128.64, 136.1, 136.3, 177.7, 177.8. IR: 3500-1704, 1166, 1067, 1011, 895, 700 cm^{-1}. HRMS (EI): *m/z* 241.0833 (M^+). Calcd for $C_{13}H_{14}NaO_3$ 241.0835.

*2-(Spiro[4.5]dec-3-en-2-yl)acetic acid (**2f**).* Colorless oil. ^1H NMR ($CDCl_3$): δ 1.23 (1H, dd, *J* = 6.9 and 13.0 Hz), 1.32-1.55 (11H, m), 2.08 (1H, dd, *J* = 8.2 and 13.0 Hz), 2.34 (1H, dd, *J* = 8.2 and 15.5 Hz), 2.47 (1H, dd, *J* = 6.9 and 15.5 Hz), 3.09-3.18, 1H, m), 5.56 (1H, dd, *J* = 2.3 and 5.7 Hz), 5.70 (1H, dd, *J* = 1.8 and 5.7 Hz). ^{13}C NMR ($CDCl_3$): δ 23.4, 23.5, 37.1, 39.2, 40.7, 41.2, 42.3, 49.7, 130.8, 141.1, 179.7. IR: 3500-2400, 2925, 1708, 1447, 1286, 1215, 1196, 946, 757 cm^{-1}. HRMS (EI): *m/z* 194.1303 (M^+). Calcd for $C_{12}H_{18}O_2$ 194.1307.

*3-5-4 Bicyclic γ-lactone **4***

ii) For direct one-pot conversion to bicyclic γ-lactone: after electrolysis, the anode metal, a magnesium rod, was removed from the electrolyzed mixture. DMF (10 mL), water (10 mL), and iodine (761 mg, 3 mmol) were successively added to the electrolyzed mixture, and then the mixture was stirred at 40 °C. After stirring at the same temperature for 6 h, 1 M hydrochloric acid (100 mL) was added to the reaction mixture and then the mixture was extracted with ethyl acetate (30 mL × 5). The combined organic layer was successively washed with saturated $NaHCO_3$ (40 mL × 3), 5% $Na_2S_2O_3$ (100 mL), and water (100 mL × 3). After dryness over $MgSO_4$ followed by evaporation of the solvent, column chromatography on silica gel (hexane/ethyl acetate = 4/1) gave bicyclic γ-lactone **4** (195 mg, 53%).

*(±)-tert-Butyl (3aR,6aR)-6a-(iodomethyl)-2-oxohexahydro-5H-furo[2,3-c]pyrrole-5-carboxylate (**4**).* White solid. mp: 116-117 °C. ^1H NMR ($CDCl_3$): δ 1.50 (9H, s), 2.48 (1H, d, *J* = 15.6 Hz), 2.93-3.01 (2H, m), 3.44 (1H, br s), 3.45 (1H, d, *J* = 11.0 Hz), 3.52 (1H, d, *J* = 11.0 Hz), 3.63 (1H, br s), 3.77-3.82 (2H, m), 3.49 (1H, d, *J* = 13.3 Hz). ^{13}C NMR ($CDCl_3$): δ 8.6, 28.2, 35.7, 41.9, 52.3, 55.4, 80.4, 91.8, 153.7, 174.3. IR: 2967, 1789, 1689, 1415, 1365, 1351, 1246, 1232, 1165, 1115, 1030, 933, 896, 766, 597 cm^{-1}. Anal. Calcd for $C_{12}H_{18}INO_4$: C, 39.25; H, 4.94; I, 34.56; N, 3.81. Found: C, 39.34; H, 4.90; N, 3.74.

Bicyclic γ-lactone **4** was also synthesized from unsaturated carboxylic acid **2a** according to the reported procedure.[38] Unsaturated carboxylic acid **2a** (241 mg, 1 mmol) was dissolved in ether (1 mL) and saturated $NaHCO_3$ (5 mL) at 0 °C. To the stirring mixture was added iodine (761 mg, 3 mmol) in THF (3 mL). After stirring at 0 °C for 3 h, the reaction mixture was extracted with ethyl acetate (30 mL×5). Similar work-up followed by similar column chromatography to direct conversion as mentioned above gave γ-lactone **4** (305 mg, 82%).

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Chapter 4

Electrochemical Studies on the Generation of Aryl and Vinyl Radicals by Electrochemical Reduction of the Corresponding Bromides in the Presence of Methyl 4-*tert*-Butylbenzoate and the Reaction Mechanism of Sequential Radical Cyclization – Fixation of Carbon Dioxide

4-1 Introduction

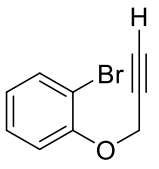
In Chapters 2 and 3, generation of aryl and vinyl radicals from the corresponding bromides successfully carried out by electrochemical reduction in the presence of methyl 4-*tert*-butylbenzoate was described, and their good performance for radical cyclization followed by fixation of carbon dioxide was also described. However, the reaction mechanism of both reactions has not yet been discussed. The exact role of methyl 4-*tert*-butylbanzoate in electrochemical generation of aryl and vinyl radicals from the viewpoint of electrochemistry is still unclear at the present stage.

Several organic electron transfer mediators without metal ions are known to be effective for selective generation of aryl radicals from the corresponding halides. Recently, Kurono and Tokuda reported electrochemical radical cyclization of aryl halides using naphthalene as an electron transfer mediator.[1] Mitsudo and Suga also reported electroreductive cyclization of aryl halides using fluorene derivatives as electron transfer mediators.[2] Methyl 4-*tert*-butylbenzoate was also reported by Senboku et al. to be an effective electron transfer mediator for electrocreductive generation of aryl radicals from 2-allyloxybromobenzenes and the following sequential aryl radical cyclization – fixation of carbon dioxide.[3] They also carried out electrochemical studies using cyclic voltammetry (CV) and clarified the role of their electron transfer mediators from electrochemical aspects. In order to clarify the role of methyl 4-*tert*-butylbenzoate in sequential electrochemical radical cyclization and fixation of carbon dioxide described in Chapters 2 and 3, electrochemical studies of aryl and vinyl bromides and methyl 4-*tert*-butylbenzoate using CV were carried out, and from the results of CV, the reaction mechanism of both reactions described in Chapters 2 and 3 is proposed. In this chapter, the results of CV of aryl and vinyl bromides and the reaction mechanism of sequential radical cyclization – fixation of carbon dioxide proposed from these results are described.

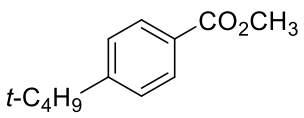
4-2 Electrochemical studies and reaction mechanism of sequential radical cyclization – fixation of two molecules of carbon dioxide by methyl 4-*tert*-butylbenzoate-mediated electrochemical reduction of 2-(2-propynyloxy)bromobenzenes in the presence of carbon dioxide

4-2-1 Cyclic voltammetry of aryl bromide

In order to obtain information about the reaction mechanism in the reaction of aryl radical cyclization described in Chapter 2, cyclic voltammetry (CV) of aryl bromide **1** and methyl 4-*tert*-butylbenzoate, shown in Scheme 1, was carried out and the results are shown in Figure 1. In CV of **1** in DMF, one irreversible reduction peak appeared at –3.2 V versus Ag/Ag^+ (Figure 1(a)). On the other hand, a reversible reduction peak at –2.9 V versus Ag/Ag^+ appeared in CV of methyl 4-*tert*-butylbenzoate (Figure 1(b), (1)). When CV of methyl 4-*tert*-butylbenzoate was performed under the conditions of (1) in the presence of 0.01 mmol of **1**, an increase in reduction peak current and a decrease in oxidation peak current of methyl 4-*tert*-butylbenzoate were observed (Figure 1(b), (2)). Further additions of **1** resulted in further increases in reduction peak current and further decreases in oxidation peak current (Figure 1(b), (3) and (4)). Finally, the oxidation peak in methyl 4-*tert*-butylbenzoate disappeared when CV of methyl 4-*tert*-butylbenzoate was carried out in the presence of 0.04 mmol (0.8 equivalents for the benzoate) of **1** (Figure 1(b), (4)). Similar results were obtained in the study on electroreductive generation of aryl radicals from 2-allyloxybromoarenes using the same mediator system.[3] These results clearly indicate that methyl 4-*tert*-butylbenzoate works as an electron transfer mediator in the present electroreductive generation of aryl radicals from aryl bromides.



1

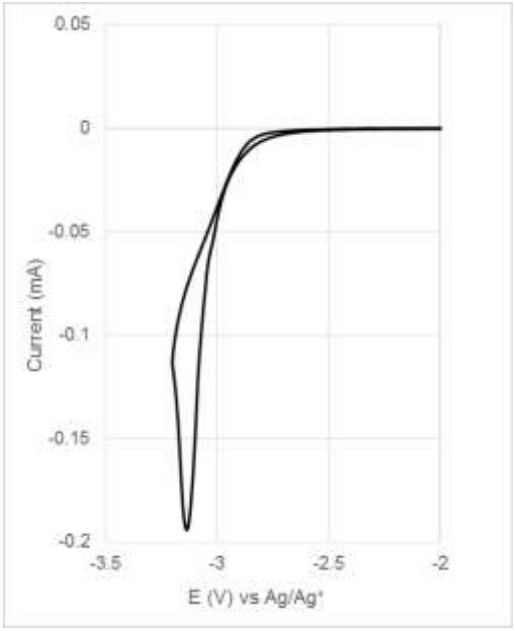


methyl 4-*tert*-butylbenzoate

Scheme 1

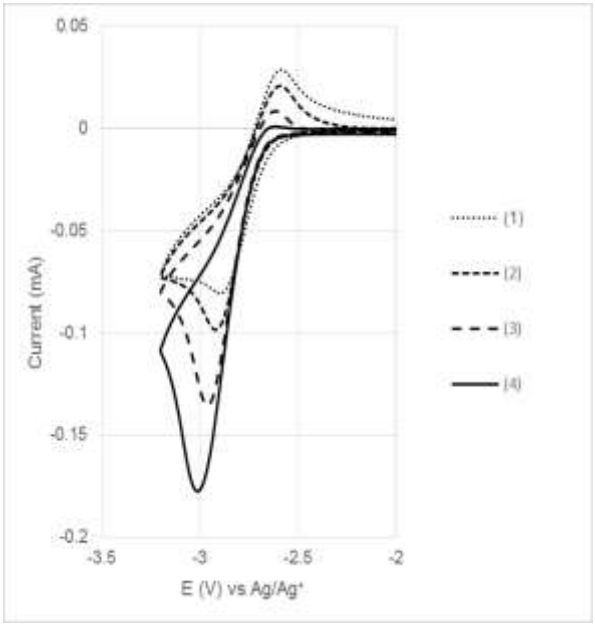
Figure 1 CV of aryl bromide **1** (a) and methyl 4-*tert*-butylbenzoate (b) in the absence and presence of aryl bromide **1**.

(a)



1 (0.075 mmol) in DMF (5 mL)

(b)

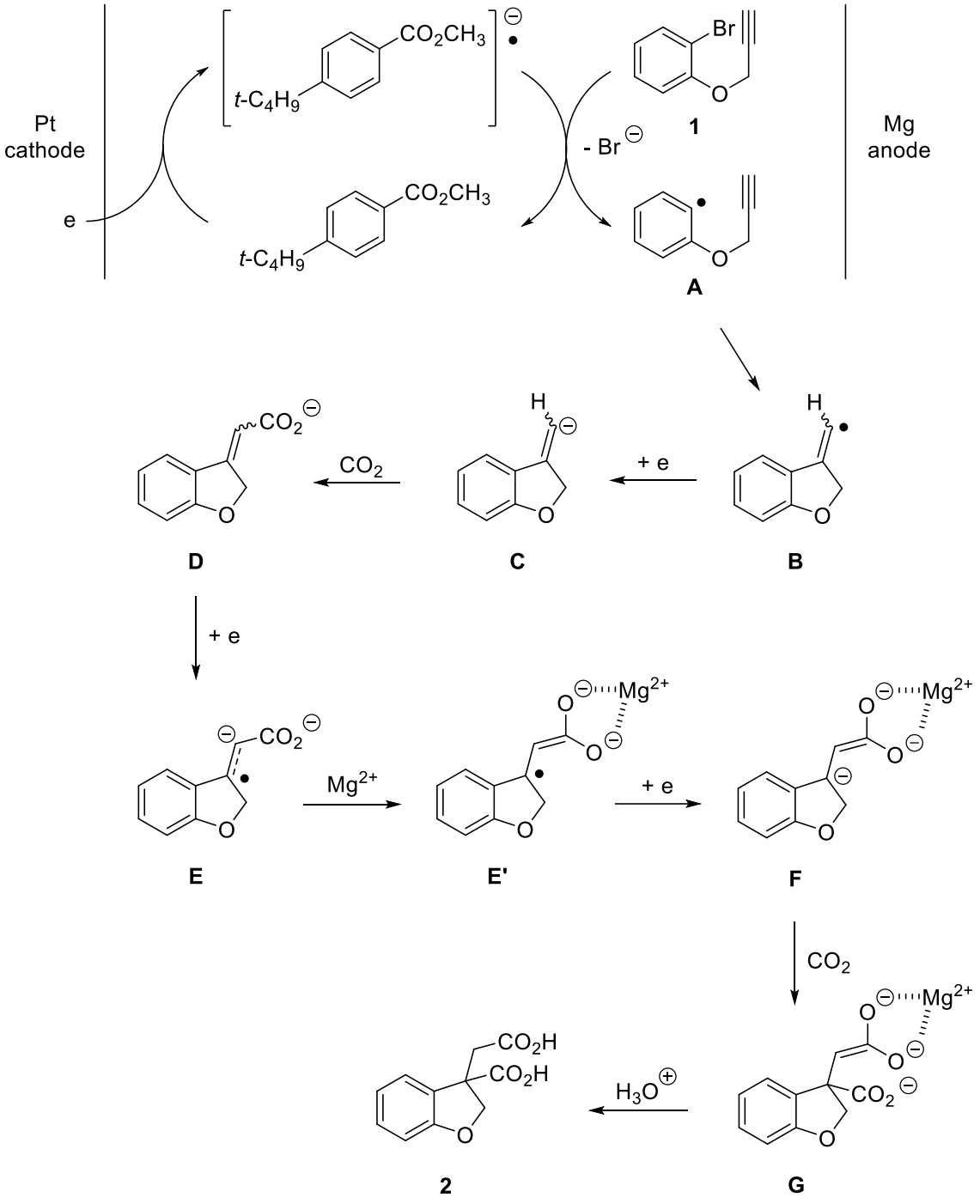


(1): methyl 4-*tert*-butylbenzoate (0.05 mmol) in DMF (5 mL)
(2): (1) + 0.01 mmol of **1**
(3): (2) + 0.01 mmol of **1**
(4): (3) + 0.02 mmol of **1**

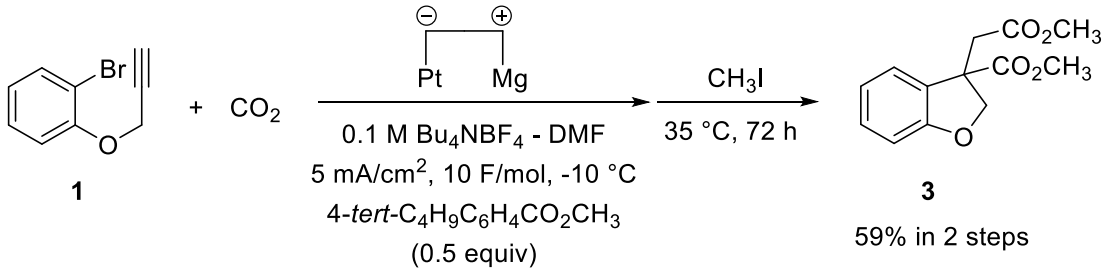
4-2-2 Reaction mechanism

From the results of CV of methyl 4-*tert*-butylbenzoate in the absence and presence of **1**, a probable reaction mechanism in the present aryl radical cyclization followed by tandem carboxylation is shown in Scheme 2. At the cathode, one-electron reduction of methyl 4-*tert*-butylbenzoate, used as an electron transfer mediator, generates the corresponding radical anion. One-electron reduction of aryl bromide **1** by the radical anion of methyl 4-*tert*-butylbenzoate generates the anion radical of **1**, resulting in carbon-bromine bond cleavage to generate aryl radical **A**.[3] In the absence of an electron transfer mediator, methyl 4-*tert*-butylbenzoate, two-electron reduction of aryl bromide **1** competitively occurs at the cathode to generate the corresponding aryl anion species, directly producing carboxylated benzoic acid (Entry 10 in Table 1, Chapter 2). Intramolecular 5-exo cyclization of aryl radical **A** with a carbon-carbon triple bond takes place efficiently to generate the corresponding cyclized vinyl radical **B**. Further one-electron reduction generates the corresponding vinyl anion **C**, which reacts with carbon dioxide to produce the corresponding α,β-unsaturated carboxylate ion **D**, which has a cinnamic acid moiety. It is known that cinnamic acid derivatives can readily be reduced and carboxylated under reductive electron transfer conditions.[4-9] Therefore, further one-electron reduction of α,β-unsaturated carboxylate ion **D** is likely to take place easily to generate the corresponding radical anion **E**. Formation of stable enolate **E'** from the radical anion **E** with magnesium cation followed by further one-electron reduction of **E'** would generate benzylic anion **F**. Selective fixation of carbon dioxide at the benzylic position gives dicarboxylate ion **G**. Acid treatment in workup gives dicarboxylic acid **2**. On the other hand, at the anode, dissolution of an Mg anode as magnesium ion proceeds, resulting in prevention of the oxidation of any species at the anode.[10,11] Direct treatment of the electrolysis mixture with iodomethane was carried out to obtain some information about any anionic intermediates in the medium at the end of the reaction. After electrolysis of **1** under the optimized reaction conditions shown in Entry 9 in Table 1, Chapter 2, additional DMF (10 mL) and an excess amount of iodomethane (50 mmol) were added to the reaction mixture and the mixture was stirred at 35 °C for 72 h. Usual workup followed by column chromatography on silica gel gave dimethyl ester **3**, probably derived from the dicarboxylate ion of **2**, in 59% isolated yield as a major product along with 18% of recovered **1** (Scheme 3). These results indicate that carboxylation of α,β-unsaturated carboxylate ion **D**

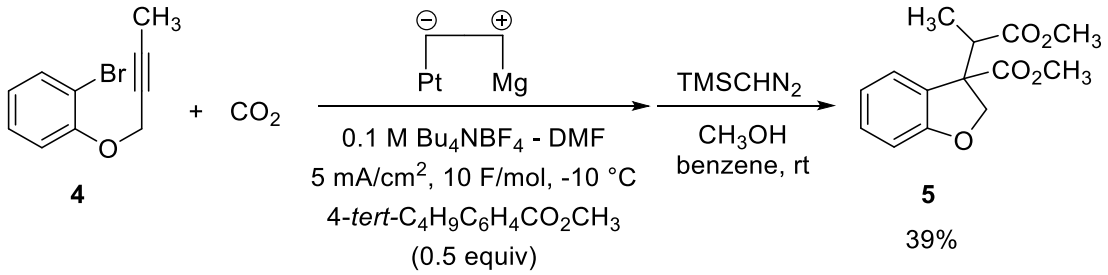
predominantly and selectively occurred only at the benzylic position (β-position) and that no carboxylation occurred at the α-position of the carboxyl group. Although electrochemical carboxylation of cinnamic acid derivatives and β-phenyl-α,β-unsaturated carbonyl compounds often gave a mixture of α- and/or β-carboxylated and α,β-dicarboxylated products along with a hydrogenated product,[4-9] β-selective acylation[12-16] and silylation[17] as well as mono-carboxylation[18] have also been reported under electroreductive[12-15,17-18] or Mg-promoted[16] reaction conditions. β-Selective electrochemical mono-carboxylation of α,β-unsaturated carbonyl compounds, flavones, has been successfully performed under similar electrolysis conditions using an undivided cell equipped with a Pt cathode and an Mg anode in DMF containing 0.1 M Bu_4NBF_4.[18] On the other hand, in the case of the reaction of **4** having an internal alkyne as a radical acceptor (Scheme 4, Entry 3 in Table 2, Chapter 2), electron transfer steps following aryl radical cyclization might be problematic since tandem radical cyclization of **6** having an internal alkyne and an alkene as radical acceptors proceeded efficiently to give tandem cyclization product **7** in good yield, 73% (Scheme 5), though it is still unclear.



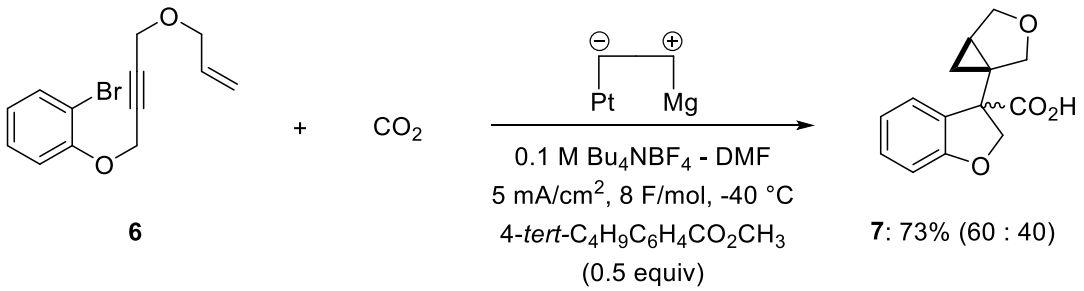
Scheme 2



Scheme 3



Scheme 4

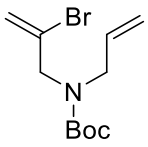


Scheme 5

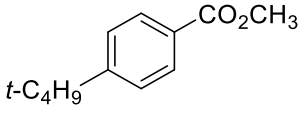
4-3 Electrochemical studies and reaction mechanism of sequential vinyl radical cyclization/fixation of carbon dioxide by methyl 4-*tert*-butylbenzoate-mediated electrochemical reduction of vinyl bromides in the presence of carbon dioxide

4-3-1 Cyclic voltammetry of vinyl bromide

To obtain information about the exact role of methyl 4-*tert*-butylbenzoate and the reaction mechanism in generaion of vinyl radicals by elctrochemical reduction of viyl bromides described in Chapter 3, CV of vinyl bromide **8** and methyl 4-*tert*-butylbenzoate, shown in Scheme 6, was carried out, and the results are shown in Figure 2. While vinyl bromide **8** provided no clear reduction peak at > –3.0 V versus Ag/Ag^+ in CV (Figure 2(a)), methyl 4-*tert*-butylbenzoate gave one reversible reduction peak at –2.9 V versus Ag/Ag^+ in CV (Figure 2(b)-(1)). CV of methyl 4-*tert*-butylbenzoate was also carried out in the presence of different amounts of vinyl bromide **8** as shown in Figure 2(b)-(2), 2(b)-(3), and 2(b)-(4). An increase in the amount of **8** in CV of methyl 4-*tert*-butylbenzoate resulted in an increase in reduction peak current and a decrease in oxidation peak current of methyl 4-*tert*-butylbenzoate. Similar phenomena were observed in electroreductive generation of aryl radicals from bromoarenes using the same mediator system.[3] These results strongly suggest that methyl 4-*tert*-butylbenzoate plays an important role and also works as an electron transfer mediator in the present electroreductive generation of a vinyl radical from vinyl bromide.



8

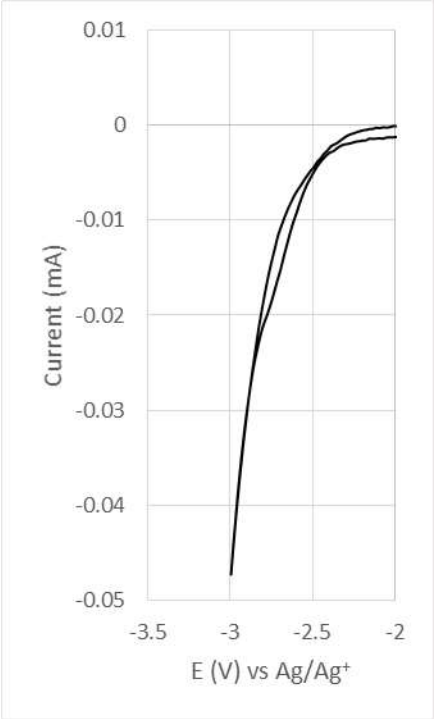


methyl 4-*tert*-butylbenzoate

Scheme 6

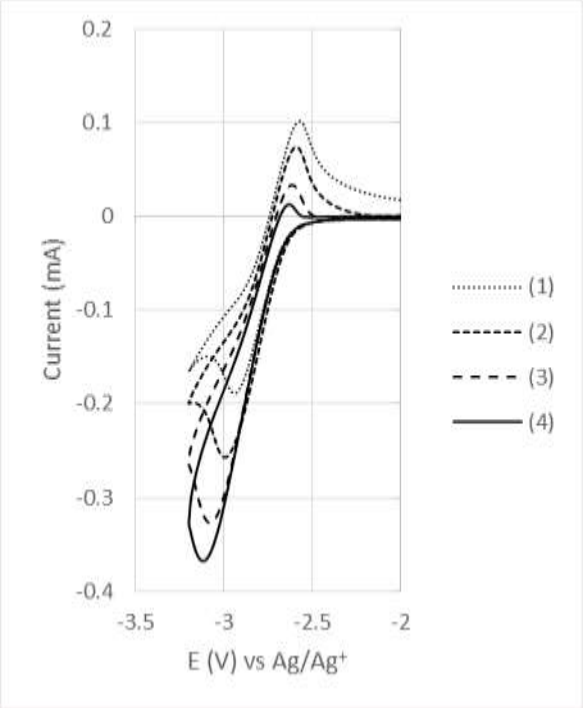
Figure 2 CV of vinyl bromide **8** (a) and methyl 4-*tert*-butylbenzoate (b) in the absence and presence of vinyl bromide **8**.

(a)



8 (0.1 mmol) in DMF (5 mL)

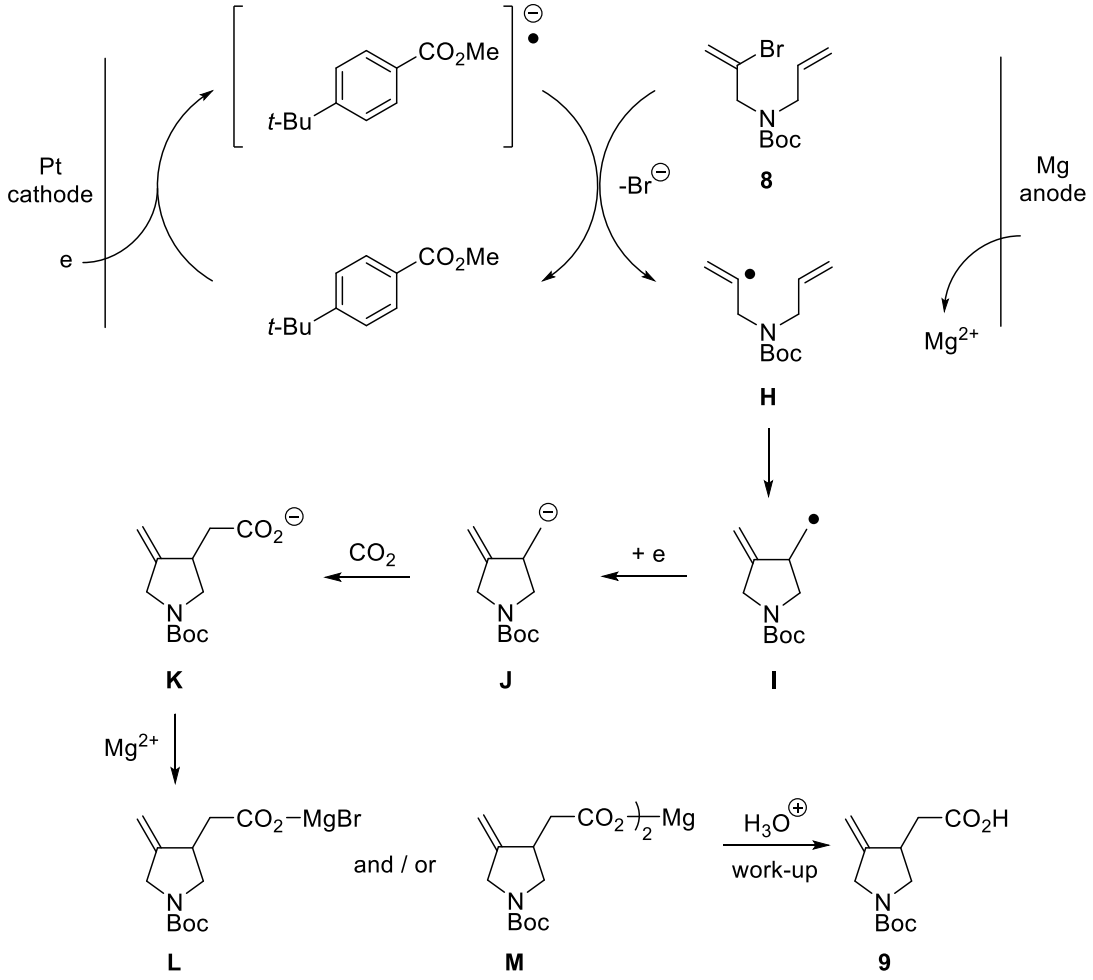
(b)



(1): methyl 4-*tert*-butylbenzoate (0.1 mmol) in DMF (5 mL)
(2): (1) + 0.025 mmol of **8**
(3): (1) + 0.075 mmol of **8**
(4): (1) + 0.1 mmol of **8**

4-3-2 Reaction mechanism

A plausible reaction mechanism in the present vinyl radical cyclization – fixation of carbon dioxide sequential reaction is shown in Scheme 7. At the cathode, one-electron reduction of methyl 4-*tert*-butylbenzoate, used as an electron transfer mediator, takes place to generate the corresponding radical anion. One-electron reduction of vinyl bromide **8** by the radical anion of methyl 4-*tert*-butylbenzoate generates the anion radical of **8**, which results in carbon-bromine bond cleavage to generate vinyl radical **H**. Cyclization of the resulting vinyl radical **H** produces cyclized radical intermediate **I**. Further one-electron reduction of **I** generates the corresponding carbo anion **J**, which reacts with carbon dioxide to give the corresponding carboxylate **K**. In the absence of an electron transfer mediator, radical cyclization and further one-electron reduction of the resulting vinyl radical at the cathode would take place competitively to reduce product selectivity of cyclized carboxylic acid. In some cases, the *gem*-disubstituent effect[19] would support cyclization to give high product selectivity even in the absence of an electron transfer mediator. On the other hand, at the anode, dissolution of a magnesium anode as magnesium ion, which would prevent oxidation of any species at the anode,[10,11] occurs, resulting in the formation of magnesium salt of carboxylate **K**, magnesium carboxylate **L** and/or **M**. Acid treatment in work-up gives carboxylic acid **9**.


Pt
cathode
e
CO2Me
t-Bu
CO2Me
t-Bu
-Br
Br
N
Boc
8
Mg
anode
Mg2+
N
Boc
H
CO2
+ e
CO2
N
Boc
K
N
Boc
J
N
Boc
I
Mg2+
CO2–MgBr
and / or
CO2)2Mg
N
Boc
L
N
Boc
M
H3O
work-up
CO2H
N
Boc
9

Scheme 7

4-3 Conclusion

In conclusion, cyclic voltammetry of aryl and vinyl bromides was carried out in the absence and presence of methyl 4-*tert*-butylbenzoate, which is an additive of the reaction described in Chapters 2 and 3 and plays an important role in both reactions. From the results, it was found that methyl 4-*tert*-butylbenzoate plays a role as an electron transfer mediator in both reactions. In electrochemical reduction of aryl and vinyl bromides in the presence of methyl 4-*tert*-butylbenzoate, one-electron reduction of methyl 4-*tert*-butylbenzoate predominantly occurs to generate the corresponding radical anion, from which electron transfer occurs to aryl and vinyl bromides to give radical anions of aryl and vinyl bromides. For selective generation of the corresponding radicals from aryl and vinyl bromides and the following carboxylation, methyl 4-*tert*-butylbenzoate was found to be an essential and critical electron transfer mediator.

4-4 Experimental

General

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a JASCO FT/IR-410 spectrometer in neat form unless otherwise stated. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded in indicated solvents with a JEOL ECX400P or ECS400 FT NMR spectrometer. The chemical shifts, δ, are given in ppm with tetramethylsilane for ^{1}H and solvents for ^{13}C as references. J values are in Hz. Peak multiplicities were given as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. MS spectra and elemental analyses were carried out using a JEOL JMS-T100GCv or Thermo Scientific Exactive and Exacter Analytical CE440 or J-Science Lab JM10, respectively, at Instrumental Analysis Division, Equipment Management Center Creative Research Institution, Hokkaido University. Electrochemical reactions were carried out using a Constant Current Power Supply (model 5944), Metronix Corp., Tokyo. Cyclic voltammetry was carried out by a Hokuto Denko HSV-100 in DMF containing 0.1 M Bu_4NBF_4 using a Pt disk electrode (ϕ 1.6 mm) as a working electrode, a Pt wire (ϕ 0.5 mm) as a counter electrode, and $Ag/Ag^+/CH_3CN/Bu_4NClO_4$ (0.01 M $AgNO_3$ in 0.1 M Bu_4NClO_4 in CH_3CN), purchased from BAS (product code: RE-7), as a reference electrode, respectively, with a scan rate of 100 mV/sec (for **1**) or 200 mV/sec (for **8** and methyl 4-*tert*-butylbenzoate in the absence and presence of **1** and **8**). Column chromatography was carried out using Kanto Kagaku Silica gel 60N. Reagents and solvents were commercially available and were used as received without further purification.

*4-4-1 Electrochemical reaction followed by direct treatment of the electrolysis mixture of **1** with iodomethane*

Electrolysis of **1** (1 mmol) was carried out as described in *2-4-2 General procedure for electrochemical reaction*. After electrolysis, the anode metal, a magnesium rod, was removed from the electrolyzed mixture, and then anhydrous DMF (10 mL) and iodomethane (7.1 g, 50 mmol) were added to the electrolyzed mixture. The mixture was then stirred at 35 °C for 72 h. To the mixture was added 1 M HCl (100 mL) and the mixture was extracted with ethyl acetate (30 mL×5). The combined organic layer was washed with saturated $NaHCO_3$ (40

mL×3) and H_2O (100 mL×3) successively and was then dried over $MgSO_4$. Evaporation followed by column chromatography on silica gel (hexane/ethyl acetate = 10/1) gave methyl 3-methoxycarbonyl-2,3-dihydrobenzo[b]furan-3-ylaceate (**3**, 149 mg, 59%) and recovered **1** (38 mg, 18%).

*Methyl 3-methoxycarbonyl-2,3-dihydrobenzo[b]furan-3-ylaceate (**3**)*. Yield: 59%. Solid, mp: 103–104 °C. ^{1}H NMR ($CDCl_3$): δ 7.23–7.15 (2H, m), 6.88 (1H, t, *J* = 7.5 Hz), 6.84 (1H, d, *J* = 8.2 Hz), 5.31 (1H, dd, *J* = 10.1 Hz), 4.44 (1H, d, *J* = 10.1 Hz), 3.74 (3H, s), 3.71 (3H, s), 3.44 (1H, d, *J* = 17.4 Hz), 2.75 (1H, d, *J* = 17.4 Hz). ^{13}C NMR ($CDCl_3$): δ 172.4.8, 171.3, 159.6, 130.1, 127.4, 123.8, 120.8, 110.3, 78.9, 53.7, 53.0, 52.0, 42.3. IR (KBr): 1731, 1596, 1484, 1364, 1297, 1258, 1230, 1213, 1168, 962, 756 cm^{-1}. Anal.: Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.35; H, 5.54.

*4-4-2 Electrochemical reaction of **4** and **6**.* See *2-5-2 General procedure for electrochemical reaction*.

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Chapter 5

Conclusion

As a conclusion, sequential radical cyclization – fixation of carbon dioxide by electrochemical reduction of aryl and vinyl bromides was successfully carried out and was described in Chapters 2 and 3. Electrochemical studies of methyl 4-*tert*-butylbenzoate, used as an electron transfer mediator in the present reaction, in the absence and presence of aryl and vinyl bromides, used as substrates, were also carried out, and the reaction mechanisms of the present sequential reactions from the results of these electrochemical studies were proposed in Chapter 4.

The first example of radical cyclization followed by anionic termination with carbon dioxide under electrochemical reduction conditions without a metal catalyst and reagents was reported in 2011. However, further investigation of this reaction system has not been carried out. In this study, application and development of this novel process were successfully carried out as a new cascade radical – anion reaction. The present reactions are important, attractive and potential as a clean and sustainable organic synthesis process.

Carbon dioxide is an abundant, economical, non-toxic and environmentally-benign carbon source and is the best C1 chemical reagent for organic synthesis. Development of the use of carbon dioxide as a C1 source in organic synthesis is an important subject from the viewpoint of green and sustainable chemistry and reuse of a carbon source. In this study, a novel fixation process for carbon dioxide was successfully developed using an electrochemical method. Although result of many studies on electrochemical fixation of carbon dioxide have been reported, only a few examples of sequential radical cyclization – fixation of carbon dioxide by an electrochemical method have been reported. Since electrochemical fixation of carbon dioxide is a totally green and environmentally benign process, the unique sequential radical cyclization – carboxylation reaction in this study would be a very important and attractive process as an environmentally benign novel organic transformation method.

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