Nickel- and Cobalt-Catalyzed Carbon–Carbon Bond-Forming Reactions Employing Carbon Dioxide

Keisuke Nogi

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Abbreviations

Ac	acetyl
Anal.	elemental analysis
APCI	atmospheric pressure chemical ionization
Ar	aryl
Bn	benzyl
bpy	2,2'-bipyridine
calcd	calculated
cod	1,5-cyclooctadiene
Cy	cyclohexyl
d.r.	diastereomeric ratio
DABCO	1,4-diazabicyclo[2,2,2]octane
DG	directing group
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino) ethane
dppf	1,1'-Bis(dipheylphosphino) ferrocene
dppe	1,3-bis(diphenylphosphino) propane
ee	enantiomeric excess
EI	electron impact
eq	equation
equiv	equivalent(s)
ESI	electrospray ionization
GC	gas chromatography
GPC	gel permeation chromatography
Hex	*n*-hexyl
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
HRMS	high resolution mass spectrometer
IR	infrared
L	ligand
LG	leaving group
m.p.	melting point
MALDI	Matrix Assisted Laser Desorption/Ionization
MPLC	medium pressure liquid chromatography
MS	mass spectrometer
neoc	neocuproine, 2,9-dimethyl-1,10-phenanthroline
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PPh_3	triphenylphosphine
PCy_3	tricyclohexylphosphine
phen	1,10-phenanthroline
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TMS	trimethylsilyl
THF	tetrahydrofuran
Tf	trifluoromethanesulfonyl
Ts	tosyl, *p*-toluenesulfonyl

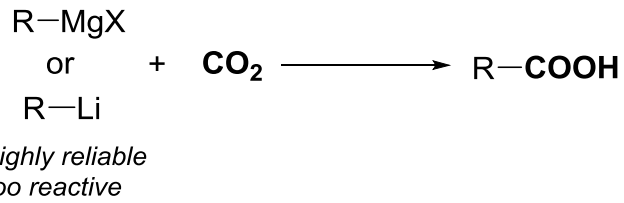
Contents

General Introduction

Carbon–carbon bond forming reactions utilizing carbon dioxide (CO_2). Transformation of carbon dioxide (CO_2) to organic compounds has been one of the most important challenges in synthetic organic chemistry owing to nontoxicity, low cost, and abundance of CO_2.[1,2] Among the chemical fixation of CO_2, carbon–carbon (C–C) bond forming reaction is the most straightforward method to produce carboxylic acids and their derivatives. Therefore, substantial efforts to develop the carboxylation reaction employing CO_2 have been made.

A typical and classical synthetic method of carboxylic acids is the reaction of highly reactive Grignard or organolithium reagents with CO_2 (Scheme 1).

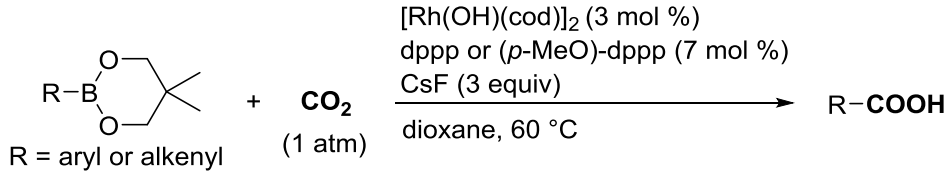
Scheme 1. Reaction of Grignard or Organolithium Reagents with CO_2



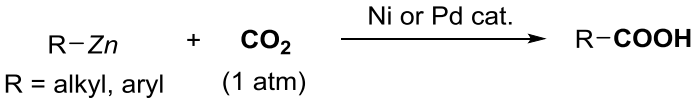
Although this protocol is a reliable and well established method to access carboxylic acids, these organometallic reagents are too reactive to be compatible with functional groups such as a carbonyl moiety. To overcome the limitation of functional group tolerance, significant number of efforts have been devoted employing organometallic reagents having *moderate* reactivity as compared to Grignard or organolithium reagents. The first carboxylation reaction of an organometallic reagent having *moderate* reactivity was achieved using organotin reagent in the presence of a palladium catalyst.[3] However, only allyl tin reagents could be employed as the substrate, and high pressure of CO_2 (33 atm) was required. Moreover, inherently, organotin reagents are highly toxic and an alternative method using other organometallic reagents had been desired. In 2006, Iwasawa and coworkers developed the carboxylation of aryl and alkenyl boronic acid esters employing a rhodium catalyst under 1 atm pressure of CO_2 (Scheme 2).[4] Carbonyl and cyano groups are compatible during the course of carboxylation reaction owing to moderate reactivity of organoboron reagent. Afterwards, the Iwasawa group and the Hou group independently found that the carboxylation of aryl and alkenyl boronic acid esters proceeded with copper catalysts.[5] In 2011, carboxylation of alkylboranes prepared by hydroboration of alkenes

was accomplished with copper catalysts.[6] Concerning the carboxylation of other organometallic reagents, the Yorimitsu and Oshima group, and the Dong group independently reported the carboxylation of organozinc reagents that have both good reactivity and functional group compatibility, in the presence of nickel or palladium catalysts (Scheme 3).[7] Later, Kondo and co-workers found that a stoichiometric amount of lithium chloride promoted the carboxylation of organozinc reagents in the absence of transition-metal catalysts.[8] Very recently, organosilane compounds were found to be potentially reactive toward CO_2 with the aid of a stoichiometric amount of cesium fluoride.[9]

Scheme 2. Rhodium-Catalyzed Carboxylation of Aryl and Alkenyl Boronic Acid Esters with CO_2

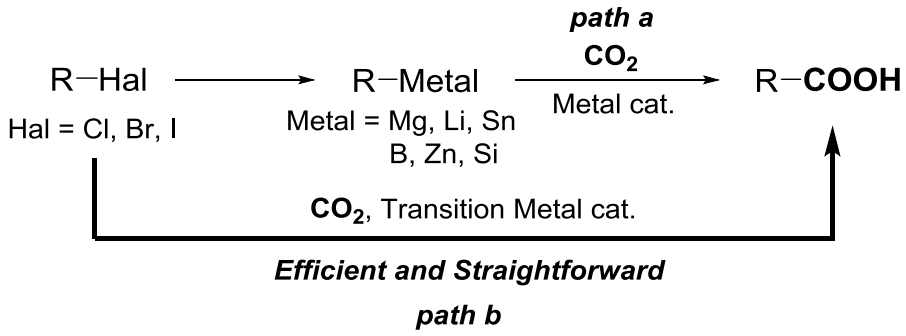


Scheme 3. Catalytic Carboxylation of Organozinc Reagents with CO_2



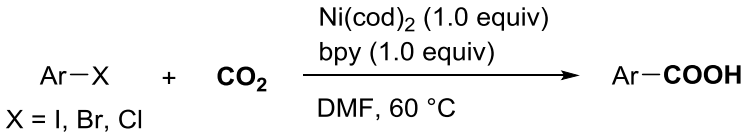
As described above, C–C bond forming reaction of CO_2 with moderately reactive organometallic reagents has been developed in the presence or absence of transition metal catalysts (Scheme 4, *path a*). However, almost all organometallic reagents must be prepared from the corresponding organic halides before the carboxylation reaction. Therefore, direct carboxylation of organic halides with CO_2 must be more straightforward method to access carboxylic acids and their derivatives (Scheme 4, *path b*).

Scheme 4. Comparison between the Carboxylation of Organometallic Reagents and Organic Halides

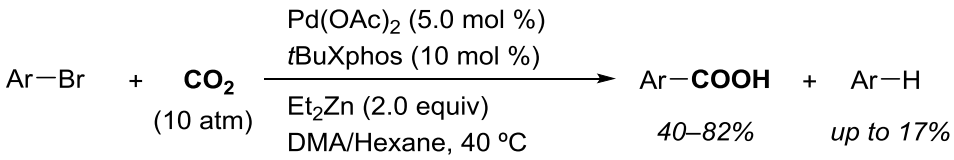


The first catalytic carboxylation of organic halides was achieved as an *electrochemical* carboxylation reaction of aryl halides in the presence of nickel or palladium catalysts.[10] However, unfortunately, electrolytic reaction is not suitable for synthetic chemistry due to limited scope of substrates as well as requirement of special equipment. In contrast, carboxylation of aryl halides was accomplished by the Osakada and Yamamoto group utilizing *stoichiometric* amount of zero-valent nickel complex (Scheme 5).[11] In 2009, Martin and co-worker discovered the carboxylation of aryl bromides catalyzed by a palladium complex with diethyl zinc (Et_2Zn) as a reducing reagent (Scheme 6).[12] Although this reaction realized catalytic carboxylation of aryl halides, it has several drawbacks; (1) only aryl bromides were converted to the carboxylic acids, and aryl chlorides and iodides could not be employed as substrates; (2) 10 atm pressure of CO_2 was required for efficient reaction progress; (3) an excess amount of highly reactive and pyrophoric Et_2Zn was necessary as a reducing reagent; (4) significant amounts (almost 20%) of protodebrominated arenes were inevitably produced as byproducts.

Scheme 5. Carboxylation of Aryl Halides Promoted by Stoichiometric Amount of Ni(0)

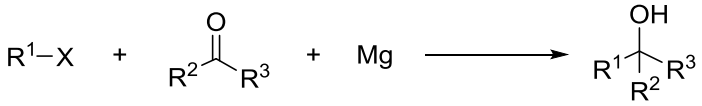


Scheme 6. Palladium-Catalyzed Carboxylation of Aryl Bromides Utilizing Et_2Zn as a Reducing Reagent



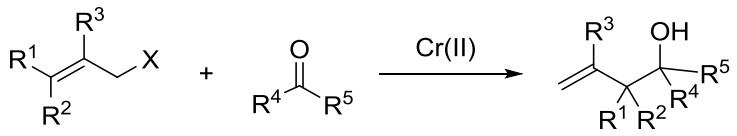
Catalytic reductive coupling reaction of organic halides with carbonyl compounds. Carbonyl compounds such as aldehydes and ketones are considered as a versatile and readily accessible building block for organic syntheses. Although the addition reaction of organometallic reagents such as Grignard or organolithium reagents to carbonyl compounds is a reliable and well-polished methodology, these organometallic reagents must be prepared from the corresponding organic halides before use. In this perspective, Barbier reaction is a more straightforward and step-economical synthetic protocol, in which the addition of organic halides to carboxyl compounds occurs employing magnesium[13] (Scheme 7) or other metal reducing reagents (Al, Zn, In, and others), through *in situ* generation of the corresponding organometallic reagents.[14] However, these reagents are often suffered from poor functional group compatibility.

Scheme 7. Barbier Reaction Mediated by Metallic Magnesium



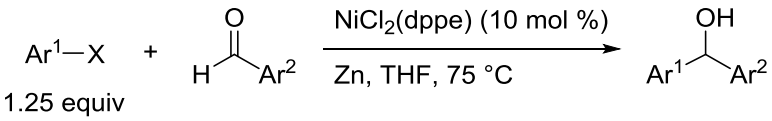
In 1977, Considerable progress in Barbier-type reaction was made by Hiyama, Nozaki, and co-workers. They achieved the allylation of carbonyl compounds in the presence of low-valent Cr(II) (Scheme 8).[15a] This reaction is called as the Nozaki-Hiyama-Kishi (NHK) reaction, and offers chemoselectivity as well as functional group compatibility.[15,16] However, more than two equivalents of air-sensitive Cr(II) salt have to be used as a reducing reagent in this system.

Scheme 8. Cr(II)-Promoted Allylation of Carbonyl Compounds



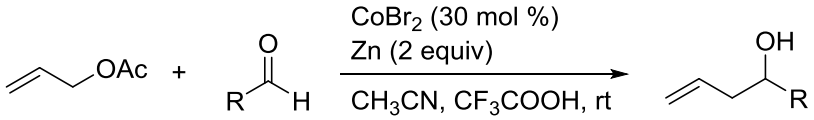
In 1996, Fürstner and co-worker developed the NHK reaction employing a catalytic amount of chromium and Mn powder as a reducing reagent.[17] However, only reactive organic halides such as iodides, triflates and allyl bromide could be adapted for this method. In 2000, the Cheng group discovered the nickel-catalyzed arylation of aromatic aldehydes with aryl bromide utilizing Zn powder as a reducing reagent (Scheme 9).[18]

Scheme 9. Nickel-Catalyzed Arylation of Aromatic Aldehydes with Aryl Bromides



It triggered extensive follow-up works to discover novel coupling reactions employing carbonyl compounds catalyzed by nickel or late transition-metals in the presence of metal powders as reducing reagents. Among them, cobalt complexes have also shown efficient catalytic activity for C–C bond forming reactions using carbonyl compounds. In 2003, Gosmini and co-workers found that sub-stoichiometric amounts of cobalt bromide ($CoBr_2$) provided efficient system for allylation of aldehydes with allyl acetates through carbon–oxygen (C–O) bond cleavage in the presence of Zn powder (Scheme 10).[19] The cobalt catalysis system could be also used for the allylation of ketones and aldimines, affording tertiary alcohols and secondary amines, respectively.[19,20]

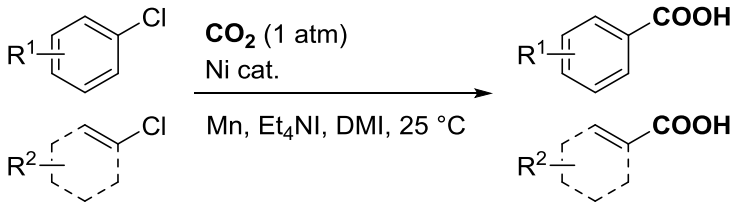
Scheme 10. $CoBr_2$-Promoted Allylation of Aldehydes with Allyl Acetates



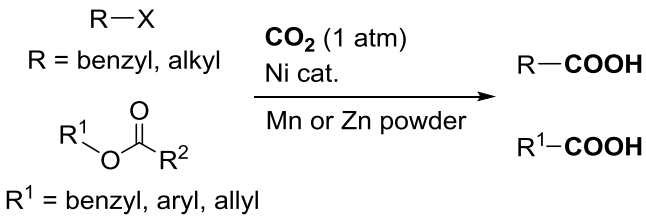
Based on these precedents, the author envisioned that catalytic C–C bond forming reaction between organic halides or esters, and CO_2 would be developed by means of a nickel or cobalt catalyst, and Zn or Mn powder as a reducing reagent.

In 2012, we developed an efficient carboxylation protocol for the aryl and alkenyl chlorides employing nickel catalysts and Mn powder as a reducing reagent (Scheme 11).[21] After this finding, Martin and co-workers have also reported the carboxylation of benzyl[22] and alkyl halides[23] with CO_2 proceeded utilizing nickel catalysts. They also accomplished the carboxylation of benzyl, aryl,[24] and allyl esters[25] through C–O bond cleavage (Scheme 12). On the other hand, we focused on the cobalt catalysts and have developed the carboxylation of propargyl acetates,[26] alkenyl triflates and sterically hindered aryl triflates.[27]

Scheme 11. Nickel-Catalyzed Carboxylation Aryl and Alkenyl Chlorides



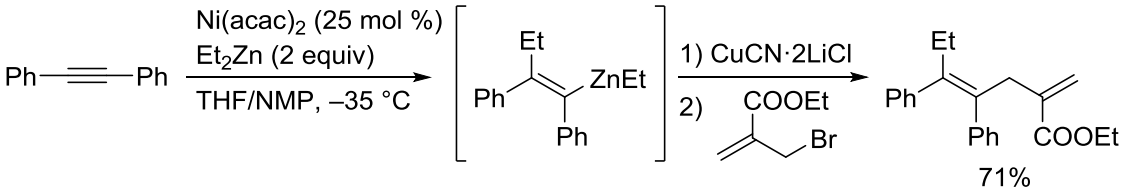
Scheme 12. Nickel-Catalyzed Carboxylation Reactions Developed by the Martin Group



Transition metal-catalyzed carbozincation of carbon–carbon triple bond. Organozinc reagents are one of the most important organometallic reagents in synthetic chemistry because they have both appropriate reactivity and wide functional group compatibility. Transition metal-promoted carbozincation of C–C multiple bond is an efficient and straightforward method to prepare sophisticated and stereodefined organozinc reagents. Among them, the carbozincation of alkynes should be an attractive synthetic method since this affords alkenyl zinc reagents which can be subsequently delivered to multi-substituted olefins. The carbozincation of alkynes was first accomplished by

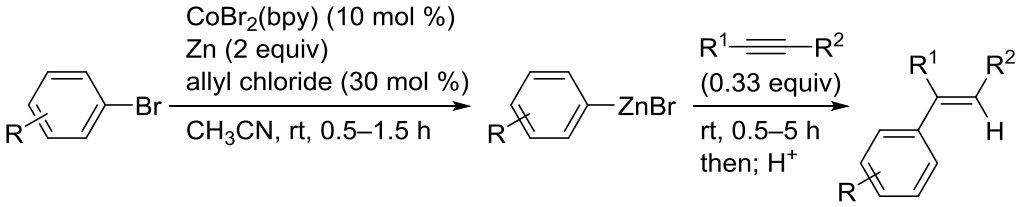
Negishi and co-workers employing a stoichiometric amount of zirconocene dihalide (X_2ZrCp_2, X = Cl, Br, I) and dialkylzinc reagent.[28] In 1997, the Knochel group developed the nickel-catalyzed *syn*-stereoselective carbozincation of internal alkynes utilizing dialkylzinc reagent.[29] They also demonstrated further derivatization of the *in situ* generated trisubstituted alkenyl zinc species employing several electrophiles, giving tetrasubstituted olefins stereoselectively (Scheme 13).

Scheme 13. Nickel-Catalyzed Carbozincation of Diphenylacetylene and Subsequent Reaction with Allyl Bromide.



Over the last two decades, considerable advance in carbozincation of alkynes has been achieved employing diverse organozinc reagents (RZnX or R_2Zn, R = aryl, alkyl, alkenyl, allyl, benzyl and alkynyl groups).[30,31] Recently, the Gosmini group found that cobalt complexes catalyzed the zincation of aryl halides with metallic Zn powder,[32] and subsequent arylzincation of alkynes also proceeded with the cobalt catalysts (Scheme 14).[33]

Scheme 14. Cobalt-Catalyzed Formation of Arylzinc Species and Subsequent Arylzincation of Alkynes.

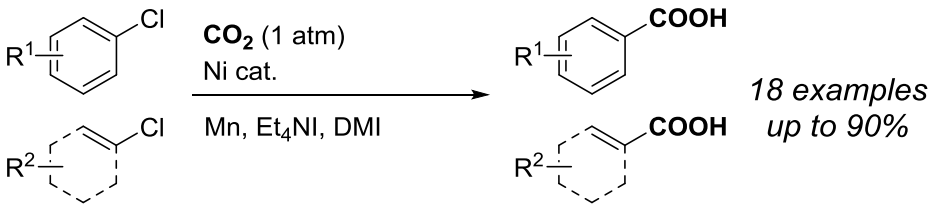


On the other hand, as mentioned above, cobalt complexes have shown catalytic activity for the carboxylation reaction utilizing CO_2.[26,27,34] Intrigued by these perceptions, the author conceived the cobalt-catalyzed carboxyzincation of alkynes, in which both carboxyl moiety and zinc atom are simultaneously incorporated, employing CO_2 and metallic Zn powder.

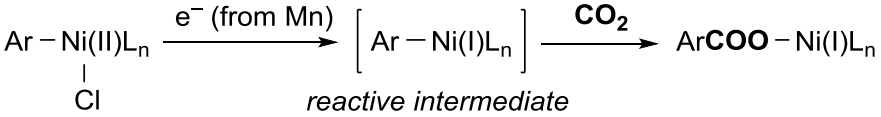
Overview of the present Thesis. Based on above mentioned precedents about the coupling reaction of organic halides and carbonyl compound, the author anticipated that C–C bond formation between organic halides and CO_2 must be achieved employing nickel or cobalt catalysts in the presence of elemental metal reducing reagents such as Zn or Mn powder. In Chapters 1–3, nickel and cobalt-catalyzed carboxylation reactions of organic halides, triflates and esters are demonstrated. These reactions proceeded well under 1 atm pressure of CO_2 utilizing Mn powder as an electron donor.

In Chapter 1, the author describes the nickel-catalyzed carboxylation of less reactive aryl chlorides employing Mn powder as a reducing reagent under 1 atm pressure of CO_2 (Scheme 15).[21] Aryl chlorides with various functional groups can be converted to the corresponding benzoic acids. Furthermore, alkenyl chlorides are also carboxylated in this system. Stoichiometric reactions revealed that *in situ* generated highly reactive Ni(I) intermediate would be indispensable for the reaction with CO_2 under mild reaction conditions (Scheme 16).

Scheme 15. Nickel-Catalyzed Carboxylation of Aryl and Alkenyl Chlorides with CO_2

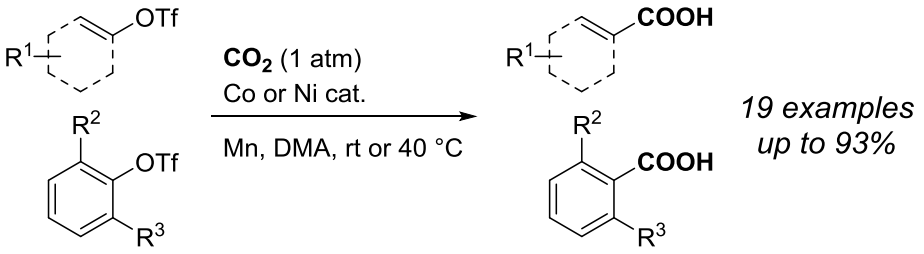


Scheme 16. Plausible Mechanism of CO_2 Insertion Step



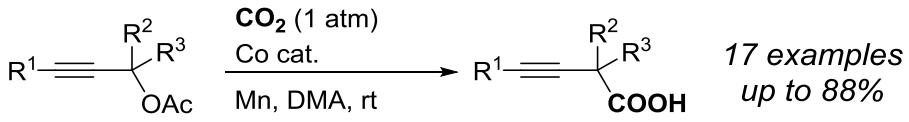
The carboxylation protocol as described in Chapter 1 has great advantage compared to the conventional carboxylation method of organic halides with CO_2. Therefore, toward further application of this methodology, the author focused his attention on the carboxylation of organic triflates as substrates due to their accessibility as well as the reliable activity for C–O bond cleavage promoted by transition metal catalysts. Chapter 2 is devoted to the carboxylation of alkenyl triflates and sterically hindered aryl triflates employing a cobalt or nickel catalyst (Scheme 17).[27] Diverse alkenyl triflates and sterically hindered aryl triflates were converted to the corresponding carboxylic acids under 1 atm pressure of CO_2.

Scheme 17. Cobalt- or Nickel-Catalyzed Carboxylation of Alkenyl and Sterically Hindered Aryl Triflates



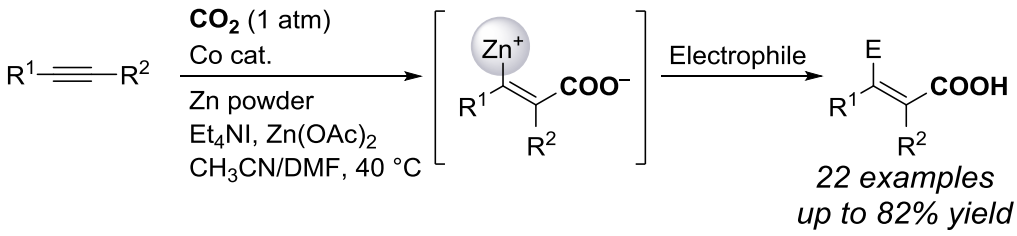
Propargyl esters are one of attractive synthons because it possesses synthetically useful alkyne moiety. Indeed, various transformations such as the palladium-catalyzed Tsuji-Trost reaction have been established employing propargyl esters as substrates. In Chapter 3, the cobalt-catalyzed carboxylation of propargyl acetates employing Mn powder as a reducing reagent is described (Scheme 18).[26] This reaction smoothly proceeded under 1 atm pressure of CO_2 at room temperature with a perfect regioselectivity.

Scheme 18. Cobalt-Catalyzed Carboxylation of Propargyl Acetates with CO_2



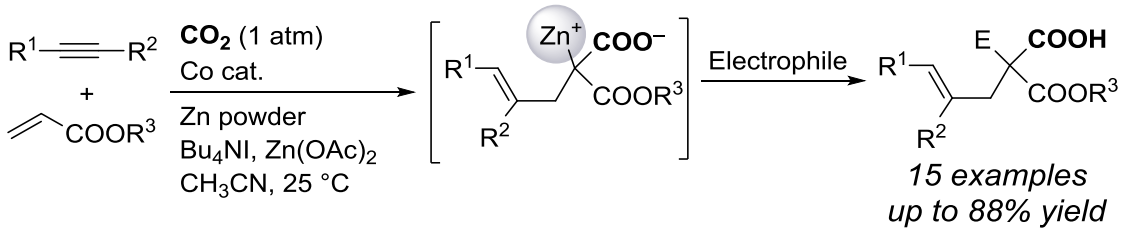
Carboxyzincation of an alkyne employing CO_2 affording *β*-zincated acrylate is highly attractive protocol in terms of not only CO_2 fixation, but also the preparation of organozinc reagents. As mentioned above, cobalt complexes promoted carbon–zinc (C–Zn) bond formation utilizing metallic Zn as well as catalytic carboxylation with CO_2. Intrigued by those presidents and consideration, cobalt-catalyzed carboxyzincation of alkynes employing CO_2 and metallic Zn powder is presented in Chapter 4 (Scheme 20).[35] Diverse internal alkynes can be converted to synthetically useful *syn*-stereoselective alkenyl zinc reagents in the presence of Zn powder under 1 atm pressure of CO_2. Indeed, the subsequent transformation of *in situ* generated alkenyl zinc reagents with several electrophiles furnished stereodefined trisubstituted acrylic acids.

Scheme 20. Cobalt-Catalyzed Carboxyzincation of Alkynes Employing CO_2 and Zn Powder



Carboxyzincation of alkynes described in Chapter 4 inspired the author to examine a multicomponent coupling reaction involving CO_2 and metallic Zn powder. In Chapter 5, the four-component coupling reaction of alkyne, acrylate, CO_2 and metallic Zn catalyzed by a cobalt complex is described (Scheme 21).[36] In this catalyst system, various coupling products were obtained moderate to good yields with perfect regio- and stereoselectivity.

Scheme 21. Cobalt-Catalyzed Carboxylative Coupling Reaction of Alkyne and Acrylate Employing CO_2 and Zn Powder



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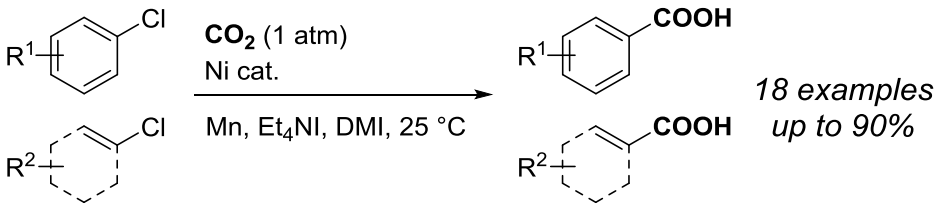
Chapter 1

Nickel-Catalyzed Carboxylation of Aryl and Alkenyl Chlorides Employing Carbon Dioxide

Nickel-catalyzed carboxylation of aryl and alkenyl chlorides employing carbon dioxide (CO_2) has been developed. The reactions proceeded under a CO_2 pressure of 1 atm at room temperature in the presence of nickel catalysts and Mn powder as a reducing agent. Various aryl chlorides could be converted to the corresponding carboxylic acids in good to high yields. Furthermore, alkenyl chlorides were successfully carboxylated with CO_2. Mechanistic study suggests that Ni(I) species is involved in the catalytic cycle.



1-1. Introduction

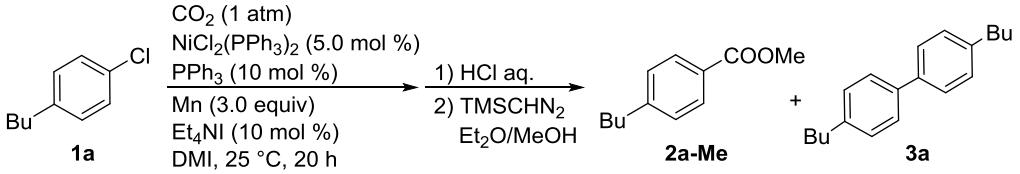
Carbon dioxide (CO_2) is an ideal C1 source owing to its abundance, low cost, nontoxicity, and good potential as a renewable source.[1] However, it is not easy to activate such a thermodynamically stable material. Therefore, efficient conversion of CO_2 with the aid of transition-metal catalysts is highly attractive.[2] In particular, hydrocarboxylation of carbon−carbon unsaturated compounds such as alkynes,[3a,b] alkenes,[3c] and 1,2- and 1,3-dienes[3d,e] is very promising. In addition, carboxylation reactions of arylzinc[4] and arylboronic esters[5] with CO_2 have been studied intensively, since in these reactions various functionalities that are not compatible with Grignard reagents were tolerated. However, these organozinc and boron compounds must be prepared from the corresponding aryl halides prior to the catalytic reactions. Thus, direct carboxylation of the parent aryl halides is most desirable, as this is a more straightforward transformation.[6] Catalytic carboxylation of aryl halides employing CO_2 was first developed as *electrochemical* reactions in the presence of nickel[7a–c] or palladium catalysts.[7d,e] Unfortunately, these were not efficient synthetic methods, and the scope of possible substrates was quite restricted. Later, carboxylation of aryl bromides and chlorides using CO_2 was carried out in the presence of a stoichiometric amount of Ni(0) complex.[8] Recently, carboxylation of aryl bromides employing CO_2 was performed *catalytically* using a palladium complex as the catalyst.[9] However, in this reaction, the catalytic activity was not satisfactory, since (1) the more reactive aryl bromides should be employed as substrates, while the less reactive and more accessible aryl chlorides did not react at all; (2) the reaction must be carried out under a CO_2 pressure of 10 atm at 40 °C to achieve good yields; (3) the highly reactive and pyrophoric $ZnEt_2$ must be employed as the reducing agent; (4) large amounts (up to 17%) of arenes were inevitably formed as byproducts through hydrogenative debromination. Herein, the author reports a much more efficient catalytic reaction, in which a less noble nickel catalyst is highly active in carboxylation of aryl chlorides as well as alkenyl chlorides under a CO_2 pressure of 1 atm at room temperature, with easy-to-handle Mn powder as the reducing agent.

1-2. Results and Discussion

Reaction of 1-butyl-4-chlorobenzene (**1a**) was carried out using a mixture of $NiCl_2(PPh_3)_2$ (5.0 mol %) and added PPh_3 (10 mol %) as a catalyst with Mn powder (3.0 equiv) as a reducing agent, in the presence of Et_4NI (10 mol %) in 1,3-dimethyl-2-imidazolidinone (DMI) at 25 °C under a CO_2 pressure of 1 atm (Table 1-1). The yield of 4-butylbenzoic acid (**2a**) was determined by gas chromatographic (GC) analysis after derivatization to the corresponding methyl ester (**2a-Me**).[10] Under standard conditions, **2a-Me** was obtained in 95% yield. Unlike the palladium-catalyzed reaction,[9] only a small

amount (<5%) of butylbenzene was obtained. Carboxylic acid **2a** was isolated from the reaction mixture in 84% yield (entry 1). Without the added PPh_3 (i.e., with only $NiCl_2(PPh_3)_2$ as the catalyst), the yield of **2a-Me** was reduced to 53%, and the biaryl (**3a**) was obtained in 27% yield (entry 2). In the absence of $NiCl_2(PPh_3)_2$, **1a** was not converted, and **2a-Me** and **3a** were not obtained at all (entry 3). When the reaction was carried out under an Ar atmosphere, **1a** was not converted (entry 4).[11] These results clearly indicated that the arylmanganese species would not be formed through the reactions of aryl chlorides with Mn powder, either in the absence or in the presence of a nickel catalyst. The Mn powder and Et_4NI were essential, and no reaction would occur without them. When Et_4NBr and Et_4NCl were used in place of Et_4NI, no conversion of **1a** was observed. By employing a mixture of $NiCl_2\{P(4\text{-}MeOC_6H_4)_3\}_2$ (5.0 mol %) with added $P(4\text{-}MeOC_6H_4)_3$ (10 mol %) as a catalyst, the yield of **2a-Me** decreased considerably (entry 5). Other ligands such as tricyclohexylphosphine (PCy_3), 1,2-diphenylphosphinoethane (dppe), and 2,2′-bipyridine (bpy) suppressed the carboxylation completely (entries 6−8). Other reducing agents such as Zn powder or Mg turning gave either a low product yield or no product (entries 9 and 10).

Table 1-1. Nickel-Catalyzed Carboxylation of **1a** Employing Carbon Dioxide[a]

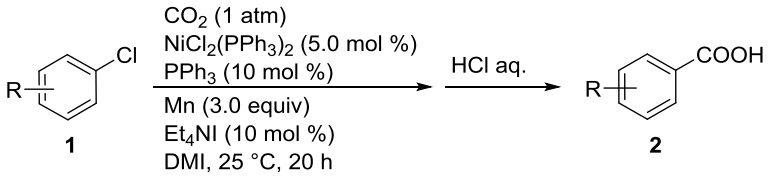


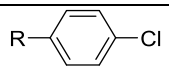
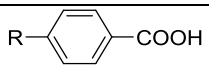
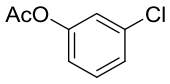
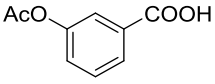
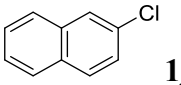
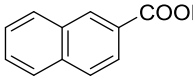
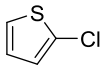
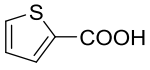
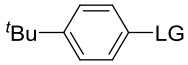
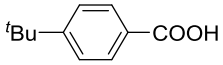
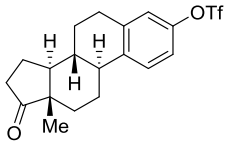
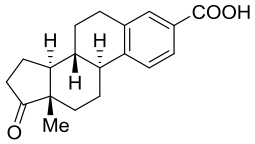
1a **2a-Me** **3a**

Entry	Catalyst System: alteration from the standard conditions	Yield of **2a-Me** (%)[b]	Yield of **3a** (%)[b]
1	Standard conditions	95 (84)[c]	0
2	Without added PPh_3	53	27
3	Without $NiCl_2(PPh_3)_2$	0	0
4	Without CO_2 (under Ar)	–	trace
5	$P(4\text{-}MeOC_6H_4)_3$ in place of PPh_3[d]	53	0
6	PCy_3 in place of PPh_3[d]	0	0
7	dppe in place of PPh_3[e]	0	0
8	bpy in place of PPh_3[e]	0	0
9	Zn in place of Mn	9	27
10	Mg in place of Mn	0	0

[a]Reaction conditions; **1a** (0.50 mmol), $NiCl_2(PPh_3)_2$ (5.0 mol %), PPh_3 (10 mol %), Mn powder (3.0 equiv), Et_4NI (10 mol %), in DMI (0.75 mL), at 25 ºC for 20 h. [b]Determined by GC analysis. [c]Isolated yield of **2a**. [d]A mixture of $NiCl_2L_2$ (5.0 mol %) and added L (10 mol %) were used as the catalyst: L = $P(4\text{-}MeOC_6H_4)_3$ or PCy_3. [e]A mixture of $NiCl_2L'$ (5.0 mol %) and L' (5.0 mol %) were used as the catalyst: L' = dppe or bpy.

Table 1-2. Nickel-Catalyzed Carboxylation of Aryl Chlorides and Other Derivatives[a,b]



Entry	Substrate **1**	Product **2**
		
1[c]	**1b**: R = OMe	**2b**: 90%
2[c]	**1c**: CF_3	**2c**: 74%
3	**1d**: F	**2d**: 81%
4	**1e**: CH_2OTBS	**2e**: 87%
5[c]	**1f**: COOMe	**2f**: 76%
6	**1g**: NMeC(O)Me	**2g**: 72%
7[d]	**1h**: B(pin)	**2h**: 58%
8	 **1i**	 **2i**: 82%
9	 **1j**	 **2j**: 78%
10[e]	 **1k**	 **2k**: 52%
		
11	**1l**: LG = Br	**2l**: 80%
12[f]	**1m**: OTs	**2l**: 73%
13[f]	**1n**: OTf	**2l**: 72%
14[f]	 **1o**	 **2o**: 51%

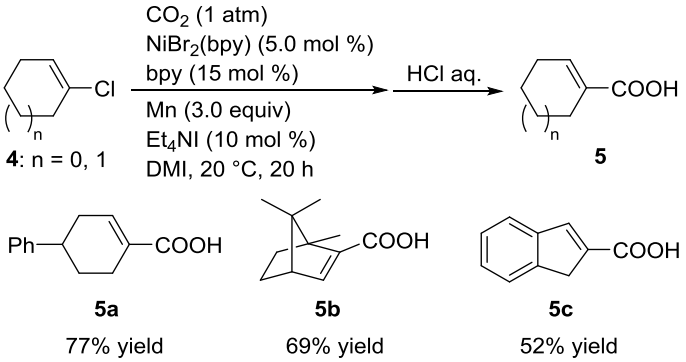
[a]Reaction conditions; **1** (0.50 mmol), $NiCl_2(PPh_3)_2$ (5.0 mol %), PPh_3 (10 mol %), Mn powder (3.0 equiv), Et_4NI (10 mol %) in DMI (0.75 mL) at 25 ºC for 20 h. [b]Isolated yield. [c]A mixture of $NiCl_2\{P(4\text{-}MeOC_6H_4)_3\}_2$ (5.0 mol %) and $P(4\text{-}MeOC_6H_4)_3$ (10 mol %) were used as catalyst at 40 ºC for 24 h. [d]At 35 ºC for 24 h. [e]At 35 ºC for 30 h. [f]$NiCl_2(PPh_3)_2$ (10 mol %), PPh_3 (20 mol %), Mn powder (3.0 equiv), Et_4NI (20 mol %) in DMI (0.75 mL) at 60 ºC for 20 h.

Carboxylation of various aryl chlorides (**1b−k**) was carried out (Table 1-2). Aryl chlorides bearing both electron-rich (entry1) and electron-poor (entries 2 and 3) moieties gave the corresponding carboxylic acids (**2b−d**) in high yields. An aryl chloride bearing tertbutyldimethylsilyl (TBS) group provided the corresponding carboxylic acid in good yield (entry 4). Gratifyingly, ester (entries 5 and 8) and amide (entry 6) functionalities, which were not tolerated with organomagnesium and organolithium reagents, remained

intact under the present reaction conditions. A boronic acid ester (entry 7) was also found to be compatible functionalities. 2-Chloronaphthalene and 2-chlorothiophene could be smoothly carboxylated (entries 9 and 10). An aryl bromide (**1l**) gave the corresponding carboxylic acid (**2l**) in 80% yield (entry 11). Aryl tosylate (**1m**) and triflates (**1n** and **1o**) also provided the corresponding carboxylic acids at 60 °C (entries 12−14). Unfortunately, *ortho*-substituted aryl chlorides and aryl chlorides bearing hydroxyl or amino groups could not be used as substrates.

To date, alkenyl chlorides[13] have not been successfully utilized in the carboxylation reactions employing CO_2. In the presence of the nickel catalyst bearing bpy as the ligand, the aliphatic alkenyl chlorides (**4a** and **4b**) afforded the corresponding α,β-unsaturated carboxylic acids (**5a** and **5b**) in high yields (Scheme 1-1). The alkenyl chloride conjugated with an aryl ring (**4c**) was also converted to the corresponding carboxylic acid **5c** in moderate yield.

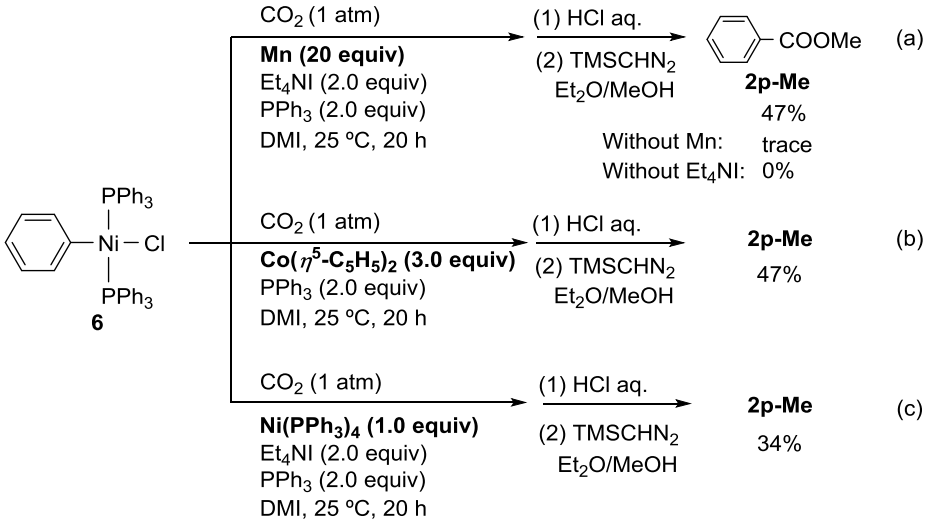
Scheme 1-1. Nickel-Catalyzed Carboxylation of Alkenyl Chlorides



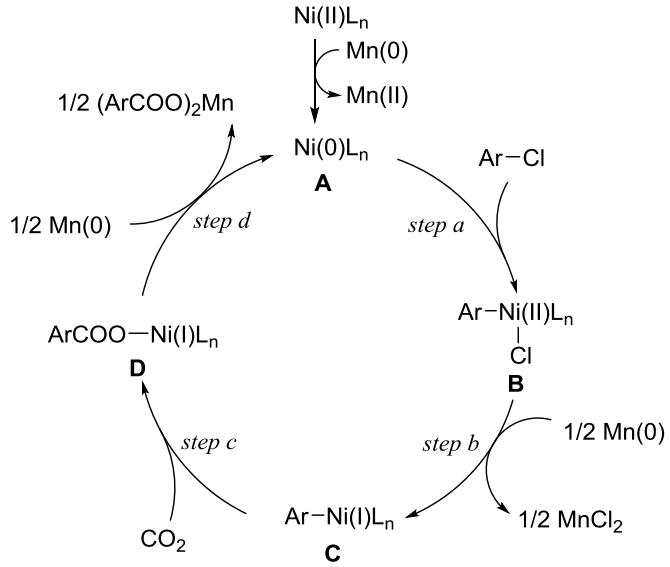
To gain insight into the reaction mechanism, the author carried out stoichiometric reactions using $NiPhCl(PPh_3)_2$ (**6**), which was prepared by oxidative addition of chlorobenzene to $Ni(PPh_3)_4$.[14] In the presence of CO_2 (1 atm), Mn powder, Et_4NI, and PPh_3 (similar conditions to the catalytic reaction), **6** afforded the carboxylated product (**2p-Me**) in 47% yield after derivatization to the corresponding methyl ester (Scheme 1-2a). However, upon removal of either Mn powder or Et_4NI from the reaction systems, either a trace amount of **2p-Me** or no product was obtained (Scheme 1-2a). Thus, both Mn and Et_4NI were found to be indispensable for the carboxylation of **6**. Interestingly, a typical homogeneous reducing agent $Co(\eta^5\text{-}C_5H_5)_2$ ($E^{\circ\prime} = -1.33$ V vs Fc/Fc^+ in CH_2Cl_2)[15] can replace the Mn/Et_4NI system to afford **2p-Me** in 47% yield (Scheme 1-2b). Therefore, the Mn/Et_4NI system may operate to reduce Ni(II) to Ni(I). Electrochemical measurements showed that Ni(II) complexes could be reduced to the corresponding Ni(I) species around −0.8 V (vs SCE in DMF).[7c] Et_4NI could assist the electron transfer from

Mn to the nickel catalyst center via the bridging of the iodide ion.[12b,16] On the other hand, it was reported that $Ni(PPh_3)_4$ reacted with $NiCl_2(PPh_3)_2$ to provide the Ni(I) species.[17] As shown in Scheme 1-2c, $Ni(PPh_3)_4$ could replace Mn to afford **2p-Me** in 34% yield. These results strongly indicate that the Ni(I) species[18] plays an important role in the present catalytic carboxylation. Such Ni(I) species were also postulated in the electrochemical carboxylation.[7c]

Scheme 1-2. Stoichiometric Reactions Relevant to Mechanism



Scheme 1-3. Plausible Reaction Mechanism



With the observations in Schemes 1-2, a plausible reaction mechanism of the nickel-catalyzed carboxylation of aryl chlorides with CO_2 is shown in Scheme 1-3. First, the Ni(II) complex must be reduced to a Ni(0) species (**A**). Then, oxidative addition of the

aryl chloride (**1**) takes place to give a Ni(II) intermediate (**B**) (step a). As suggested by the stoichiometric reaction in Scheme 1-2, Ni(II) would be reduced by the Mn/Et_4NI system to afford Ni(I) intermediate (**C**) (step b). The generation of Ni(I) species was observed in electrochemical reactions.[7c] Then, nucleophilic attack of Ni(I) (**C**) with CO_2 affording the carboxylatonickel intermediate (**D**) (step c). Finally, reduction of **D** by Mn gives the corresponding manganese carboxylate, and the Ni(0) catalyst species is regenerated (step d).

1-3. Conclusion

A nickel-catalyzed, highly efficient carboxylation of aryl and vinyl chlorides employing CO_2 has been developed. The present reactions proceeded under a CO_2 pressure of 1 atm at room temperature. The Ni(I) species would be involved in the catalytic cycle with the aid of the Mn/Et_4NI system as an efficient reducing agent.

1-4. Experimental Section

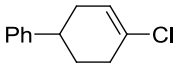
1-4-1. Instrumentation and Chemicals

DMF and DMI were distilled and stored over activated MS-4A. Mn powder (99.99%) was purchased from Sigma-Aldrich and stored under a nitrogen atmosphere. Zn powder was activated by washing with HCl aq. and stored under a nitrogen atmosphere. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Dichloronickel phosphine complexes and a dibromonickel(bipyridine) were prepared according to the literature.[19] IR spectra were obtained on a SHIMADZU FTIR-8300 spectrometer. ^1H and ^{13}C NMR spectra were measured with a JEOL ECX-400P spectrometer. The ^1H NMR chemical shifts are reported relative to tetramethylsilane (TMS, 0.00 ppm) or DMSO-d_6 (2.50 ppm). The ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ (77.0 ppm) or DMSO-d_6 (39.5 ppm). GC-MS data were recorded on a Shimadzu GCMS-QP5050A with a direct inlet. High-resolution mass spectra (EI-HRMS and ESI-HRMS) were obtained with JEOL JMX-SX102A and Thermo SCIENTIFIC Exactive LC-MS spectrometers. GC analysis was carried out using a Shimadzu GC-17A equipped with an integrator (C-R8A) with a capillary column (CBP-1, 0.25 mm i.d. × 25 m). Column chromatography was carried out on silica gel (Kanto N60, spherical, neutral, 63-210 μm). TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck Silica gel $60F_{254}$.

1-4-2. Preparation of Substrates

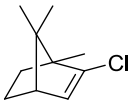
Aryl chlorides **1a**, **1b**, **1c**, **1d**, **1f**, **1h**, **1j, 1k** and aryl bromide **1l** were purchased from commercial suppliers. Aryl chlorides (**1e**,[20] **1g**[21], **1i**[22]), aryl tosylate **1m**[23] and aryl triflates (**1n, 1o**[24]) were prepared according to previous methods.

Preparation of 4a[25]



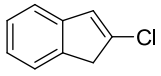
Under an inert atmosphere, PCl_5 (14 g, 67 mmol) was suspended in cyclohexane (50 mL) and the suspension was refluxed until PCl_5 was dissolved. Then, a solution of 4-phenylcyclohexanone (11 g, 65 mmol) in CH_2Cl_2 (10 mL) was added within 10 min. The mixture was refluxed for additional 1 h, allowed to cool to room temperature, and poured into ice water (100 mL) containing NaOH (2.3 g). The biphasic mixture was stirred for 30 min and extracted with Et_2O. The organic layer was washed first with sat. $NaHCO_3$ aq. until pH ca. 7, then with brine, and dried over $MgSO_4$. After filtration and evaporation of all volatiles, **4a** was obtained (12 g, 64 mmol, 98%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.87-2.05 (m, 2H), 2.20-2.29 (m, 1H), 2.34-2.37 (m, 1H), 2.39-2.42 (m, 1H), 2.48-2.59 (m, 1H), 2.78-2.85 (m, 1H), 5.87-5.90 (m, 1H), 7.19-7.23 (m, 3H), 7.29-7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.7, 33.2, 33.9, 39.0, 124.1, 126.3, 126.8, 128.5, 131.8, 145.6. EI-HRMS: Calcd. for $C_{12}H_{13}Cl$ ($[M]^+$), 192.0706. Found, 192.0701.

Preparation of 4b



The compound was synthesized with PCl_5 (9.4 g, 45 mmol) and (1R,4R)-(+)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-one (6.1 g, 40 mmol) by the method similar to that used for **4a**. Purified by silica gel chromatography using hexane as an eluent. A white solid (0.90 g, 5.3 mmol, 13%) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (s, 3H), 0.86 (s, 3H), 1.01 (s, 3H), 1.18-1.05 (m, 2H), 1.59-1.53 (m, 1H), 1.90-1.84 (m, 1H), 2.36 (t, J = 3.6 Hz, 1H), 5.82 (d, J = 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1, 19.3, 20.0, 25.7, 30.9, 51.7, 56.5, 56.6, 128.7, 140.0. EI-HRMS: Calcd. for $C_{10}H_{15}Cl$ ($[M]^+$), 170.0862. Found, 170.0862.

Preparation of 4c[26]



The compound was synthesized with PCl_5 (8.3 g, 40 mmol) and 2-indanone (5.0 g, 38 mmol) by the method similar to that used for **4a**. The residue was purified by silica gel chromatography using hexane as an eluent. Further purification by distillation *in vacuo* (3 Torr, 65 ºC) gave a colorless liquid (3.9 g, 26 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.50 (s, 2H), 6.71 (s, 1H), 7.12-7.16 (m, 1H), 7.20-7.26 (m, 2H), 7.32 (d, J = 7.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 43.3, 120.3, 123.2, 124.7, 126.7, 128.5, 137.2, 141.0, 143.4

1-4-3. Experimental Procedure of Nickel-Catalyzed Carboxylation

Typical procedure for the carboxylation of 1a (entry 1, Table 1-1)

A 50 mL Schlenk flask was dried with a heating-gun under vacuum. The flask was charged with $NiCl_2(PPh_3)_2$ (16 mg, 0.025 mmol), PPh_3 (13 mg, 0.050 mmol), Mn powder (82 mg, 1.5 mmol) and tetraethylammonium iodide (Et_4NI) (13 mg, 0.050 mmol). The flask was evacuated and refilled with CO_2. This sequence was repeated five times. Then, DMI (0.75 mL) and 1-butyl-4-chlorobenzene **1a** (85 μL, 0.50 mmol) was added via airtight syringes, and the resulting mixture

was stirred at 25 ºC for 20 h. The reaction mixture was diluted with Et_2O (5.0 mL) and was added tridecane (50 μL, 0.21 mmol) as an internal standard. To a remaining mixture, 6 N HCl aq. (3.0 mL) was added. After stirring 10 min, organic layer was separated and dried with $MgSO_4$ (50 mg). Then, Methanol (1.0 mL) and $TMSCHN_2$ (2.0 M sol. in Et_2O, 0.50 ml, 1.0 mmol) was added and the suspension was stirred for 30 min. The conversion of **1a** as well as the yield of **2a-Me** and **3a** were determined by GC analysis.

General procedure for carboxylation of aryl and vinyl chlorides (Table 1-2, Scheme 1-1)

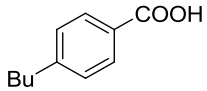
A 50 mL Schlenk flask was dried with a heating-gun under vacuum. The flask was charged with $NiCl_2(PPh_3)_2$ (16 mg, 0.025 mmol), PPh_3 (13 mg, 0.050 mmol), Mn powder (82 mg, 1.5 mmol) and Et_4NI (13 mg, 0.050 mmol). The flask was evacuated and refilled with CO_2. This sequence was repeated five times. Then, DMI (0.75 mL) and **1** (0.50 mmol) was added via airtight syringes, and the resulting mixture was stirred at 25 ºC for 20 h. After reaction, 6 N HCl aq. (3 mL) and Et_2O (5 mL) was added, and stirred at room temperature for 10 min. The mixture was extracted with Et_2O (5 mL × 5). The collected organic layer was combined and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was purified by silica gel chromatography using first Hexane/EtOAc (5/1, v/v) and then EtOAc as an eluent.

General procedure for Stoichiometric reaction (Scheme 1-2)

A 50 mL Schlenk flask was dried with a heating-gun under vacuum. The flask was charged with $NiPhCl(PPh_3)_2$[14a] (0.14 g, 0.20 mmol), PPh_3 (0.11 g, 0.40 mmol), Mn powder (0.22 g, 4.0 mmol) and Et_4NI (0.10 g, 0.40 mmol). The flask was evacuated and refilled with CO_2. This sequence was repeated five times. Then, DMI (6.0 mL) was added via airtight syringes, and the resulting mixture was stirred at 25 ºC for 20 h. The reaction mixture was diluted with Et_2O (5.0 mL), 6 N HCl aq. (3.0 mL) and was added tridecane (50 μL, 0.21 mmol) as an internal standard. The mixture was roughly extracted with Et_2O (5.0 mL × 5). The collected organic layer was combined and dried over anhydrous $MgSO_4$. After removal of solvent, the residue was treated with $TMSCHN_2$ (2.0 M sol. in Et_2O, 0.5 ml, 1 mmol) in Et_2O/MeOH (5/1, v/v, 6 ml). The yield of **2p-Me** was determined by GC analysis.

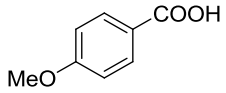
1-4-4. Characterization of the Compounds

*4-Butylbenzoic acid (**2a**)*[9]



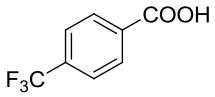
White solid (75 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J = 7.3 Hz, 3H), 1.34-1.38 (m, 2H), 1.58-1.66 (m, 2H), 2.67 (t, J = 7.8 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 8.03 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.3, 33.2, 35.8 126.8, 128.6, 130.3, 149.6, 172.7.

*4-Methoxybenzoic acid (**2b**)*[5a]



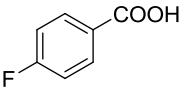
White solid (69 mg, 90%); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 3.83 (s, 3H), 7.03 (d, J = 9.0 Hz, 2H), 7.91 (d, J = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 55.5, 113.8, 123.0, 131.4, 162.9, 167.1.

*4-Trifluoromethylbenzoic acid (**2c**)*[9]



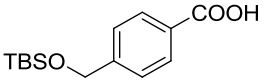
White solid (70 mg, 74%); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 7.89 (d, J = 8.4 Hz, 2H), 8.15 (d, J = 8.4 Hz, 2H), 13.49 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 123.8 (q, J = 272 Hz), 125.6 (q, J = 4 Hz), 130.1, 132.5 (q, J = 32 Hz), 134.6, 166.2.

*4-Fluorobenzoic acid (**2d**)*[5a]



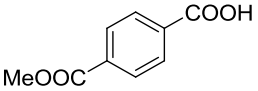
White solid (57 mg, 81%); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 7.33 (t, J = 8.8 Hz, 2H), 8.02 (dd, J = 5.7, 8.7 Hz, 2H), 13.05 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 115.6 (d, J = 22 Hz), 127.4 (d, J = 3 Hz), 132.1 (d, J = 9 Hz), 164.9 (d, J = 251 Hz), 166.6.

*4-[(tert-Butyldimethylsilyloxy)methyl]benzoic acid (**2e**)*[27]



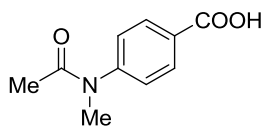
White solid (0.12 g, 87%); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 0.09 (s, 6H), 0.91 (s, 9H), 4.79 (s, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 12.88 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ -5.6, 18.0, 25.8, 63.9, 125.8, 129.3, 129.4, 146.3, 167.2.

*Methyl hydrogen terephthalate (**2f**)*[5a]



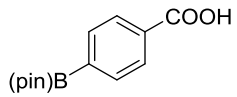
White solid (68 mg, 76%); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 3.90 (s, 3H), 8.07 (s, 4H), 13.37 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 52.5, 129.4, 129.6, 133.2, 134.8, 165.6, 166.6.

*4-(N-Acetyl-N-methylamino)benzoic acid (**2g**)*



White solid (70 mg, 72%); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.89 (brs, 3H), 3.21 (s, 3H), 7.46 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 13.06 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 22.4, 36.7, 126.7, 129.1, 130.4, 148.1, 166.7, 169.1. IR (KBr): 3100-2500 (br), 1721.2, 1629.6, 1594.8, 1390.4, 1259.3, 1235.2, 795.5, 558.3 cm^{-1}. ESI-HRMS: Calcd. for $C_{10}H_{12}N_1O_3$ ([M+H$^+$]), 194.0812. Found, 194.0811.

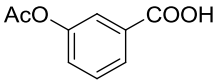
*4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)benzoic acid (**2h**)*[28]



White solid (73 mg, 58%); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 1.31 (s, 12H), 7.79 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H), 13.09 (br, 1H). ^{13}C NMR

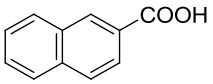
(100 MHz, DMSO-d_6): δ 24.7, 84.0, 128.5, 133.2, 134.5, 167.2.

*3-Acetoxybenzoic acid (**2i**)*[29]



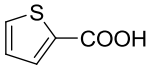
White solid (74 mg, 82%); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 3H), 7.40 (ddd, J = 1.1, 2.4, 8.2 Hz, 1H), 7.55 (dd, J = 7.9, 7.9 Hz, 1H), 7.68 (dd, J = 1.9, 1.9 Hz, 1H), 7.84 (ddd, J = 1.9, 1.9, 7.9, 1H), 13.18 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.8, 122.6, 126.4, 126.6, 129.8, 132.3, 150.5, 166.5, 169.2.

*2-Naphthoic acid (**2j**)*[30]



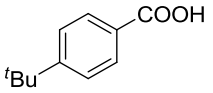
White solid (67 mg, 78%); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60-7.69 (m, 2H), 7.99-8.04 (m, 3H), 8.13 (d, J = 8.2 Hz, 1H), 8.63 (s, 1H), 13.11 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 125.2, 126.8, 127.7, 128.1, 128.2, 128.3, 129.3, 130.5, 132.2, 134.9, 167.5.

*2-Thiophenoic acid (**2k**)*[9]



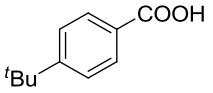
Brown solid (33 mg, 52%); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.19 (dd, J = 3.8, 4.9 Hz, 1H), 7.73 (dd, J = 1.2, 3.7 Hz, 1H), 7.89 (dd, J = 1.2, 5.0 Hz, 1H), 13.06 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 128.2, 133.2, 133.3, 134. 6, 162.9.

*4-tert-Butylbenzoic acid [**2l** from 1-bromo-4-tert-butylbenzene (**1l**)]*[30]



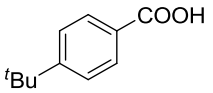
White solid (71 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 9H), 7.49 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.1, 35.2, 125.5, 126.5, 130.1, 157.6, 172.4.

*4-tert-Butylbenzoic acid [**2l** from 4-tert-butylphenyltosylate (**1m**)]*[30]



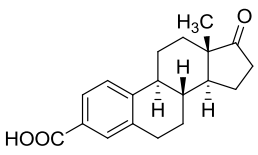
White solid (65 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 9H), 7.49 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.1, 35.2, 125.5, 126.5, 130.1, 157.6, 172.4.

*4-tert-Butylbenzoic acid [**2l** from 4-tert-butylphenyltriflate (**1n**)]*[30]



White solid (64 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 9H), 7.49 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.1, 35.2, 125.5, 126.5, 130.1, 157.6, 172.4.

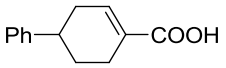
*Compound **2o***



White solid (75 mg, 51%); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.83 (s, 3H), 1.37-1.58 (m, 6H), 1.77-1.80 (m, 1H), 1.94-2.00 (m, 2H), 2.03-2.12 (m, 1H), 2.27-2.33 (m, 1H), 2.39-2.48 (m, 2H), 2.90-2.91 (m, 2H), 7.40 (d, J = 8.2 Hz, 1H), 7.65 (s, 1H), 7.68 (d, J = 8.2 Hz, 1H), 12.72 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.4, 21.0, 25.0, 25.6, 28.6, 31.2, 35.2, 37.1, 43.9, 47.1, 49.5,

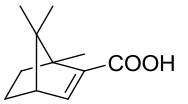
125.4, 126.5, 128.0, 130.0, 136.5, 144.7, 167.3, 219.4. IR (KBr): 3100-2500 (br), 1741.4, 1679.7, 1609.3, 1430.9, 1303.6, 1269.9, 761.7, 754.0 cm^{-1}. EI-HRMS: Calcd. for $C_{19}H_{22}O_3$ ($[M]^+$), 298.1569. Found, 298.1555.

*4-Phenyl-1-cyclohexenoic acid (**5a**)*[31]



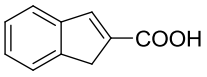
White solid (77 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72-1.82 (m, 1H), 2.04-2.08 (m, 1H), 2.32-2.39 (m, 2H), 2.51-2.59 (m, 2H), 2.78-2.85 (m, 1H), 7.21-7.23 (m, 4H), 7.30-7.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ24.4, 29.3, 33.9, 39.0, 126.4, 126.8, 128.5, 129.6, 141.8, 145.8, 172.5.

*Compound **5b***



Pale yellow solid (62 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.795 (s, 3H), 0.802 (s, 3H), 0.99 (ddd, J = 3.6, 9.1, 12.2 Hz, 1H), 1.14 (ddd, J = 3.6, 9.1, 12.2 Hz, 1H), 1.25 (s, 3H), 1.62 (ddd, J = 3.6, 8.6, 12.2 Hz, 1H), 1.97-1.90 (m, 1H), 2.47 (t, J = 3.6 Hz, 1H), 7.09 (d, J = 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8, 19.1, 19.3, 24.4, 31.0, 52.3, 53.8, 57.1, 140.2, 150.2, 170.8. IR (KBr) 3100-2500 (br), 1672.0, 1582.3, 1421.3, 1276.7, 1248.7, 1074.2, 944.0, 764.6, 699.1 cm^{-1}. ESI-HRMS: Calcd. for $C_{11}H_{17}O_2$ ($[M+H^+]$), 181.1223. Found, 181.1222.

*1H-indene-2-carboxylic acid (**5c**)*[32]



Pale yellow solid (42 mg, 52%); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.63 (d, J = 1.4 Hz, 2H), 7.32-7.37 (m, 2H), 7.54-7.60 (m, 2H), 7.69 (s, 1H), 12.51 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.1, 123.3, 124.3, 126.7, 127.3, 138.4, 140.1, 142.6, 144.6, 165.7.

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(10) See the Experimental Section for details.

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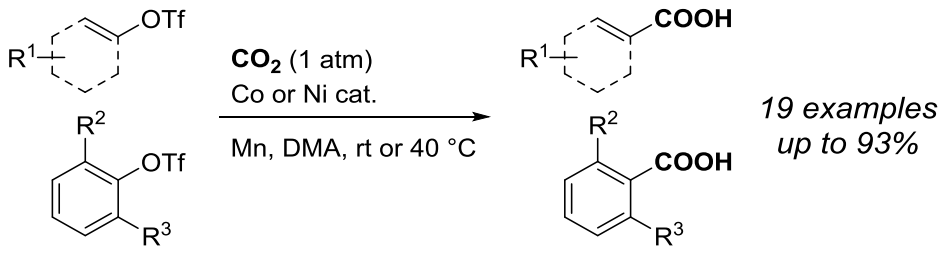
Chapter 2

Cobalt- and Nickel-Catalyzed Carboxylation of Alkenyl and Sterically Hindered Aryl Triflates Utilizing Carbon Dioxide

A highly efficient cobalt-catalyzed carboxylation reaction of alkenyl triflates has been developed. By employing Mn powder as a reducing reagent, diverse alkenyl triflates can be converted to the corresponding α,β-unsaturated carboxylic acids under 1 atm pressure of CO_2 at room temperature. Moreover, the carboxylation of sterically hindered aryl triflates smoothly proceeds in the presence of a nickel or cobalt catalyst.

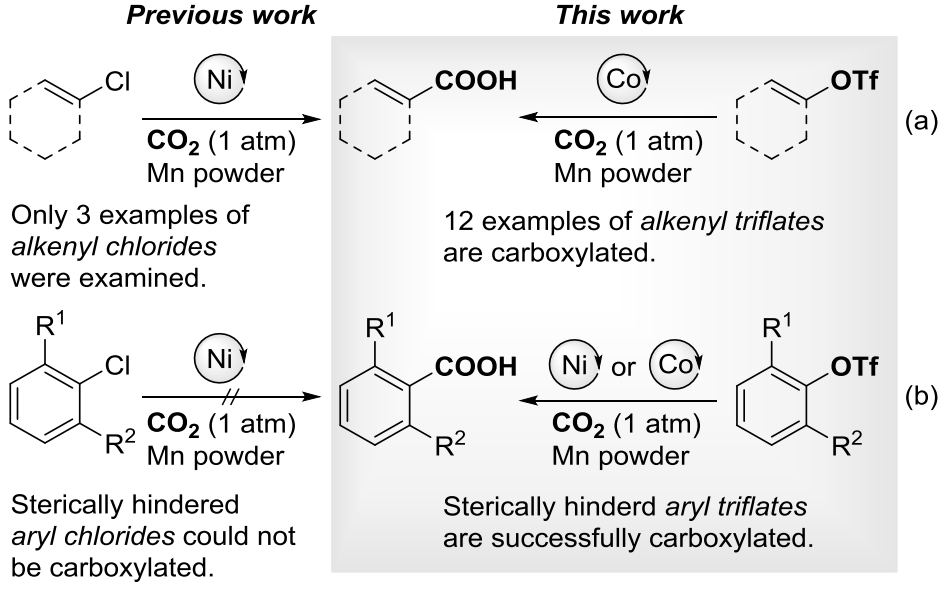


2-1. Introduction

Carbon dioxide (CO_2) is considered an ideal C1-synthon for organic synthesis because of its nontoxicity, low cost, and availability as a renewable resource.[1] Therefore, the development of new catalytic methods enabling chemical fixation of CO_2 with concomitant C–C bond formation is considered an important current challenge.[2] In this regard, reductive catalytic carboxylation reactions of organic electrophiles with CO_2 have been studied intensively.[3–5] Catalytic carboxylation of aryl bromides with a palladium catalyst was reported by the Martin group in 2009 with an excess amount of pyrophoric Et_2Zn as a reducing reagent.[3b] In 2012, we reported the first catalytic carboxylation of less reactive aryl chlorides as well as alkenyl chlorides with a nickel catalyst.[4a] The reaction proceeded under 1 atm pressure of CO_2 at room temperature employing easy-to-handle Mn powder as a reducing reagent. Martin and co-workers have also developed nickel-catalyzed reductive carboxylation reactions of various organic halides and esters.[5]

While the carboxylation reactions of aryl chlorides afford a wide variety of products with high functional group tolerance, the previous paper[4a] posed the following two significant problems: (1) only three simple alkenyl chlorides (without other functionalities) were employed as substrates, but reactivity of more easily accessible alkenyl triflates was not examined (Scheme 2-1a, left); (2) sterically hindered *ortho*-substituted aryl chlorides, even 2-chlorotoluene, did not afford carboxylated products with only low conversions of substrates (Scheme 2-1b, left).

Scheme 2-1. Reductive Carboxylation of Alkenyl and Sterically Hindered Aryl Electrophiles

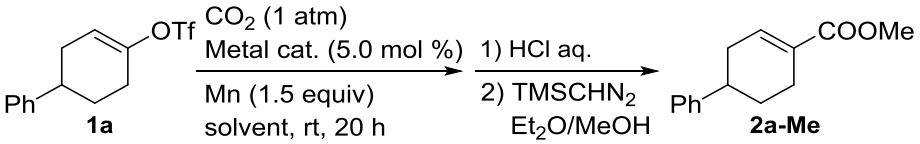


To compensate for the former results described in Chapter 1,[4a] the author focuses his attention on the reactivity of alkenyl and aryl trifluoromethanesulfonates (triflates) as substrates. They are easily prepared from the corresponding ketones, aldehydes, or phenol derivatives and are often employed in synthetic organic chemistry as useful reagents.[6] In this Chapter, the author describes highly efficient reductive carboxylations of alkenyl triflates (Scheme 2-1a, right) and sterically hindered aryl triflates (Scheme 2-1b, right) employing Mn powder as a reducing reagent in the presence of a cobalt or nickel catalyst.[7,8]

2-2. Results and Discussion

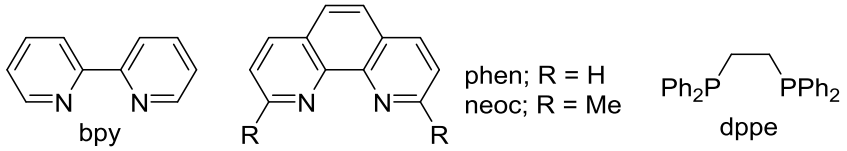
The reaction of an alkenyl triflate **1a** was examined with Mn powder (1.5 equiv) as a reducing reagent under 1 atm pressure of CO_2 at room temperature (Table 2-1). The yield of α,β-unsaturated carboxylic acid (**2a**) was determined by gas chromatographic (GC) analysis after derivatization to the corresponding methyl ester (**2a-Me**). First, the carboxylation reaction of **1a** was carried out employing $NiBr_2$(bpy) (5 mol %, bpy = 2,2'-bipyridine) as a catalyst in the presence of additional bpy (15 mol%) and tetraethylammonium iodide (Et_4NI, 10 mol %) in 1,3-dimethyl-2-imidazolidinone (DMI) solvent, i.e. under the optimal reaction conditions of the former carboxylation of alkenyl chlorides.[4a] In the reaction, **2a-Me** was obtained in 43% GC yield (entry 1), but ca. 30% of diene was formed as the homocoupled product of **1a**. To improve the selectivity, the author switched the catalyst to a cobalt complex that showed excellent catalytic activity for the carboxylation of propargyl acetates with CO_2.[4b] Use of CoI_2(bpy) showed low catalytic activity in both DMI and DMA solvents, but no homocoupling reaction of **1a** occurred (entries 2 and 3). The yield of **2a-Me** was increased substantially with 1,10-phenanthroline (phen) as the ligand (entry 4). Finally, CoI_2(neoc) (neoc = 2,9-dimethyl-1,10-phenanthroline) as the catalyst afforded **2a-Me** in 86% yield and the corresponding carboxylic acid **2a** was isolated in 79% yield (entry 5).[9] The catalyst *in situ* prepared from CoI_2 and neoc also worked well and afforded the product in 86% yield. Phosphine ligands were not effective at all (entries 6 and 7). In place of Mn, Zn powder afforded the product in low yield (entry 8). The cobalt catalyst and Mn powder were indispensable for this carboxylation reaction (entries 9 and 10).

Table 2-1. Optimization of the Reaction Conditions with **1a**[a]



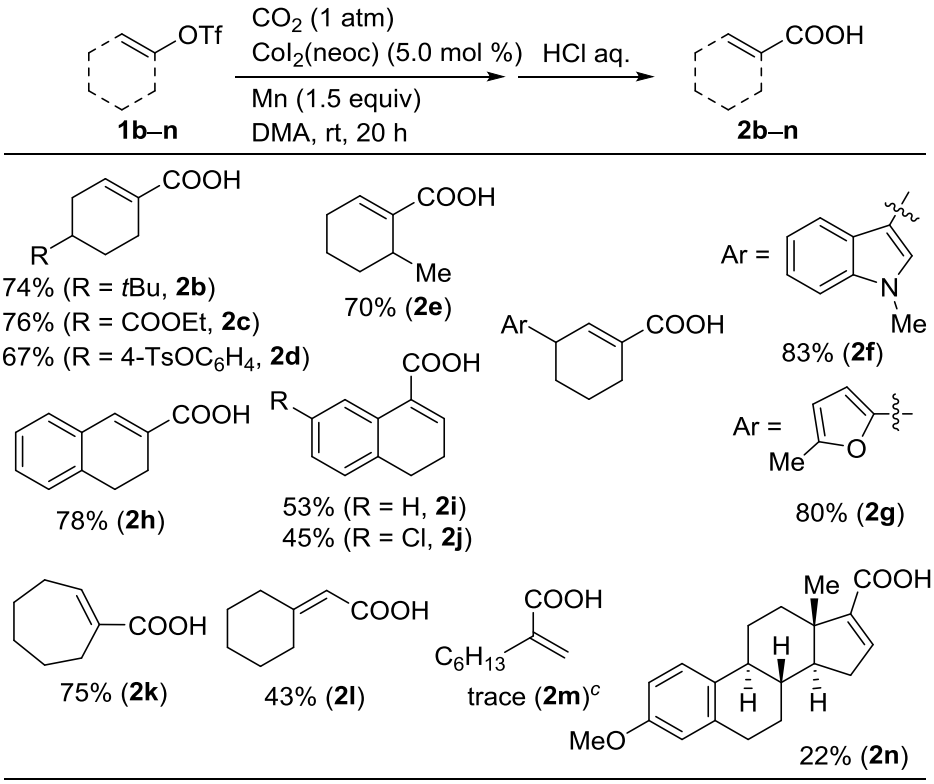
Entry	Metal catalyst	Solvent	Yield of **2a-Me** (%)[b]
1[c]	$NiBr_2$(bpy)	DMI	43
2	CoI_2(bpy)	DMI	10
3	CoI_2(bpy)	DMA	23
4	CoI_2(phen)	DMA	76
5	CoI_2(neoc)	DMA	86 (79)[d]
6	$CoI_2(PPh_3)_2$	DMA	0
7	CoI_2(dppe)	DMA	0
8[e]	CoI_2(neoc)	DMA	32
9[f]	CoI_2(neoc)	DMA	0
10	Without catalyst	DMA	0

[a]Reaction conditions; **1a** (0.25 mmol), metal catalyst (5.0 mol %), Mn powder (1.5 equiv) in solvent (0.50 mL), at room temperature for 20 h. [b]Determined by GC analysis using tridecane as an internal standard. [c]bpy (15 mol %) and Et_4NI (10 mol %) were added. [d]Isolated yield of **2a** as the carboxylic acid. [e]Zn powder (1.5 equiv) was used in place of Mn. [f]Without Mn.



Under the optimal reaction conditions (Table 2-1, entry 5), carboxylation of various alkenyl triflates was carried out (Table 2-2). Ester (**2c**), indole (**2f**), and furan (**2g**) moieties were well tolerated under the reaction conditions.[10] Importantly, the triflate moiety was selectively carboxylated even in the presence of *p*-toluenesulfonate (**2d**) and chloro (**2j**) functionalities which could be potentially reactive under the carboxylation conditions. Conjugated alkenyl triflates (**1h**–**j**) were converted to the corresponding carboxylic acids (**2h**–**j**) in moderate to high yields. A seven-membered cyclic substrate (**1k**) also afforded the α,β-unsaturated carboxylic acid **2k** in 75% yield. Alkenyl triflate **1l** prepared from the corresponding aldehyde gave the product **2l** in moderate yield. Unfortunately, **1m** having an *exo*-methylene moiety gave a trace amount of product owing to extensive side reactions. An estrone-based alkenyl triflate (**1n**) furnished the product **2n** in 22% yield due to a preferential homocoupling reaction (41% yield) of **1n**.

Table 2-2. Cobalt-Catalyzed Carboxylation of Alkenyl Triflates[a,b]

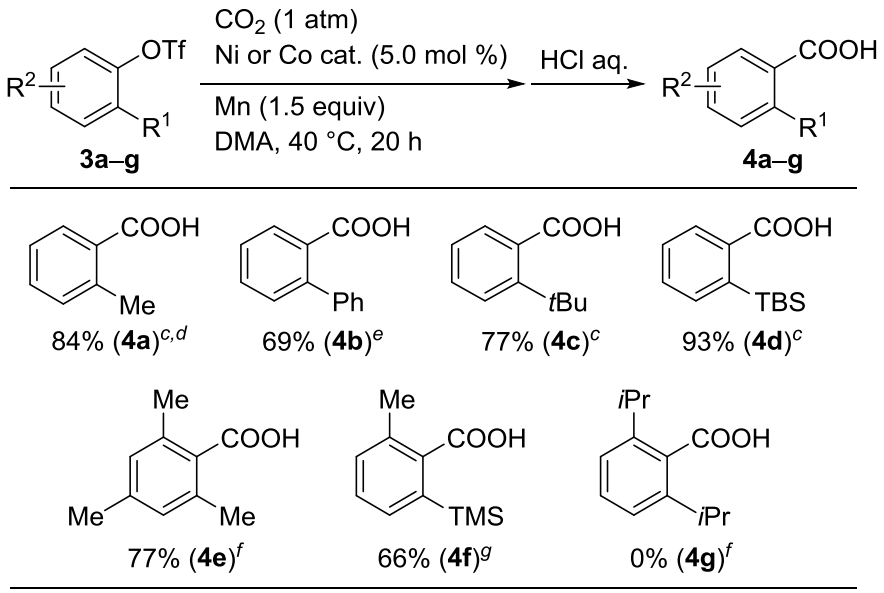


[a]Reaction conditions; **1** (0.25 mmol), CoI_2(neoc) (5.0 mol %), Mn powder (1.5 equiv) in DMA (0.50 mL) at room temperature for 20 h. [b]Isolated yield. [c]Determined by GC and GC-MS analysis after methylesterification.

As mentioned above, *ortho*-substituted aryl chlorides could not be carboxylated with the protocol described in Chapter 1.[4a] Even 2-chlorotoluene did not give the desired carboxylation product. Thus, the author changed the substrate from the aryl chloride to 2-methylphenyl triflate **3a**. Fortunately, **3a** successfully furnished the carboxylated product **4a** in 84% isolated yield in the presence of $NiI_2(PPh_3)_2$ (5.0 mol %) and additional PPh_3 (10 mol %) at room temperature (Table 2-3). Other 2-substituted aryl triflates (**3b–d**) provided the corresponding benzoic acids (**4b–d**) in good to excellent yields. It is noteworthy that bulky substituents such as *tert*-butyl and TBS (*tert*-butyldimethylsilyl) moieties did not hamper the carboxylation reaction. As for more sterically hindered 2,6-disubstituted aryl triflates, 2,4,6-trimethylphenyl triflate **3e** only afforded the carboxylated product (**4e**) in 15% yield even at elevated temperature (60 °C) in the presence of the nickel catalyst. In contrast, a cobalt catalyst CoI_2(neoc) was found to be more active and successfully afforded **4e** in 77% yield at 40 °C. More sterically demanding 2-methyl-6-(trimethylsilyl)phenyl triflate (**3f**) was also carboxylated to **4f** in 66% yield with a higher catalyst loading (10 mol%). However, 2,6-diisopropylphenyl

triflate (**3g**) did not give the product (**4g**). Regarding less hindered substrates, phenyl triflate afforded benzoic acid in 54% yield utilizing $NiI_2(PPh_3)_2$ (5.0 mol %) and PPh_3 (10 mol %) as the catalyst.

Table 2-3. Cobalt- and Nickel-Catalyzed Carboxylation of Sterically Hindered Aryl Triflates[a,b]



[a]Reaction conditions; **3** (0.25 mmol), nickel or cobalt catalyst (5.0 mol %), Mn powder (1.5 equiv) in DMA (0.50 mL) at 40 °C for 20 h. [b]Isolated yield. [c]$NiI_2(PPh_3)_2$ (5.0 mol %) was used. [d]PPh_3 (10 mol %) was added, room temperature. [e]NiI_2(neoc) (5.0 mol %) was used, at room temperature. [f]CoI_2(neoc) (5.0 mol %) was used. [g]CoI_2(neoc) (10 mol %) was used.

2-3. Conclusion

In conclusion, the author developed highly efficient carboxylation reactions of various alkenyl triflates employing a cobalt catalyst and Mn powder as a reducing reagent under 1 atm pressure of CO_2 at room temperature. Furthermore, the carboxylation of sterically hindered 2-substituted and 2,6-disubstituted aryl triflates proceeded smoothly with a nickel or cobalt catalyst.

2-4. Experimental Section

2-4-1. General Methods and Materials

DMA and DMI were distilled with CaH_2 and stored over activated MS-4A. Mn powder (≥99%) was purchased from Sigma-Aldrich and stored under a nitrogen atmosphere. Zn powder was activated by washing with HCl aq. and stored under a nitrogen atmosphere. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. IR

spectra were obtained on an FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a spectrometer (500 or 400 MHz). The ^{1}H NMR chemical shifts are reported relative to tetramethylsilane (TMS, 0.00 ppm), acetone-d_6 (2.05 ppm), or DMSO-d_6 (2.50 ppm). The ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ (77.0 ppm), acetone-d_6 (29.0 ppm), or DMSO-d_6 (39.5 ppm). GC-MS data were recorded on a low-resolution EI-MS (quadrupole). High-resolution mass spectra were obtained with EI-HRMS (magnetic sector), ESI-HRMS (Orbitrap), APCI-HRMS (Orbitrap), and MALDI-HRMS (Orbitrap). GC analysis was carried out using a gas chromatographic analyzer equipped with a capillary column (0.25 mm i.d. × 30 m). UV/vis spectra were recorded with a spectrophotometer. Column chromatography was carried out on silica gel (spherical, neutral, 40–50 μm or 63–210 μm). TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of silica gel. Alkenyl triflates **1a**–**b**,[11] **1f**–**g**,[12] **1h**,[13] **1m**,[8c] and **1n**,[14] as well as aryl triflates **3a**,[15] **3b**,[16] **3c**,[15] **3d**,[17] **3e**[18] and **3g**[18] were prepared according to the literature procedures. CoI_2(bpy), CoI_2(phen), $CoI_2(PPh_3)_2$, CoI_2(dppe), $NiBr_2$(bpy), and $NiI_2(PPh_3)_2$ were also prepared according to the literature procedures.[4b,19]

2-4-2. Preparation of CoI_2(neoc) and NiI_2(neoc)

CoI_2(neoc) was prepared according to a published method for $CoBr_2$(neoc).[20] A 50 mL Schlenk flask was dried with a heating-gun under vacuum. The flask was charged with CoI_2 (0.31 g, 1.0 mmol), 2,9-dimethyl-1,10-phenanthroline (neoc, 0.23 g, 1.1 mmol), and ethanol (5 mL) under an Ar atmosphere. The resulting solution was stirred at 80 °C for 2 h. A light green solid was precipitated and isolated by filtration. The solid was filtered, washed with ethanol and hexane subsequently, and dried in vacuo. The desired complex was obtained in 83% yield (0.43 g, 0.83 mmol) and used without further purification. Stable under 250 °C; UV-vis (CH_3CN) λ_{max}, nm: 212, 272, 320, 390 (sh), 670 (br). Anal. Calcd for $C_{14}H_{12}CoI_2N_2 \cdot 1/2CH_3CH_2OH$: C, 33.12; H, 2.78; N, 5.15. Found: C, 33.07; H, 2.53; N, 5.41. MALDI-HRMS (*m/z*): $[M–I]^+$ calcd for $C_{14}H_{12}CoIN_2$, 393.93717; found, 393.93678.

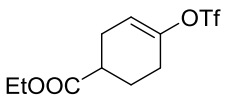
NiI_2(neoc) was prepared by the same procedure (0.50 mmol scale, 0.23 g, 0.45 mmol, 89%). Light brown solid; mp 220–230 °C (dec); UV-vis (CH_3CN) λ_{max}, nm: 208, 248, 276, 360; Anal. Calcd for $C_{14}H_{12}NiI_2N_2 \cdot 1/2CH_3CH_2OH$: C, 33.13; H, 2.78; N, 5.15. Found: C, 33.03; H, 2.56; N, 5.40. MALDI-HRMS (*m/z*): $[M–I]^+$ calcd for $C_{14}H_{12}IN_2Ni$, 392.93932; found, 392.93976.

2-4-3. General Procedure for Preparation of Alkenyl Triflates

To a mixture of ketone (10 mmol) and 2-chloropyridine (11 mmol) in CH_2Cl_2 (20 mL), the solution of Tf_2O (12 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 ºC and the mixture was stirred for 30 min at 0 °C. The resulting mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by adding H_2O (20 mL). The organic layer was washed with sat. $NaHCO_3$ aq. and brine, and dried over $MgSO_4$. After filtration and removal of volatiles, the

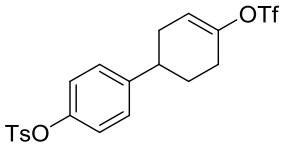
residue was purified with silica gel chromatography using hexane as an eluent.

*Ethyl 4-(trifluoromethanesulfonyloxy)cyclohex-3-ene-1-carboxylate (**1c**)*



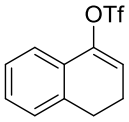
Colorless oil (7.0 mmol scale, 1.0 g, 3.4 mmol, 49%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.78-5.76 (m, 1H), 4.16 (q, J = 7.2 Hz, 2H), 2.62-2.57 (m, 1H), 2.48-2.40 (m, 4H), 2.17-2.11 (m, 1H), 1.97-1.89 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 148.4, 118.5 (q, J_{C-F} = 320.1 Hz), 116.9, 60.8, 37.8, 26.6, 26.1, 25.0, 14.1. ESI-HRMS (*m/z*): [M+Na] calcd for $C_{10}H_{13}F_3O_5SNa$, 325.0328; found, 325.0322.

*4-[4-(Trifluoromethanesulfonyloxy)cyclohex-3-en-1-yl]phenyl 4-methylbenzene-1-sulfonate (**1d**)*



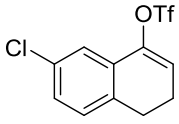
White solid (5.0 mmol scale, 1.6 g, 3.3 mmol, 66%); mp 93–95 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 6.95-6.92 (m, 2H), 5.84-5.82 (m, 1H), 2.86-2.81 (m, 1H), 2.56-2.24 (m, 7H), 2.06-2.01 (m, 1H), 1.94-1.86 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.8, 148.2, 145.3, 143.4, 132.5, 129.7, 128.5, 127.9, 122.5, 118.5 (q, J_{C-F} = 320.1 Hz), 117.8, 38.1, 31.4, 29.5, 27.6, 21.7. ESI-HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{19}F_3O_6S_2Na$, 499.0467; found, 499.0456.

*3,4-Dihydronaphthalen-1-yl trifluoromethanesulfonate (**1i**)*[8c]



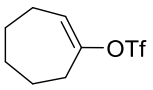
Colorless oil (7.0 mmol scale, 1.9 g, 6.7 mmol, 96%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.33 (m, 1H), 7.28-7.24 (m, 2H), 7.18-7.16 (m, 1H), 6.01 (t, J = 4.7 Hz, 1H), 2.87 (t, J = 8.2 Hz, 2H), 2.51 (td, J = 8.2, 4.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.4, 136.2, 129.2, 128.7, 127.8, 126.9, 121.2, 118.6 (q, J_{C-F} = 320.4 Hz), 117.7, 26.9, 22.3.

*7-Chloro-3,4-dihydronaphthalen-1-yl trifluoromethanesulfonate (**1j**)*



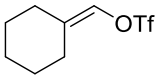
Colorless oil (2.8 mmol scale, 0.55 g, 1.8 mmol, 63%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, J = 1.8 Hz, 1H), 7.23 (dd, J = 8.1, 2.0 Hz, 1H), 7.11 (d, J = 7.9 Hz, 1H), 6.08 (t, J = 4.9 Hz, 1H), 2.83 (t, J = 8.1 Hz, 2H), 2.52 (td, J = 8.2, 4.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.2, 134.4, 132.9, 130.2, 129.0 (two peaks overlap absolutely, confirmed with the HMQC and HMBC spectra), 121.4, 119.2, 118.6 (q, J_{C-F} = 320.4 Hz), 26.2, 22.3. APCI-HRMS (*m/z*): $[M-H]^-$ calcd for $C_{11}H_7ClF_3O_3S$, 310.9762; found, 310.9760.

*1-Cyclohepten-1-yl trifluoromethanesulfonate (**1k**)*[11]



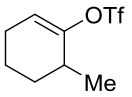
Pale brown oil (6.0 mmol scale, 0.52 g, 2.1 mmol, 35%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.88 (t, J = 6.4 Hz, 1H), 2.53-2.51 (m, 2H), 2.17-2.14 (m, 2H), 1.74-1.61 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.1, 123.1, 118.6 (q, J_{C-F} = 320.1 Hz), 33.2, 29.9, 26.3, 24.8, 24.7.

*Cyclohexylidenemethyl trifluoromethanesulfonate (**1l**)*



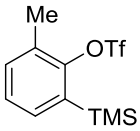
Pale yellow oil (5.0 mmol scale, 0.40 g, 1.6 mmol, 33%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.38 (s, 1H), 2.28-2.26 (br m, 2H), 2.07-2.05 (br m, 2H), 1.59-1.57 (br m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 133.8, 127.7, 118.7 (q, J_{C-F} = 321.1 Hz), 29.8, 27.5, 26.4, 26.04, 26.00. EI-HRMS (*m/z*): $[M]^+$ calcd for $C_8H_{11}F_3O_3S$, 244.0381; found, 244.0374.

2-4-4. Preparation of 6-Methylcyclohex-1-en-1-yl Trifluoromethanesulfonate (1e)[11]



A mixture of potassium bis(trimethylsilyl)amide (KHMDS, 10 mL of 0.5 M toluene solution) and THF (25 mL) was cooled to –78 °C under an Ar atmosphere. To the solution was added dropwise the solution of 2-methylcyclohexanone (4.0 mmol) in THF (5.0 mL), and the resulting mixture was stirred at –78 °C for 1 h. Then, $PhNTf_2$ (5.0 mmol) was added in one-portion, and the reaction mixture was allowed to warm to room temperature. After stirring for 6 h, H_2O (10 mL) was added, and the resulting mixture was extracted with Et_2O (2 × 20 mL). The combined organic layer was washed with brine and dried over $MgSO_4$. After filtration and removal of volatiles, purification of the residue by silica gel chromatography using hexane as an eluent gave **1e** (colorless oil, 0.53 g, 2.1 mmol, 53%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.73 (td, J = 4.1, 1.2 Hz, 1H), 2.58-2.51 (m, 1H), 2.19-2.15 (m, 2H), 1.96-1.90 (m, 1H), 1.70-1.43 (m, 3H), 1.14 (d, J = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.4, 118.6 (q, J_{C-F} = 320.1 Hz), 118.2, 32.4, 31.5, 24.5, 19.2, 17.8.

2-4-5. Preparation of 2-Methyl-6-(trimethylsilyl)phenyl Trifluoromethanesulfonate (3f)



A mixture of 2-bromo-6-methylphenol (10 mmol), TMSCl (10 mmol), and THF (20 mL) was cooled to 0 °C under an Ar atmosphere. To the solution was added dropwise triethylamine (10 mmol), and the resulting solution was allowed to warm to room temperature. After stirring for 2 h, white precipitate was filtered off and the filtrate was concentrated under vacuum to afford the crude mixture of (2-bromo-6-methylphenoxy)trimethylsilane. The crude mixture was placed in 100 mL round bottled flask and diluted with THF (20 mL) under Ar atmosphere. The mixture was cooled to –78 °C and *n*-BuLi in hexane (1.65 M, 9.1 mL, 15 mmol) was added slowly. The whole mixture was stirred for 1h at –78 °C. Then, Tf_2O (15 mmol) was added via syringe and the resulting solution was allowed to warm to room temperature. After stirring for 1 h, the reaction was quenched by adding H_2O and the mixture was extracted with Et_2O (2 × 20 mL). The combined organic layer was subsequently washed with $NaHCO_3$ aq. and brine, and dried over $MgSO_4$. After filtration and removal of all volatiles, purification of the residue by silica gel chromatography using hexane as an eluent gave **3f** (Colorless oil, 1.7 g, 5.3 mmol, 53%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 6.7 Hz, 1H), 7.29-7.25 (m, 2H), 2.38 (s, 3H), 0.38 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 151.1, 134.8, 134.5,

133.7, 131.4, 127.9, 118.6 (q, J_{C-F} = 319.8 Hz), 17.3, 0.1. ESI-HRMS (*m/z*): $[M-H]^-$ calcd for $C_{11}H_{14}F_3O_3SSi$, 311.0390; found, 311.0392.

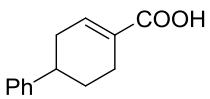
2-4-6. A Procedure for Carboxylation of 1a (Table 2-1, entry 5)

A 20 mL Schlenk flask was charged with Mn powder (21 mg, 0.38 mmol) and dried with a heating-gun under vacuum. Then, the flask was charged with CoI_2(neoc) (6.5 mg, 0.013 mmol). The flask was evacuated and refilled with CO_2. This sequence was repeated five times. Then, DMA (0.50 mL) and **1a** (59 μL, 0.25 mmol) were added via airtight syringes, and the resulting mixture was stirred at room temperature for 20 h. After the reaction, tridecane (50 μL, 0.21 mmol) as an internal standard, Et_2O (5 mL), and 1 M HCl aq. (3 mL) were added to the reaction mixture. After stirring for 10 min, the organic layer was separated, dried over $MgSO_4$, and filtrated. Then, methanol (1 mL) and $TMSCHN_2$ (2.0 M in Et_2O, 0.5 mL, 1.0 mmol) were added to the resulting solution, and it was stirred for 10 min. The yield of **2a-Me** was determined by GC analysis.

2-4-7. Representative Procedure for the Carboxylation of Alkenyl Triflates (1b-n) and Aryl Triflates (3a-g).

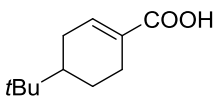
A 20 mL Schlenk flask was charged with Mn powder (21 mg, 0.38 mmol) and dried with a heating-gun under vacuum. Then, the flask was charged with CoI_2(neoc) (6.5 mg, 0.013 mmol). The flask was evacuated and refilled with CO_2. This sequence was repeated five times. Then, DMA (0.50 mL) and **1** (0.25 mmol) were added via airtight syringes, and the resulting mixture was stirred at room temperature for 20 h. After the reaction, 1 M HCl aq. (3 mL) and Et_2O (5 mL) were added, and the whole solution was stirred at room temperature for 10 min. The mixture was extracted with Et_2O (5 mL × 5). The collected organic layer was combined and dried over anhydrous $MgSO_4$. After removal of volatiles, the residue was purified by silica gel chromatography using hexane/acetone (6/1, v/v) as an eluent.

*4-Phenylcyclohex-1-ene-1-carboxylic acid (**2a**)*[4b]



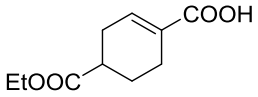
White solid (40 mg, 79%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.30 (m, 2H), 7.23-7.21 (m, 4H), 2.83-2.77 (m, 1H), 2.58-2.51 (m, 2H), 2.38-2.31 (m, 2H), 2.07-2.03 (m, 1H), 1.80-1.72 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9, 145.8, 141.8, 129.7, 128.5, 126.8, 126.3, 39.0, 33.9, 29.3, 24.4.

*4-tert-Butylcyclohex-1-ene-1-carboxylic acid (**2b**)*[21]



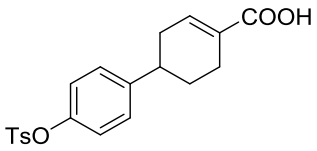
White solid (34 mg, 74%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14-7.12 (m, 1H), 2.52-2.48 (m, 1H), 2.31-2.25 (m, 1H), 2.16-2.08 (m, 1H), 2.00-1.90 (m, 2H), 1.31-1.25 (m, 1H), 1.18-1.10 (m, 1H), 0.89 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.0, 143.0, 129.6, 43.2, 32.1, 27.7, 27.1, 25.2, 23.5.

*4-(Ethoxycarbonyl)cyclohex-1-ene-1-carboxylic acid (**2c**)*



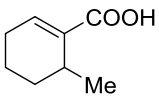
White solid (38 mg, 76%); mp 97–98 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12-7.10 (br m, 1H), 4.18-4.14 (m, 2H), 2.59-2.45 (m, 4H), 2.29-2.22 (m, 1H), 2.13-2.08 (m, 1H), 1.76-1.68 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.0, 172.3, 140.2, 129.3, 60.6, 38.2, 28.0, 24.7, 23.1, 14.2. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{10}H_{13}O_4$, 197.0819; found, 197.0815. IR (neat): 3100-2800 (br), 1720.5, 1683.9, 1645.3, 1379.1, 1249.9, 1174.7, 1141.9, 1089.8, 1033.9, 856.4, 763.8 cm^{-1}.

*4-{4-[(4-Methylbenzenesulfonyl)oxy]phenyl}cyclohex-1-ene-1-carboxylic acid (**2d**)*



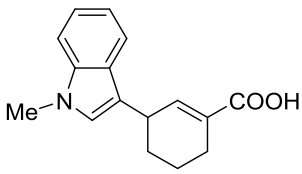
White solid, (62 mg, 67%); mp 238–240 °C; ^{1}H NMR (500 MHz, DMSO-D_6): δ 12.17 (br s, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 7.9 Hz, 2H), 7.27 (d, J = 8.9 Hz, 2H), 6.95-6.90 (m, 3H), 2.78-2.72 (m, 1H), 2.42-2.19 (m, 7H), 1.86-1.84 (m, 1H), 1.68-1.60 (m, 1H). ^{13}C NMR (126 MHz, DMSO-D_6): δ 167.9, 147.3, 145.7, 145.3, 138.1, 131.6, 130.2, 130.1, 128.3, 128.1, 121.8, 37.7, 32.8, 28.9, 24.4, 21.1. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{20}H_{19}O_5S$, 371.0959; found, 371.0953. IR (neat): 3100-2800 (br), 1716.7, 1681.9, 1674.2, 1558.5, 1541.1, 1506.4, 1456.3, 1373.3, 1278.8, 1197.8, 1174.7, 1153.4, 1089.8, 864.1, 750.3, 723.3 cm^{-1}.

*6-Methylcyclohex-1-ene-1-carboxylic acid (**2e**)*[8d]



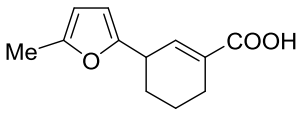
White solid (25 mg, 70%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (t, J = 4.0 Hz, 1H), 2.72-2.66 (m, 1H), 2.28-2.12 (m, 2H), 1.67-1.55 (m, 4H), 1.11 (d, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.1, 142.2, 134.7, 29.5, 27.5, 26.2, 20.2, 17.0.

*3-(1-Methyl-1H-indol-3-yl)cyclohex-1-ene-1-carboxylic acid (**2f**)*



White solid (53 mg, 83%); mp 166–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.89 (br s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.29-7.28 (m, 2H), 7.24-7.21 (m, 1H), 7.11 (t, J = 7.3 Hz, 1H), 6.76 (s, 1H), 3.88 (br s, 1H), 3.71 (s, 3H), 2.38-2.35 (m, 2H), 2.06-2.01 (m, 1H), 1.83-1.75 (m, 2H), 1.71-1.66 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.3, 144.7, 137.2, 129.8, 126.7, 126.4, 121.7, 118.9, 118.9, 116.9, 109.3, 33.4, 32.6, 29.2, 23.9, 20.4. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{16}H_{16}NO_2$, 254.1187; found, 254.1185. IR (neat): 3100-2800 (br), 1716.6, 1670.3, 1626.0, 1558.5, 1541.1, 1506.4, 1473.6, 1456.3, 1288.5, 1257.6, 808.2, 733.0 cm^{-1}.

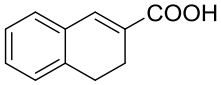
*3-(5-Methylfuran-2-yl)cyclohex-1-ene-1-carboxylic acid (**2g**)*



Yellow solid (41 mg, 80%); mp 97–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16-7.14 (m, 1H), 5.88 (d, J = 3.1 Hz, 1H), 5.86 (d, J =

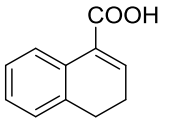
3.1 Hz, 1H), 3.62-3.59 (m, 1H), 2.33-2.29 (m, 2H), 2.26 (s, 3H), 2.00-1.95 (m, 1H), 1.86-1.79 (m, 1H), 1.77-1.70 (m, 1H), 1.69-1.61 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.0, 154.4, 151.0, 141.3, 130.6, 105.9 (two peaks overlap absolutely, confirmed with the HMQC and HMBC spectra), 35.8, 27.1, 23.8, 20.2, 13.5. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{12}H_{13}O_3$, 205.0870; found, 205.0867. IR (neat): 3100-2800 (br), 1683.9, 1635.6, 1558.5, 1508.3, 1417.7, 1288.5, 1020.3, 788.9 cm^{-1}.

*3,4-Dihydronaphthalene-2-carboxylic acid (**2h**)*[22]



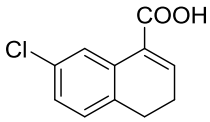
Pale yellow solid (34 mg, 78%); ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.45 (br s, 1H), 7.47 (s, 1H), 7.32 (d, J = 7.0 Hz, 1H), 7.28-7.21 (m, 3H), 2.81 (t, J = 8.4 Hz, 2H), 2.47 (t, J = 8.4 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 168.0, 136.5, 135.4, 132.3, 129.9, 129.3, 128.3, 127.5, 126.7, 26.9, 21.9.

*3,4-Dihydronaphthalene-1-carboxylic acid (**2i**)*[23]



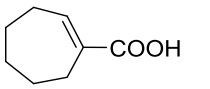
Pale yellow solid (23 mg, 53%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 4.7 Hz, 1H), 7.26-7.16 (m, 3H), 2.78 (t, J = 7.8 Hz, 2H), 2.47-2.43 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.9, 143.0, 136.2, 130.4, 129.9, 127.7, 127.5, 126.6, 126.2, 27.4, 23.7.

*7-Chloro-3,4-dihydronaphthalene-1-carboxylic acid (**2j**)*



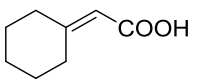
White solid (24 mg, 45%); mp 189–191 °C; ^{1}H NMR (500 MHz, acetone-d_6): δ 8.03 (s, 1H), 7.38 (t, J = 4.9 Hz, 1H), 7.21 (app. d, J = 1.2 Hz, 2H), 2.76 (t, J = 7.9 Hz, 2H), 2.44 (td, J = 8.0, 5.0 Hz, 2H). ^{13}C NMR (126 MHz, acetone-d_6): δ 166.3, 142.4, 135.1, 132.9, 131.5, 128.98, 128.96, 127.1, 126.0, 26.4, 23.2. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{11}H_8ClO_2$, 207.0218; found, 207.0215. IR (neat): 3100-2800 (br), 1716.7, 1683.9, 1558.5, 1541.1, 1506.4, 1489.1, 1473.6, 1456.3, 1174.7, 889.2, 835.2, 814.0, 715.6 cm^{-1}.

*Cyclohep-1-ene-1-carboxylic acid (**2k**)*[21]



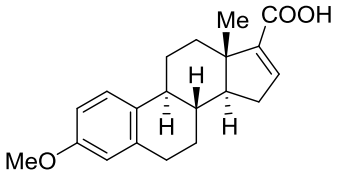
Pale yellow solid (26 mg, 75%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (t, J = 6.7 Hz, 1H), 2.52 (dd, J = 5.5, 5.5 Hz, 2H), 2.32 (dd, J = 11.3, 6.4 Hz, 2H), 1.81-1.76 (m, 2H), 1.58-1.51 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8, 147.3, 135.9, 32.0, 29.0, 26.9, 26.1, 25.6.

*2-Cyclohexylideneacetic acid (**2l**)*[24]



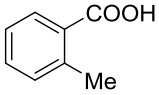
White solid (15 mg, 42%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.63 (s, 1H), 2.83 (t, J = 5.8 Hz, 2H), 2.22 (t, J = 6.1 Hz, 2H), 1.68-1.59 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2, 166.8, 112.5, 38.3, 30.1, 28.7, 27.9, 26.2.

*Product **2n***



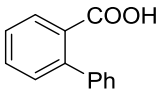
White solid (17 mg, 22%); mp 231–233 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, J = 8.5 Hz, 1H), 6.97-6.96 (m, 1H), 6.72 (dd, J = 8.7, 2.6 Hz, 1H), 6.64 (d, J = 2.7 Hz, 1H), 3.78 (s, 3H), 2.96-2.85 (m, 2H), 2.42-2.27 (m, 4H), 2.17-2.11 (m, 1H), 1.94-1.90 (m, 1H), 1.75-1.60 (m, 4H), 1.51-1.42 (m, 1H), 0.97 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.8, 157.5, 146.4 (two peaks overlap absolutely, confirmed with the HMQC and HMBC spectra), 137.8, 132.7, 126.1, 113.9, 111.5, 55.8, 55.2, 46.0, 44.2, 37.1, 34.7, 31.9, 29.6, 27.7, 26.4, 16.0. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{20}H_{23}O_3$, 311.1653; found, 311.1656. IR (neat): 3100-2800 (br), 2358.9, 1674.2, 1600.9, 1498.7, 1427.3, 1282.7, 1053.1, 964.4, 902.7, 808.2, 781.2, 731.0 cm^{-1}.

*2-Methylbenzoic acid (**4a**)*[25]



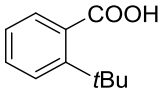
White solid (29 mg, 84%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (d, J = 7.9 Hz, 1H), 7.46-7.43 (m, 1H), 7.30-7.27 (m, 2H), 2.67 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.6, 141.4, 133.0, 132.0, 131.6, 128.4, 125.9, 22.2.

*2-Phenylbenzoic acid (**4b**)*[26]



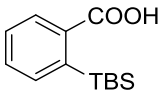
White solid (34 mg, 69%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, J = 7.9 Hz, 1H), 7.55 (td, J = 7.6, 1.2 Hz, 1H), 7.43-7.32 (m, 7H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.3, 143.4, 141.0, 132.1, 131.2, 130.7, 129.3, 128.4, 128.1, 127.3, 127.2.

*2-tert-Butylbenzoic acid (**4c**)*[27]



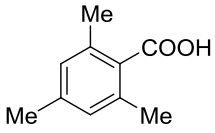
Pale yellow solid (34 mg, 77%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.48 (m, 2H), 7.40 (td, J = 7.8, 1.4 Hz, 1H), 7.25 (td, J = 7.5, 1.1 Hz, 1H), 1.48 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 178.2, 148.2, 131.7, 130.5, 129.0, 127.1, 125.5, 36.0, 31.4.

*2-(tert-Butyldimethylsilyl)benzoic acid (**4d**)*



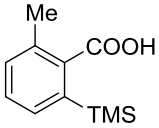
Carboxylation of **3d** was carried out on 0.50 mmol scale. White solid (0.11 g, 93%); mp 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 7.2 Hz, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 0.95 (s, 9H), 0.34 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 140.3, 137.1, 135.9, 131.3, 130.3, 128.6, 27.8, 18.3, –2.4. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{13}H_{19}O_2Si$, 235.1160; found, 235.1157. IR (neat): 3200-2800 (br), 1683.9, 1562.3, 1417.7, 1275.0, 1259.5, 1149.6, 1114.91, 921.9, 839.0, 823.6, 808.2, 771.5, 736.8, 707.9 cm^{-1}.

*2,4,6-Trimethylbenzoic acid (**4e**)*[28]



White solid (32 mg, 77%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (s, 2H), 2.42 (s, 6H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.9, 140.1, 136.2, 129.3, 128.8, 21.1, 20.3.

*2-Methyl-6-(trimethylsilyl)benzoic acid (**4f**)*



White solid (35 mg, 66%); mp 96–98 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 7.3 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 2.50 (s, 3H), 0.34 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.2, 139.4, 136.9, 135.9, 132.3, 131.5, 129.8, 20.6, 0.1. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{11}H_{15}O_2Si$, 207.0847; found, 207.0842. IR (neat): 3100-2800 (br), 1689.6, 1296.2, 1250.0, 1126.4, 879.5, 835.2, 792.7, 752.2 cm^{-1}.

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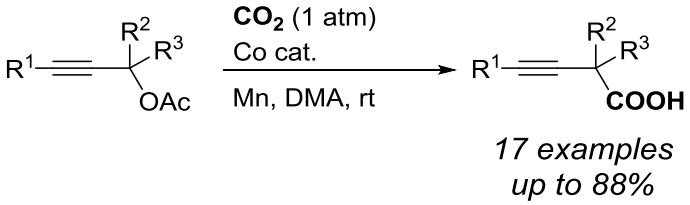
Chapter 3

Cobalt-Catalyzed Carboxylation of Propargyl Acetates with Carbon Dioxide

The cobalt-catalyzed carboxylation of propargyl acetates utilizing 1 atm pressure of carbon dioxide (CO_2) is described. The reaction proceeds at room temperature by employing Mn powder as a reducing reagent. Various propargyl acetates are converted to the corresponding carboxylic acids in good to high yields.



3-1. Introduction

Carbon dioxide (CO_2) is an environmentally friendly raw material and its utilization as a sustainable carbon source is one of the most important challenges in homogeneous transition-metal catalysis.[1] In particular, carbon–carbon (C–C) bond forming reactions using CO_2 are the most promising synthetic molecular transformation.[1a] Reactions of highly reactive Grignard and organolithium reagents with CO_2 are fundamental for the C–C bond formation, but chemoselectivity with these reagents is very poor. In contrast, less reactive organoboronic esters[2a–c] and organozinc reagents[2d,e] were found to react with CO_2 with good chemoselectivity in the presence of a transition metal catalyst. However, all these organometallic compounds are mainly synthesized from the corresponding aryl halides. Thus, the direct carboxylation of aryl halides is more straightforward and efficient. We reported the nickel-catalyzed direct carboxylation of aryl and alkenyl chlorides with CO_2 (1 atm) at room temperature,[3a,b] while carboxylations of more reactive aryl bromides[3c] and benzyl chlorides[3d] as well as inert C–O bonds[3e] were also reported.[4]

Reactions of allylic and propargylic compounds with CO_2 afford a variety of unsaturated carboxylic acids. To date, these transformations require a stoichiometric amount of the corresponding Grignard, organolithium, or other organometallic reagents.[5] In addition, these reactions also have problems in regioselectivity and chemoselectivity.

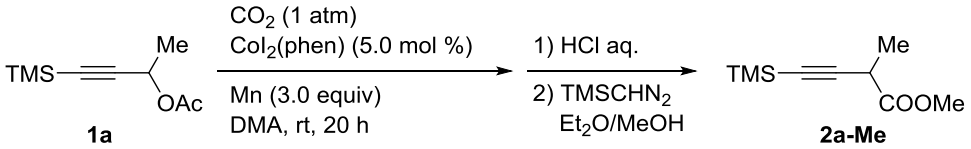
Therefore, the development of a new selective methodology is highly desirable. Allyl and propargyl esters (typically, acetates or carbonates) are well known as efficient *electrophiles* in transition metal-catalyzed C–C bond forming reactions.[6] In order to utilize these electrophiles with CO_2, umpolung[7] reactivity of these esters is crucial. Actually, the reactions of *allyl* esters with CO_2 were carried out under electrochemical conditions in the presence of palladium or nickel catalysts;[8] however, the yields and regioselectivities were low. Furthermore, there is no precedent for the carboxylation of *propargyl* esters with CO_2.[9] Herein, the author describes the cobalt-catalyzed carboxylation of propargyl acetates with CO_2 utilizing Mn powder as a reducing agent. Various propargyl acetates were converted to the corresponding carboxylic acids under 1 atm pressure of CO_2 at room temperature.

3-2. Results and Discussion

The carboxylation of propargyl acetate **1a** was carried out under CO_2 (1 atm) at room temperature, in the presence of CoI_2(phen)[10,11] (5 mol %, phen = 1,10-phenanthroline) and Mn powder (3.0 equiv) in DMA (*N*,*N*-dimethylacetamide) solvent (Table 3-1). The yield of the corresponding carboxylic acid (**2a**) was determined by gas chromatographic (GC) analysis after derivatization to the corresponding methyl ester (**2a-Me**). Under the standard conditions, **2a-Me** was obtained in 83% yield (entry 1). Compound **2a** was

isolated from the reaction mixture in 82% yield. Without CoI_2(phen), **2a-Me** was not obtained (entry 2). In the absence of phen (i.e., CoI_2 as the catalyst), **1a** was not converted (entry 3). Without Mn powder, the carboxylation did not proceed at all (entry 4). When the amount of Mn powder was reduced to 1.2 equiv, the yield of **2a-Me** was decreased to 74% (entry 5). $CoBr_2$(phen) was also a good catalyst and afforded **2a-Me** in 80% yield (entry 6). Employing CoI_2(bpy) (bpy = 2,2'-bipyridine) as a catalyst, **2a-Me** was obtained in 76% yield (entry 7). Thus, phen and bpy showed comparable efficiency as the ligand. In contrast, $CoI_2(PPh_3)_2$ and CoI_2(dppe) (dppe = 1,2-diphenylphosphinoethane) suppressed the carboxylation reaction considerably (entries 8 and 9). Other reducing agents such as Zn powder or Mg turnings gave **2a-Me** in moderate yields (entries 10 and 11). $NiCl_2(PPh_3)_2$, which was an efficient catalyst for the carboxylation of aryl chlorides,[3a] did not show good catalytic activity (entry 12). Other nickel catalysts such as $NiBr_2$(bpy) and NiI_2(phen) were not efficient. With regard to the choice of solvent, 1,3-dimethyl-2-imidazolidinone (DMI) and DMF were also suitable, while reactions in THF and toluene afforded **2a-Me** in 26% and 0% yields, respectively.

Table 3-1. Optimization of Reaction Conditions[a]



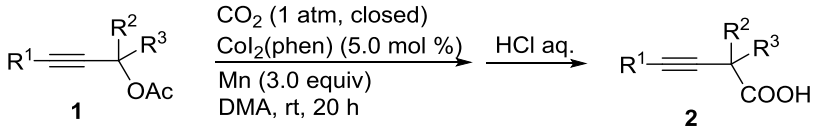
Entry	Change from the Standard Conditions	Yield of **2a-Me** (%)[b]
1	none	83 (82)[c]
2	Without CoI_2(phen)	0
3	CoI_2 in place of CoI_2(phen)	0
4	Without Mn powder	0
5	Mn Powder (0.60 mmol, 1.2 equiv)	74
6	$CoBr_2$(phen) (in place of CoI_2(phen))	80
7	CoI_2(bpy)	76
8	$CoI_2(PPh_3)_2$	23
9	CoI_2(dppe)	0
10	Zn (in place of Mn)	41
11	Mg	57
12[d]	$NiCl_2(PPh_3)_2$ in place of CoI_2(phen)	7

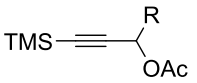
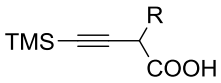
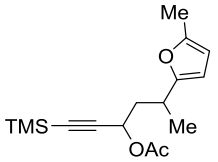
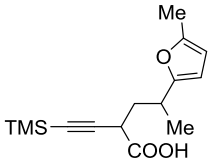
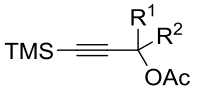
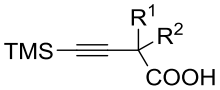
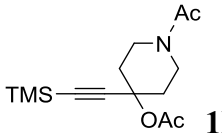
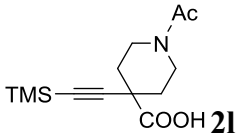
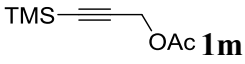
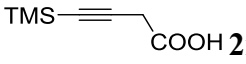
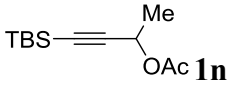
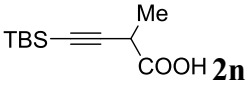
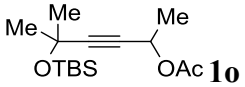
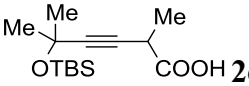
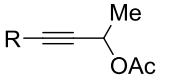
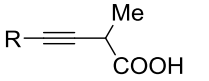
[a]Reaction conditions; **1a** (0.50 mmol), CoI_2(phen) (5.0 mol %), Mn powder (3.0 equiv), CO_2 (1 atm), in DMA (0.50 mL), at room temperature for 20 h. [b]Determined by GC analysis. [c]Isolated yield of **2a**. [d]Et_4NI (10 mol %) was added.

The carboxylation of various propargyl acetates was carried out in the presence of CoI_2(phen) or CoI_2(bpy) as a catalyst (Table 3-2). The carboxylation reactions of trimethylsilyl (TMS) group substituted propargyl acetates derived from secondary alcohols (**1b**–**h**) proceeded smoothly and the corresponding carboxylic acids (**2b**–**h**) were obtained in high yields (entries 1–7). It is noteworthy that ester (**1e**), chloro (**1f**), terminal alkene (**1g**), and furan (**1h**) functionalities were compatible in the reaction (entries 4–7). When the carboxylation of acetates derived from tertiary alcohols was examined with CoI_2(phen), conversion of starting material remained low. In that case, CoI_2(bpy) was found to be a good catalyst and provided the carboxylated products (**2i–l**) in good to high yields (entries 8–11). Amide functionality (**1l**) was also tolerated in the reaction (entry 11). The acetate of primary propargylic alcohol (**1m**) also provided the corresponding carboxylic acid (**2m**) in moderate yield (entry 12). A substituent on the alkyne moiety (R^1, Table 3-2) affects the carboxylation considerably. As the substituent R^1 became less bulky, the yields of the carboxylated products (**2**) decreased; **1n** (R^1 = TBS), **1o** (R^1 = CMe_2(OTBS)), **1p** (R^1 = *t*Bu), and **1q** (R^1 = Cy) afforded the corresponding products (**2n**–**q**) in 88%, 55%, 57%, and 26% yields, respectively (entries 13–16). Propargyl acetate having phenyl ring (**1**: R^1 = Ph, R^2 = Me, R^3 = H) afforded the product in 9% yield. Substrate bearing terminal alkyne moiety (**1**: R^1 = H, R^2 = Me, R^3 = H) did not provide the carboxylated product.[12]

The TMS group of the products in Table 3-2 could be easily removed via protodesilylation[13] in the presence of a suitable base. When α,α-disubstituted carboxylic acid **2a** was used, the reaction with tetrabutylammonium fluoride (TBAF, 1.0 M in THF) provided the corresponding carboxylic acid **2r** in 78% yield (Scheme 3-1a). In contrast, when **2a** or **2d** was treated with KOH (crushed), carboxylic acids bearing an allenyl moiety (**2s**, **2t**) were selectively obtained in 80% and 65% yields, respectively (Scheme 3-1b). A protodesilylation reaction of **2a** with K_2CO_3 resulted in the formation of a mixture of **2r** and **2s** (**2r**/**2s** = 1/3). On the other hand, α,α,α-trisubstituted carboxylic acids such as **2i** and **2j** reacted with K_2CO_3 to give **2u** and **2v** in 98% and 79% yields (Scheme 3-1c). Aryl and alkenyl carbons were introduced onto the terminal alkyne moiety of **2u** and **2v** by the Sonogashira coupling reaction[14a] (**2w** and **2x**, Scheme 3-1d and 3-1e). Moreover, gold-catalyzed intramolecular cyclization[14b] of **2v** provided unsaturated γ-lactone **2y** in a good yield (Scheme 3-1f). Thus these TMS moieties are very useful for the further derivatization reactions.

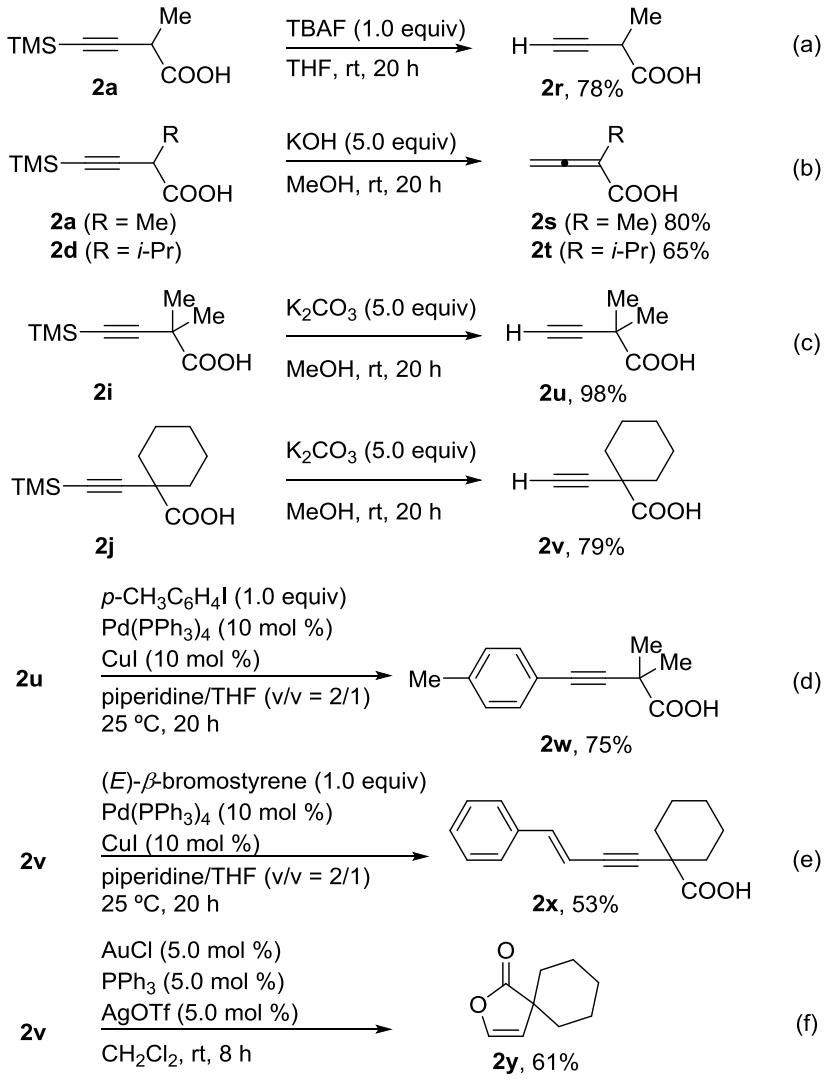
Table 3-2. Cobalt-Catalyzed Carboxylation of Propargyl Acetates



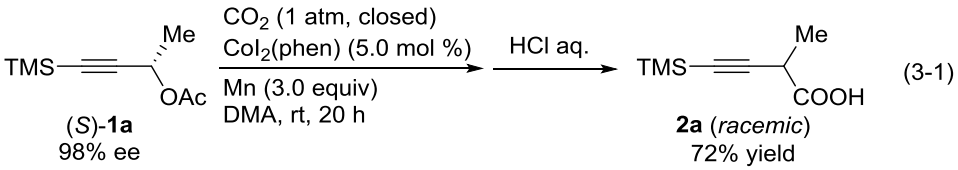
Entry	Substrate **1**	Product **2**	Yield (%)[b]
			
1	**1b**: R = Bu	**2b**	80
2	**1c**: R = $(CH_2)_2Ph$	**2c**	75
3	**1d**: R = *i*Pr	**2d**	79
4	**1e**: R = $(CH_2)_4COOMe$	**2e**	65
5	**1f**: R = $(CH_2)_4Cl$	**2f**	85
6	**1g**: R = $(CH_2)_3CH{=}CH_2$	**2g**	73
7	 mixture of diastereomers in 4:5 **1h**	 mixture of diastereomers in 4:5 **2h**	87
			
8[c]	**1i**: R^1, R^2 = Me	**2i**	71
9[c]	**1j**: R^1, R^2 = $(CH_2)_5$	**2j**	80
10[c]	**1k**: R^1= Me, R^2 = *n*-C_6H_{13}	**2k**	80
11[c]	 **1l**	 **2l**	46
12	 **1m**	 **2m**	40
13	 **1n**	 **2n**	88
14	 **1o**	 **2o**	55
			
15	**1p**: R= *t*-Bu	**2p**	57
16	**1q**: R= Cy	**2q**	26

[a]Reaction conditions; propargyl acetate (**1**, 0.50 mmol), CoI_2(phen) (5.0 mol %), Mn powder (3.0 equiv), CO_2 (1 atm), in DMA (0.50 mL), at room temperature for 20 h. [b]Isolated yield. [c]CoI_2(bpy) (5.0 mol %) was used as a catalyst.

Scheme 3-1. Derivatization of Carboxylated Products **2**



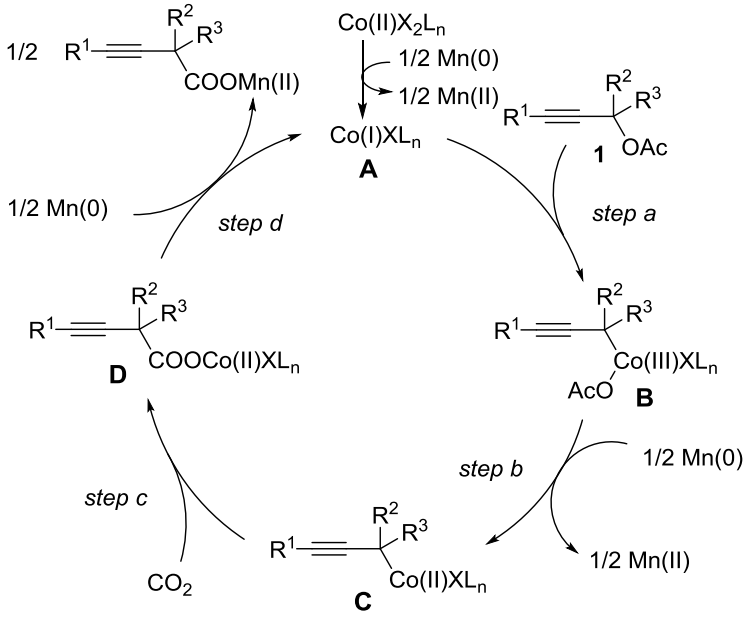
When an optically pure (*S*)-**1a** was employed as the substrate in the present carboxylation, a racemic **2a** was obtained in 72% yield (eq 3-1).



A plausible reaction mechanism is shown in Scheme 3-2. Initially, the reduction of a Co(II) complex with Mn powder affords a Co(I) catalyst species (**A**). Then, oxidative addition of a propargyl acetate (**1**) with Co(I) takes place via C–O bond cleavage, giving

a Co(III) intermediate (**B**) (*step a*). Subsequent reduction of propargyl Co(III) with manganese gives propargyl cobalt(II) species (**C**) (*step b*).[3a,b,15] Then, the more nucleophilic[3b] Co(II) species (**C**) reacts with CO_2 giving the carboxylatocobalt intermediate (**D**) (*step c*). Finally, the reduction of **D** with manganese affords the corresponding manganese carboxylate and regenerates the Co(I) species (**A**) (*step d*).

Scheme 3-2. Plausible Reaction Mechanism



3-3. Conclusion

The author developed a cobalt-catalyzed carboxylation of propargyl acetates utilizing CO_2 under 1 atm pressure of CO_2 at room temperature. Various propargyl acetates especially bearing a silyl group on the alkyne moiety were smoothly converted to the corresponding carboxylic acids with perfect regioselectivity. In addition, the silyl group could be converted to other functional groups after carboxylation reaction.

3-4. Experimental Section

3-4-1. Instrumentation and Chemicals

THF and toluene were dried and purified by usual procedures.[16] DMA and DMI were distilled with CaH_2 and stored over activated MS-4A. Mn powder (99.99%) was purchased from Sigma-Aldrich and stored under a nitrogen atmosphere. Zn powder was activated by washing with HCl aq. and stored under a nitrogen atmosphere. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. IR spectra were obtained on a SHIMADZU FTIR-8300 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a JEOL

ECX-400P spectrometer. The ^{1}H NMR chemical shifts are reported relative to tetramethylsilane (TMS, 0.00 ppm) or acetone-d_6 (2.05 ppm). The ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ (77.0 ppm) or acetone-d_6 (29.0 ppm). GC-MS data were recorded on a Shimadzu GCMS-QP5050A with a direct inlet. High-resolution mass spectra (EI-HRMS, ESI-HRMS and APCI-HRMS) were obtained with JEOL JMX-SX102A (EI-HRMS) and Thermo SCIENTIFIC Exactive LC-MS spectrometers (ESI-HRMS and APCI-HRMS). GC analysis was carried out using a Shimadzu GC-17A equipped with an integrator (C-R8A) with a capillary column (CBP-1, 0.25 mm i.d. × 25 m). Optical rotations were recorded on a JASCO DIP-1000 digital polarimeter at room temperature, using the sodium D line. Column chromatography was carried out on silica gel (Kanto N60, spherical, neutral, 63-210 μm). TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck Silica gel $60F_{254}$.

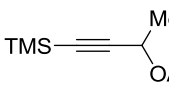
3-4-2. Preparation of Cobalt Complexes

CoI_2(phen) was prepared according to the literature procedure for $CoBr_2$(phen).[10] A 50 mL Schlenk flask was dried with a heating-gun under vacuum. The flask was charged with CoI_2 (0.16 g, 0.50 mmol), phen (90 mg, 0.50 mmol), and THF (2.0 mL) under an Ar atmosphere. The resulting solution was stirred at room temperature for 10–12 h. A yellow solid was precipitated and isolated with filtration. After washing with Et_2O and drying in vacuo, the complex was obtained in 89% yield (0.22 g, 0.45 mmol) and used without further purification. Anal. Calcd for $C_{12}H_8CoI_2N_2 \cdot 2/3THF$: C, 32.56; H, 2.48; N, 5.18%. Found: C, 32.56; H, 2.63; N, 5.23%.

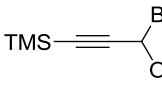
CoI_2(bpy), $CoI_2(PPh_3)_2$ and CoI_2(dppe) were prepared similarly.

3-4-3. Preparation of Propargyl Acetates

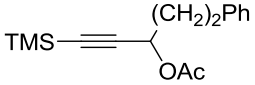
To a mixture of terminal acetylene (10 mmol) in THF (20 mL), *n*-BuLi (10 mmol, 1.64 M in hexane, 6.1 mL) was added dropwise at 0 ºC and the mixture was stirred for 30 min. Then, aldehyde or ketone (10 mmol) were added, and the solution was stirred for 30 min at 0 ºC. After adding Ac_2O (1.2 mL, 12 mmol), the resulting mixture was warmed to room temperature and stirred for 1 h. To the resulting solution, H_2O (10 mL) and Et_2O (10 mL) were added. The organic layer was washed with sat. $NaHCO_3$ aq. and brine, and dried over $MgSO_4$. After removal of volatile, the residue was purified by silica gel chromatography using hexane/EtOAc (30/1 w/w) as an eluent. **1j**[17] and **1q**[18] were prepared in the same way.



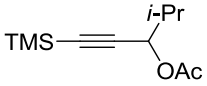
1a: Synthesized with 50 mmol scale. Colorless oil (3.5 g, 19 mmol, 38%); ^{1}H NMR (400 MHz, $CDCl_3$): δ0.17 (s, 9H), 1.47 (d, J = 6.8 Hz, 3H), 2.08 (s, 3H), 5.46 (q, J = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.2, 21.1, 21.5, 60.6, 89.5, 103.5, 169.8. Anal. Calcd for $C_{19}H_{16}O_2Si$: C, 58.65; H, 8.75%. Found: C, 58.59; H, 8.99%.



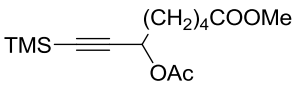
1b: Colorless oil (1.9 g, 8.2 mmol, 82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (d, J = 0.9 Hz, 9H), 0.91 (t, J = 7.0 Hz, 3H), 1.32-1.44 (m, 4H), 1.71-1.77 (m, 2H), 2.08 (d, J = 0.9 Hz, 3H), 5.38 (t, J = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.2, 13.9, 21.1, 22.2, 27.1, 34.5, 64.4, 90.2, 102.8, 169.9. Anal. Calcd for $C_{12}H_{22}O_2Si$: C, 63.66; H, 9.80%. Found: C, 63.42; H, 9.99%.



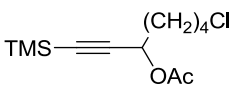
1c: Colorless oil (1.7 g, 6.2 mmol, 62%); ^{1}H NMR (400 MHZ, $CDCl_3$): δ 0.19 (s, 9H), 2.05-2.13 (m, 5H, two peaks overlapped), 2.77 (t, J = 8.2 Hz, 2H), 5.39 (t, J = 6.6 Hz, 1H), 7.20 (t, J = 7.0 Hz, 3H), 7.31-7.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.2, 21.0, 31.3, 36.4, 63.9, 90.8, 102.3, 126.1, 128.4, 128.5, 140.8, 169.8. Anal. Calcd for $C_{16}H_{22}O_2Si$: C, 70.03; H, 8.08%. Found: C, 70.15; H, 8.22%.



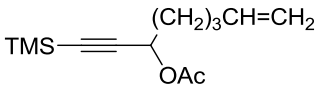
1d: Colorless oil (1.6 g, 7.5 mmol, 75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 0.98 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 1.93-2.02 (m, 1H), 2.09 (s, 3H), 5.24 (d, J = 5.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.2, 17.4, 18.2, 21.0, 32.4, 69.2, 90.8, 101.4, 169.9. Anal. Calcd for $C_{11}H_{20}O_2Si$: C, 62.21; H, 9.49%. Found: C, 62.44; H, 9.65%.



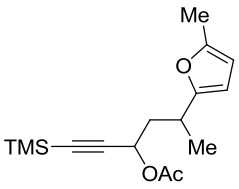
1e: Colorless oil (5 mmol scale, 1.0 g, 3.5 mmol, 70%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 1.43-1.50 (m, 2H), 1.64-1.79 (m, 4H), 2.08 (s, 3H), 2.33 (t, J = 7.5 Hz, 2H), 3.67 (s, 3H), 5.38 (t, J = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.3, 21.0, 24.4, 24.5, 33.8, 34.4, 51.5, 64.0, 90.5, 102.4, 169.8, 173.8. Anal. Calcd for $C_{14}H_{24}O_4Si$: C, 59.12; H, 8.51%. Found: C, 58.89; H, 8.52%.



1f: Colorless oil (1.8 g, 6.9 mmol, 69%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 1.56-1.65 (m, 2H), 1.75-1.86 (m, 4H), 2.09 (s, 3H), 3.55 (t, J = 6.8 Hz, 2H), 5.40 (t, J = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.3, 21.0, 22.3, 31.9, 33.9, 44.6, 64.0, 90.6, 102.2, 169.8. Anal. Calcd for $C_{12}H_{21}ClO_2Si$: C, 55.26; H, 8.12%. Found: C, 55.26; H, 8.41%.

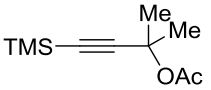


1g: Colorless oil (9 mmol scale, 1.3 g, 5.5 mmol, 61%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 1.49-1.55 (m, 2H), 1.72-1.79 (m, 2H), 2.07-2.12 (m, 5H), 4.96-5.05 (m, 2H), 5.39 (t, J = 6.6 Hz, 1H) 5.74-5.84 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.2, 21.1, 24.2, 33.1, 34.2, 64.2, 90.4, 102.6, 115.0, 138.1, 169.9. APCI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{23}O_2Si$, 239.1462; found, 239.1458.

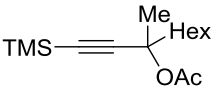


1h: Colorless oil (2.4 g, 8.2 mmol, 82%); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers, dr = 4:5): δ 0.16 (d, J = 4.5 Hz, 9H), 1.25-1.27 (m, 3H), 1.83-2.21 (m, 5H), 2.24 (d, J = 4.1 Hz, 3H), 2.92-2.99 (m, 1H),

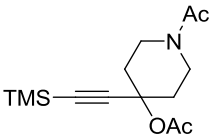
5.29-5.39 (m, 1H), 5.83-5.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.2, 13.5, 13.5, 19.1, 19.4, 21.0, 21.0, 21.0, 29.7, 30.0, 40.6, 40.8, 62.7, 62.9, 90.2, 90.2, 90.4, 90.5, 102.5, 102.6, 104.7, 104.8, 105.7, 150.4, 150.4, 156.8, 169.7, 169.7. Anal. Calcd for $C_{16}H_{24}O_3Si$: C, 65.71; H, 8.27%. Found: C, 65.53; H, 8.38%.



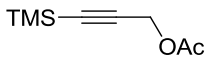
1i: Colorless oil (1.1 g, 5.5 mmol, 55%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.16 (s, 9H), 1.65 (s, 6H), 2.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.1, 22.0, 29.0, 72.3, 88.2, 106.4, 169.1. Anal. Calcd for $C_{10}H_{18}O_2Si$: C, 60.56; H, 9.15%. Found: C, 60.30; H, 9.40%.



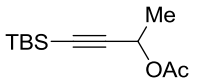
1k: Colorless oil (1.7 g, 6.3 mmol, 63%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.16 (s, 9H), 0.89 (t, J = 6.8 Hz, 3H), 1.30-1.34 (m, 6H), 1.42-1.47 (m, 2H), 1.64 (s, 3H), 1.74-1.81 (m, 1H), 1.88-1.96 (m, 1H), 2.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.1, 14.1, 22.0, 22.5, 24.1, 26.4, 29.1, 31.7, 41.3, 75.7, 89.3, 105.8, 169.1 Anal. Calcd for $C_{15}H_{28}O_2Si$: C, 67.11; H, 10.51%. Found: C, 66.88; H, 10.74%.



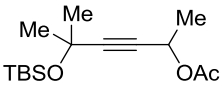
1l: White solid (0.61 g, 2.2 mmol, 22%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.18 (s, 9H), 1.85-1.96 (m, 2H), 2.06 (s, 3H), 2.10 (s, 3H), 2.14-2.20 (m, 1H), 2.24-2.30 (m, 1H), 3.31 (ddd, J = 13.8, 10.0, 3.4 Hz, 1H), 3.43 (ddd, J = 13.7, 9.9, 3.3 Hz, 1H), 3.60-3.66 (m, 1H), 4.06-4.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.2, 21.4, 21.8, 36.3, 36.8, 38.1, 43.0, 73.3, 92.6, 102.8, 168.8, 168.8. ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{14}H_{24}NO_3Si$, 282.1520; found, 282.1523.



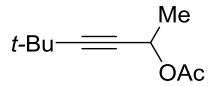
1m: To a mixture of 3-(trimethylsilyl)-2-propyn-1-ol (1.5 mL, 10 mmol) and acetyl chloride (0.85 mL, 12 mmol) in CH_2Cl_2 (20 mL), pyridine (1.2 mL, 15 mmol) was added dropwise at 0 ºC. The solution was sttired at room temperature for 1 h. After the addition of H_2O (20 mL), organic layer was washed with 1 M HCl aq. (10 mL × 2) and brine (10 mL). The resulting organic layer was dried over $MgSO_4$ and all volatiles were removed by a rotary evaporator. The residue was purified by silica gel chromatography using hexane/EtOAc (30/1 w/w) as an eluent. Colorless oil (1.3 g, 7.6 mmol, 76%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.16 (s, 9H), 2.07 (s, 3H), 4.65 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.4, 20.7, 52.7, 92.0, 98.9, 170.1. Anal. Calcd for $C_8H_{14}O_2Si$: C, 56.43; H, 8.29%. Found: C, 56.27; H, 8.18%.



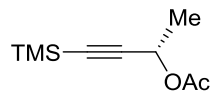
1n: Colorless oil (1.0 g, 4.4 mmol, 44%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.93 (s, 9H), 1.48 (d, J = 6.8 Hz, 3H), 2.07 (s, 3H), 5.46 (q, J = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –4.8, 16.5, 21.1, 21.5, 26.0, 60.6, 87.7, 104.3, 169.8. Anal. Calcd for $C_{12}H_{22}O_2Si$: C, 63.66; H, 9.80%. Found: C, 63.76; H, 10.08%.



1o: Colorless oil (7 mmol scale, 0.92 g, 3.2 mmol, 46%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.15 (s, 6H), 0.86 (s, 9H), 1.44 (s, 6H), 1.46 (d, J = 6.3 Hz, 3H), 2.06 (s, 3H), 5.48 (q, J = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –3.1, 17.9, 21.0, 21.3, 25.7, 32.8, 60.3, 66.1, 80.7, 90.0, 169.8. ESI-HRMS (*m/z*): $[M+NH_4]^+$ calcd for $C_{15}H_{32}O_3SiN$, 302.2146; found, 302.2148.



1p: Colorless oil (0.43 g, 2.6 mmol, 26%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H), 1.44 (d, J = 6.8 Hz, 3H), 2.06 (s, 3H), 5.46 (q, J = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 21.9, 27.3, 30.8, 60.8, 93.5, 169.9. EI-HRMS (*m/z*): $[M]^+$ calcd for $C_{10}H_{16}O_2$, 168.1150; found, 168.1154.



(*S*)-**1a**: To a solution of (*S*)-4-trimethylsilyl-3-butyn-2-ol[19] (3.2 mmol) and acetyl chloride (0.35 mL, 4 mmol) in CH_2Cl_2 (20 mL) was added pyridine (0.46 mL, 6 mmol) at 0 ºC and resulting mixture was stirred for 2 h. The reaction was quenched by addition of sat. $NaHCO_3$ aq. (10 mL) and organic layer was washed with 1 M HCl aq. and brine, and dried over $MgSO_4$. After the removal of solvent, the residue was purified by silica-gel chromatography using hexane/EtOAc (30/1 w/w) as an eluent. Colorless oil (0.51 g, 2.8 mmol, 86%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 1.47 (d, J = 6.8 Hz, 3H), 2.08 (s, 3H), 5.46 (q, J = 6.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.2, 21.1, 21.5, 60.6, 89.5, 103.5, 169.8. $[\alpha]^{25}_D$ –137.9 (c 1.070, $CHCl_3$, 98% ee). Enantiomeric excess of this compound was determined by GC analysis with a capillary column (CP-Chirasil Dex CB, 0.25 mm i.d. × 25 m)

3-4-4. Experimental Procedures

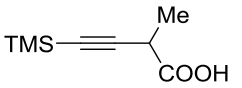
Typical procedure for the carboxylation of 1a (entry 1, Table 3-1)

A 20 mL Schlenk flask was dried with a heating-gun under vacuum. The flask was charged with CoI_2(phen) (12 mg, 0.025 mmol) and Mn powder (82 mg, 1.5 mmol). The flask was evacuated and refilled with CO_2. This sequence was repeated five times. Then, DMA (0.5 mL) and 1-methyl-3-(trimethylsilyl)prop-2-ynyl acetate **1a** (0.10 mL, 0.50 mmol) were added via airtight syringes, and the resulting mixture was stirred at room temperature for 20 h. After the reaction, tridecane (50 μL, 0.21 mmol) as an internal standard, Et_2O (5.0 mL), and 1 M HCl aq. (3.0 mL) were added to the reaction mixture. After stirring for 10 min, organic layer was transferred to a flask containing anhydrous $MgSO_4$ (50 mg). Then, methanol (1.0 mL) and $TMSCHN_2$ (2.0 M in Et_2O, 0.50 ml, 1.0 mmol) were added to the suspension, and it was stirred for 30 min. The yield of **2a-Me** was determined by GC analysis.

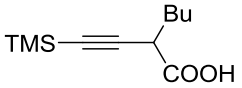
General procedure for the carboxylation of propargyl acetates (Table 3-2)

A 20 mL Schlenk flask was dried with a heating-gun under vacuum. The flask was charged with CoI_2(phen) (12 mg, 0.025 mmol) or CoI_2(bpy) (12 mg, 0.025 mmol) and Mn powder (82 mg,

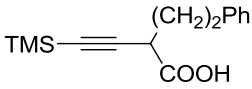
1.5 mmol). The flask was evacuated and refilled with CO_2. This sequence was repeated five times. Then, DMA (0.50 mL) and **1** (0.50 mmol) were added via airtight syringes, and the resulting mixture was stirred at room temperature for 20 h. After reaction, 1 M HCl aq. (3 mL) and Et_2O (5 mL) were added, and stirred at room temperature for 10 min. The mixture was extracted with Et_2O (5 mL × 5). The collected organic layer was combined and dried over anhydrous MgSO4. After removal of volatile, the residue was purified by silica gel chromatography using hexane/EtOAc (4/1, v/v) as an eluent.



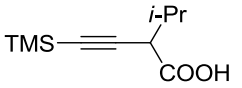
2a: Yellow oil (70 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 1.47 (d, J = 7.2 Hz, 3H), 3.49 (q, J = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.1, 18.0, 33.2, 87.8, 102.4, 177.5. Anal. Calcd for $C_8H_{14}O_2Si$: C, 56.43; H, 8.29%. Found: C, 56.58; H, 8.44%. IR (neat): 3300-2700 (br), 2179.2, 1719.2, 1413.6, 1286.3, 1250.6, 1224.6, 1120.4, 940.1, 844.7, 760.8 cm^{-1}.



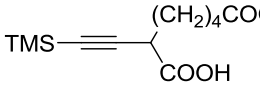
2b: Yellow oil (85 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.16 (s, 9H), 0.92 (t, J = 7.2 Hz, 3H), 1.31-1.51 (m, 4H), 1.74-1.91 (m, 2H), 3.39 (dd, J = 6.3, 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.1, 13.8, 22.1, 29.0, 32.0, 38.9, 88.9, 101.4, 177.1. Anal. Calcd for $C_{11}H_{20}O_2Si$: C, 62.21; H, 9.49%. Found: C, 62.40; H, 9.59%. IR (KBr): 3300-2500 (br), 2179.2, 1717.3, 1414.7, 1250.6, 843.7, 759.8 cm^{-1}.



2c: Yellow oil (98 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.20 (s, 9H), 2.05-2.21 (m, 2H), 2.74-2.87 (m, 2H), 3.38 (dd, J = 5.9, 8.2 Hz, 1H), 7.19-7.22 (m, 3H), 7.27-7.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.1, 32.9, 33.7, 38.1, 89.7, 100.9, 126.2, 128.5, 128.6, 140.6, 175.9. Anal. Calcd for $C_{15}H_{20}O_2Si$: C, 69.19; H, 7.74%. Found: C, 69.31; H, 7.80%. IR (KBr): 3200-2500 (br), 1713.4, 1276.7, 1252.5, 1235.2, 840.8, 750.9, 747.3, 701.0 cm^{-1}.

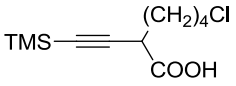


2d: Yellow oil (78 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.18 (s, 9H), 1.05 (dd, J = 2.3, 6.8 Hz, 6H), 2.18-2.30 (m, 1H), 3.26 (d, J = 5.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.1, 18.8, 20.8, 31.0, 46.4, 89.9, 100.0, 176.8. Anal. Calcd for $C_{10}H_{18}O_2Si$: C, 60.56; H, 9.15%. Found: C, 60.45; H, 9.23%. IR (neat): 3500-2500 (br), 2183.0, 1715.4, 1414.5, 1290.1, 1250.6, 1024.0, 843.7, 760.8 cm^{-1}.

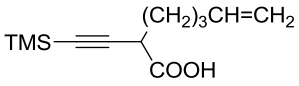


2e: Yellow oil (88 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 1.45-1.59 (m, 2H), 1.64-1.72 (m, 2H), 1.75-1.92 (m, 2H), 2.34 (t, J = 7.5 Hz, 2H), 3.39 (dd, J = 6.1, 7.9 Hz, 1H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.2, 24.3, 26.4, 31.8, 33.8, 38.7, 51.6, 89.0, 101.1, 174.0, 176.4. Anal. Calcd for $C_{13}H_{22}O_4Si$: C, 57.74; H, 8.20%. Found: C, 57.96; H, 8.37%. IR (neat): 3500-2700 (br), 1741.4,

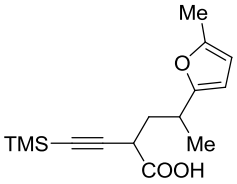
1717.3, 1438.6, 1250.6, 1208.2, 1175.4, 844.7, 760.8 cm^{-1}.



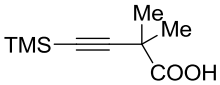
2f: Yellow oil (0.11 g, 85%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.18 (s, 9H), 1.60-1.69 (m, 2H), 1.77-1.90 (m, 4H), 3.41 (t, J = 6.8 Hz, 1H), 3.55 (t, J = 6.6 Hz, 2H), 10.89 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.1, 24.2, 31.4, 31.9, 38.8, 44.5, 89.4, 100.8, 176.6, 176.8. Anal. Calcd for $C_{11}H_{19}ClO_2Si$: C, 53.53; H, 7.76%. Found: C, 53.58; H, 7.92%. IR (neat): 3500-2500 (br), 1717.3, 1415.5, 1288.2, 1250.6, 844.7, 760.8 cm^{-1}.



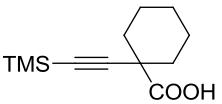
2g: Yellow oil (82 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 1.52-1.64 (m, 2H), 1.75-1.90 (m, 2H), 2.10 (q, J = 6.9 Hz, 2H), 3.40 (t, J = 7.0 Hz, 1H), 4.96-5.05 (m, 2H), 5.74-5.84 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ –0.1, 26.0, 31.6, 33.0, 38.8, 89.0, 101.1, 115.0, 138.0, 177.3. APCI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{12}H_{21}O_2Si$, 225.1305; found, 225.1302. IR (neat): 3300-2800 (br), 2179.2, 1718.3, 1414.5, 1250.6, 843.7, 760.8 cm^{-1}.



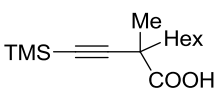
2h: Yellow oil (0.12 g, 87%); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers, dr = 4:5): δ 0.19 (d, J = 5.9 Hz, 9H), 1.28 (dd, J = 12.9, 7.0 Hz, 3H), 1.88-2.22 (m, 2H), 2.26 (s, 3H), 2.97-3.10 (m, 1H), 3.31-3.45 (m, 1H), 5.83-5.85 (m, 1H), 5.90 (dd, J = 7.7, 3.2 Hz, 1H), 11.08 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.1, –0.1, 13.5, 13.5, 18.5, 19.8, 30.8, 31.2, 36.8, 37.5, 38.0, 38.1, 88.8, 89.1, 101.0, 101.1, 105.2, 105.5, 105.6, 150.6, 150.7, 156.0, 156.6, 177.0, 177.1. ESI-HRMS (*m/z*): $[M–H]^–$ calcd for $C_{15}H_{21}O_3Si$, 277.1265; found, 277.1269. IR (neat): 3500-2500 (br), 1718.3, 1413.6, 1250.6, 1219.8, 1020.2, 844.7, 783.0, 760.8 cm^{-1}.



2i: Pale orange solid (66 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.16 (s, 9H), 1.51 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.0, 27.1, 39.0, 86.4, 107.3, 180.2. Anal. Calcd for $C_9H_{16}O_2Si$: C, 58.65; H, 8.75%. Found: C, 58.41; H, 8.87%. IR (KBr): 3300-2500 (br), 1707.7, 1295.0, 1251.6, 899.6, 841.8, 761.7 cm^{-1}.

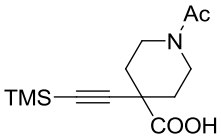


2j: Pale orange solid (89 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.18 (s, 9H), 1.19-1.26 (m, 1H), 1.66-1.74 (m, 7H), 1.94 (d, J = 9.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.0, 22.2, 25.3, 34.6, 44.6, 89.4, 105.4, 179.3. Anal. Calcd for $C_{12}H_{20}O_2Si$: C, 64.24; H, 8.98%. Found: C, 64.03; H, 9.19%. IR (KBr): 3300-2500 (br), 1699.0, 1278.6, 1249.7, 868.8, 840.8, 760.8 cm^{-1}.

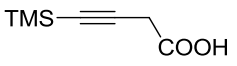


2k: Yellow oil (0.10 g, 80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 0.89 (t, J = 6.8 Hz, 3H), 1.29-1.44 (m, 8H), 1.47 (s, 3H), 1.65 (dt, J = 4.5, 11.8 Hz, 1H), 1.83 (dt, J = 4.7, 12.5, Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.0, 14.0, 22.5,

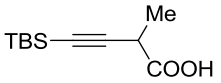
25.1, 25.5, 29.2, 31.5, 40.0, 43.8, 87.9, 106.5, 179.5. Anal. Calcd for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30%. Found: C, 65.84; H, 10.58%. IR (neat): 3500-2500 (br), 2173.4, 1709.6, 1459.9, 1408.8, 1277.6, 1250.6, 881.3, 843.7, 759.8 cm^{-1}.



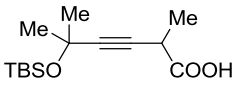
2l: White solid (63 mg, 46%); ^1H NMR (400 MHz, $CDCl_3$): δ 0.15 (s, 9H), 1.80-1.96 (m, 4H), 2.12 (s, 3H), 3.12 (t, J = 11.6 Hz, 1H), 3.46 (t, J = 11.3 Hz, 1H), 3.69 (d, J = 13.6 Hz, 1H), 4.37 (d, J = 13.6 Hz, 1H), 11.75 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.1, 21.0, 33.6, 34.1, 38.4, 42.7, 43.1, 90.6, 103.4, 169.9, 174.6. ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{22}NO_3Si$, 268.1363; found, 268.1361. IR (KBr): 3700-2500 (br), 1726.0, 1602.6, 1480.1, 1457.0, 1442.5, 1254.5, 1050.1, 858.2, 839.8 cm^{-1}.



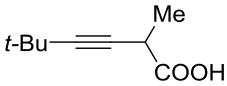
2m: Orange oil (32 mg, 40%); ^1H NMR (400 MHz, $CDCl_3$): δ 0.18 (s, 9H), 3.39 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.2, 26.9, 89.1, 96.3, 174.2. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_7H_{11}O_2Si$, 155.0534; found, 155.0535. IR (neat): 3300-2700 (br), 2187.8, 1714.4, 1392.4, 1255.4, 1244.8, 1220.7, 1048.1, 845.6, 760.8 cm^{-1}.



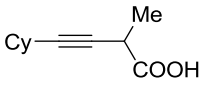
2n: Yellow oil (94 mg, 88%); ^1H NMR (400 MHz, acetone-d_6): δ 0.08 (s, 6H), 0.94 (s, 9H), 1.38 (d, J = 7.2 Hz, 3H), 3.49 (q, J = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ –4.5, 17.1, 18.4, 26.3, 33.3, 84.7, 106.2, 172.0. Anal. Calcd for $C_{11}H_{20}O_2Si$: C, 62.21; H, 9.49%. Found: C, 61.98; H, 9.78%. IR (neat): 3500-2500 (br), 1720.2, 1250.6, 838.9, 810.9, 776.2 cm^{-1}.



2o: Yellow oil (75 mg, 55%); ^1H NMR (400 MHz, acetone-d_6): δ 0.16 (s, 6H), 0.84 (s, 9H), 1.35 (d, J = 7.2 Hz, 3H), 1.41 (s, 6H), 3.44 (q, J = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ –2.9 (d, J = 1.9 Hz), 18.2, 18.4, 26.1, 32.2, 33.4 (d, J = 1.9 Hz), 66.9, 81.9, 87.7, 172.2. Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69%. Found: C, 62.41; H, 9.92%. IR (neat): 3500-2500 (br), 1720.2, 1245.8, 1163.8, 1041.4, 777.2 cm^{-1}.



2p: Yellow oil (44 mg, 57%); ^1H NMR (400 MHz, $CDCl_3$): δ 1.21(s, 9H), 1.42 (d, J = 7.2 Hz, 3H), 3.41 (q, J = 7.2 Hz, 1H), 11.64 (br s, 1H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 27.3, 31.0, 32.2, 75.3, 91.8, 178.7. EI-HRMS (m/z): $[M]^+$ calcd for $C_9H_{14}O_2$, 154.0994; found, 154.0993. IR (neat): 3300-2500 (br), 1715.4, 1457.9, 1415.5, 1364.4, 1288.2, 1204.3 cm^{-1}.

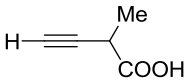


2q: Yellow oil (23 mg, 26%); ^1H NMR (400 MHz, $CDCl_3$): δ 1.26-1.33 (m, 3H), 1.39-1.52 (m, 6H), 1.65-1.72 (m, 2H), 1.75-1.81 (m, 2H), 2.34-2.41 (m, 1H), 3.44 (dq, J = 1.8, 7.1 Hz, 1H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 24.8, 25.9, 29.0, 32.3, 32.6, 76.8, 87.8, 178.2. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{11}H_{15}O_2$, 179.1078; found, 179.1079.

IR (neat): 3700-2500 (br), 1712.5, 1451.2, 1381.8, 1256.4, 967.1 cm^{-1}. IR (neat): 3700-2500 (br), 1712.5, 1451.2, 1381.8, 1256.4, 967.1 cm^{-1}.

Procedure for desilylation of 2a using TBAF (Scheme 3-1a)

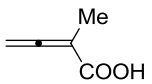
To a solution of propargyl carboxylic acid **2a** (85 mg, 0.50 mmol) in THF (1.0 mL), TBAF (0.50 mmol, 1 M in THF, 0.50 mL) was added and then the mixture was stirred overnight at room temperature. The resulting mixture was extracted with Et_2O (10 mL) and H_2O (10 mL) and the combined organic layers were dried over $MgSO_4$. Et_2O and THF were removed with carefully evaporation. The residue was purified by reduced distillation with Kugel-roll oven (6 Torr, 100 ºC) and **2r** was obtained.



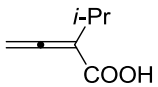
2r: Colorless oil (38 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (d, J = 7.2 Hz, 3H), 2.29 (d, J = 2.7 Hz, 1H), 3.49 (dq, J = 2.3, 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 32.0, 71.5, 80.7, 177.2. APCI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_5H_7O_2$, 99.0441; found, 99.0449. IR (neat): 3700-2700 (br), 1727.9, 1640.2, 1218.8, 659.5 cm^{-1}.

Procedure for desilylation of 2a and 2d using KOH (Scheme 3-1b)

To a solution of propargyl carboxylic acid **2a** (0.50 mmol) in methanol (1.0 mL), crushed KOH (0.14 g, 2.5 mmol) was added and then the mixture was stirred overnight at room temperature. The resulting mixture was diluted with Et_2O (20 mL) and extracted with H_2O three times. The combined basic aqueous layer was acidified to pH = 1 using 1 M HCl aq. and extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous $MgSO_4$ and evaporated to yield **2s**. Carboxylic acid **2t** was obtained similarly using **2d** as the substrate.



2s: White solid (39 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88 (t, J = 2.9 Hz, 3H), 5.15 (q, J = 2.9 Hz, 2H), 11.18 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 78.3, 95.1, 173.0, 215.0. Anal. Calcd for $C_5H_6O_2$: C, 61.22; H, 6.16%. Found: C, 61.42; H, 6.39%. IR (KBr): 3300-2500 (br), 1962.2, 1684.5, 1423.2, 1309.4, 1142.6, 869.7 cm^{-1}.

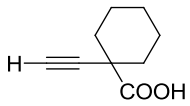


2t: Orange oil (41 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (d, J = 6.8 Hz, 6H), 2.60-2.72 (m, 1H), 5.22 (d, J = 2.3 Hz, 2H), 10.98 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.8, 26.5, 80.4, 106.7, 172.9, 213.7. ESI-HRMS (*m/z*): $[M–H]^–$ calcd for $C_7H_9O_2$, 125.0608; found, 125.0608. IR (neat): 3300-2500 (br), 2661.3, 1962.2, 1936.2, 1683.6, 1466.6, 1411.64, 1385.6, 1280.5, 1046.2, 846.6, 752.1 cm^{-1}.

Procedure for desilylation of 2i and 2j (Scheme 3-1c)

To a solution of carboxylic acid **2i** (0.57 g, 3.1 mmol) in methanol (30 mL), K_2CO_3 (2.1 g, 15 mmol) was added in one portion, and the resulting mixture was stirred overnight at room temperature. After the reaction, Et_2O (20 mL) and saturated $NaHCO_3$ aq. (20 mL) were added to

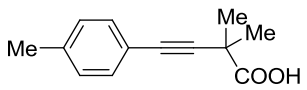
the reaction mixture, and the organic layer was washed with saturated $NaHCO_3$ aq. three times. The combined aqueous phase was acidified again to pH = 1 using 1 M HCl aq. and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated to yield **2u** as pale yellow oil (0.34 g, 3.0 mmol, 98%). All the resonances in NMR spectrums were in good agreement with the literature values.[20] Carboxylic acid **2v** was obtained similarly using **2j** as the substrate.



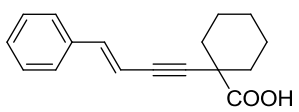
2v: The reaction was carried out on 8.0 mmol scale. Yellow solid (0.96 g, 6.3 mmol, 79%); ^{1}H NMR (400 MHz, acetone-d_6): δ 1.24-1.90 (m, 10H), 2.77 (d, J = 0.9 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d_6): δ 23.0, 25.9, 35.3, 43.6, 73.3, 85.4, 174.0. APCI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_9H_{13}O_2$, 153.0910; found, 153.0909. IR (KBr): 3300-2800 (br), 1700.9, 1451.2, 1294.0, 1256.4, 1063.6, 930.5, 752.1, 651.8, 556.4, 498.5, 429.1 cm^{-1}.

Procedure for Sonogashira-Coupling reactions of 2u and 2v (Scheme 3-1d, e)

To a solution of 4-iodotoluene (0.11 g, 0.50 mmol), $Pd(PPh_3)_4$ (57 mg, 0.025 mmol) and CuI (9.5 mg, 0.050 mmol) in piperidine/THF (1.5 mL, 2/1, v/v), was added **2u** (59 mg, 0.50 mmol). The resulting mixture was then stirred at 25 ºC for 20 h under an Ar atmosphere. After addition of 1 M HCl aq., the aqueous layer was washed with Et_2O (20 mL) three times and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of volatile, the residue was purified by silica gel chromatography using hexane/EtOAc (5/1, v/v) as an eluent, and then, **2w** was obtained. Coupling product **2x** was also obtained under the similarly using **2v** and β-bromostyrene (*E*/*Z* = 93/7).



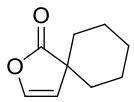
2w: Pale orange solid (76 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (s, 6H), 2.33 (s, 3H), 7.09 (d, J = 7.7 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 27.1, 38.7, 82.4, 90.0, 119.8, 128.9, 131.6, 138.2, 179.8. ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{15}O_2$, 203.1067; found, 203.1065. IR (KBr): 3100-2900 (br), 1789.6, 1290.1, 1246.8, 1091.5, 1004.7, 925.7, 798.4 cm^{-1}.



2x: Pale yellow solid (68 mg, 53%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23-1.31 (m, 1H), 1.63-1.86 (m, 7H), 2.01 (d, J = 12.2 Hz, 2H), 6.20 (d, J = 16.3 Hz, 1H), 6.95 (d, J = 16.3 Hz, 1H), 7.24-7.38 (m, 5H), 9.96 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 25.3, 34.7, 44.5, 83.8, 91.2, 107.9, 126.2, 128.5, 128.5, 136.2, 141.3, 179.6. APCI-HRMS (m/z): $[M+H]^+$ calcd for $C_{17}H_{19}O_2$, 255.1380; found, 255.1375. IR (KBr): 3300-2800 (br), 1703.8, 1448.3, 1280.5, 1256.4, 955.6, 751.1, 693.3, 521.7 cm^{-1}.

Procedure for intramolecular cyclization reaction of 2v (Scheme 3-1f)

In a 20 mL Schrenk flask, AuCl (5.8 mg, 5.0 mol %) and PPh_3 (6.6 mg, 5.0 mol %) were dissolved in CH_2Cl_2 (5.0 mL) and stirred for 5 min under an Ar atmosphere. The solution was further stirred for additional 10 min after adding AgOTf (6.4 mg, 5.0 mol %). Then, carboxylic acid **2v** (76 mg, 0.50 mmol) was added and the resulting mixture was stirred at room temperature for 8 h. After removal of volatile, the residue was purified by silica gel chromatography using hexane/EtOAc (50/1, v/v) as an eluent to afford **2y**.



2y: Colorless oil (46 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35-1.86 (m, 10H), 5.84 (d, J = 3.6 Hz, 1H), 6.81 (d, J = 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.1, 22.2, 33.4, 47.4, 114.5, 141.2, 181.6. APCI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_9H_{13}O_2$, 153.0910; found, 153.0908. IR (neat): 3116.4, 2934.2, 2858.0, 1791.6, 1616.1, 1452.1, 1348.0, 1285.3, 1265.1, 1183.1, 1162.9, 1119.5, 1079.9, 1051.0, 994.1, 918.0, 849.5, 724.1, 569.9 cm^{-1}.

Procedure for carboxylation of (*S*)-1a (eq 3-1)

A 20 mL Schlenk flask was dried with a heating-gun under vacuum. The flask was charged with CoI_2(phen) (12 mg, 0.025 mmol) and Mn powder (82 mg, 1.5 mmol). The flask was evacuated and refilled with CO_2. This sequence was repeated five times. Then, DMA (0.50 mL) and (*S*)**-1a** (0.10 mL, 0.50 mmol) were added via airtight syringes, and the resulting mixture was stirred at room temperature for 20 h. After reaction, 1 M HCl aq. (3 mL) and Et_2O (5 mL) was added, and stirred at room temperature for 10 min. The mixture was extracted with Et_2O (5 mL × 5). The collected organic layer was combined and dried over anhydrous $MgSO_4$. After removal of volatile, the residue was purified by silica gel chromatography using hexane/EtOAc (4/1, v/v) as an eluent to afford **2a**. Yellow oil (60.9 mg, 72%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 1.47 (d, J = 7.2 Hz, 3H), 3.49 (q, J = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ –0.1, 18.0, 33.2, 87.8, 102.4, 177.5. $[\alpha]^{24}_D$ +0.6 (c 0.932, $CHCl_3$). This compound was identified as racemic mixture by GC analysis with a capillary column (CP-Chirasil Dex CB, 0.25 mm i.d. × 25 m) after the derivatization of the corresponding methyl ester.

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(8) (a) Torii, S.; Tanaka, H.; Hamatani, T.; Morisaki, K.; Jutand, A.; Pfluger, F.; Fauvarque, J.-F. *Chem. Lett.* **1986**, 169–172. (b) Medeiros, M. J.; Pintaric, C.; Olivero, S.; Dunach, E. *Electrochimica Acta* **2011**, *56*, 4384–4389.

(9) In the nickel-catalyzed carboxylation of benzylic chlorides with CO_2,[3d] $C_6H_5C{\equiv}CCH_2Cl$ was used as a substrate and afforded $C_6H_5C{\equiv}CCH_2COOH$ in only 29% yield; other propargylic substrates were not examined in the reaction.

(10) CoI_2(phen) was synthesized by a similar method for $CoBr_2$(phen); Hilt, G.; Hess, W.; Vogler, T.; Hengst, C. *J. Organomet. Chem*. **2005**, *690*, 5170–5181.

(11) See the Experimental Section for details.

(12) In those cases including entries 14–16 in Table 3-2, most substrates were consumed

and some oligomerizations occurred judging from GPC (gel permeation chromatography) analysis of the resulting reaction mixtures.

(13) (a) Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 732–757. (b) Scott, L. T.; Cooney, M. J.; Johnels, D. *J. Am. Chem. Soc*. **1990**, *112*, 4054–4055.

(14) (a) Sonogashira. K. *J. Organomet. Chem.* **2002**, *653*, 46–49. (b) Shi, H.; Fang, L.; Tan, C.; Shi, L.; Zhang, W.; Li, C.-C.; Luo, T.; Yang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 14944–14947.

(15) Qian, X.; Auffrant, A.; Felouat, A.; Gosmini, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10402–10405.

(16) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals, 5th ed.*; Burrerworth-Heinemann: Oxford, U. K., 2003.

(17) Ghosh, N.; Nayak S.; Sahoo, A. K. *J. Org. Chem.* **2011**, *76*, 500–511.

(18) Yu, M.; Zhang G.; Zhang, L. *Org. Lett*. **2007**, *9*, 2147–2150.

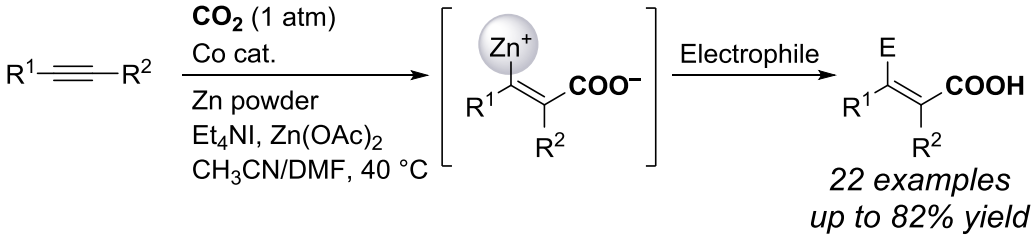
(19) Peh, G.-R.; Eloreancig, P. E. *Org. Lett*. **2012**, *14*, 5614–5617.

(20) Wash, P. L.; Maverick, E.; Chiefari J.; Lightner, D. A. *J. Am. Chem. Soc*. **1997**, *119*, 3802–3806.

Chapter 4

Cobalt-Catalyzed Carboxyzincation of Alkynes Utilizing Carbon Dioxide and Zinc Powder

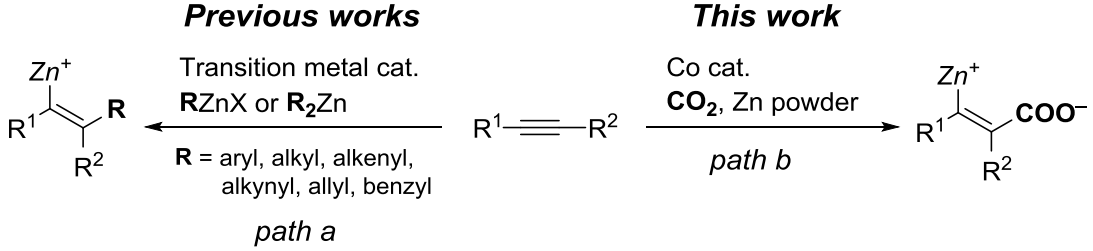
The cobalt-catalyzed carboxyzincation of alkynes utilizing CO_2 (1 atm) and Zn powder is described. The reaction enables concurrent formation of C–C and C–Zn bonds affording *β*-zincated acrylic derivatives stereoselectively. Resulting alkenyl zinc moiety possesses sufficient reactivity and following transformation with various electrophiles furnished stereodefined multi-functionalized olefins.



4-1. Introduction

Organozinc reagent is one of the most important organometallic intermediates in organic synthesis because of their appropriate reactivity as well as compatibility with a broad range of functional groups.[1] Transition metal-catalyzed carbozincation of alkynes is an attractive and straightforward method for the preparation of alkenylzinc reagents with the concomitant construction of a new carbon–carbon (C–C) bond. To date, employing the corresponding organozinc reagents (RZnX or R_2Zn), diverse carbon substituents (R = aryl, alkyl, alkenyl, alkynyl, allyl, and benzyl groups) have been introduced onto alkynes (Scheme 4-1, *path a*).[2,3]

Scheme 4-1. Carbozincation of an Alkyne



Meanwhile, carbon dioxide (CO_2) is an attractive C1 source and utilization of CO_2 as chemical feedstock is a significant challenge for both scientific and industrial societies. Among the research for chemical fixation of CO_2, substantial efforts have been devoted to establish the efficient synthetic route of carboxylic acid and their derivatives from CO_2 through C–C bond formation.[4] In this perspective, carboxyzincation of unsaturated hydrocarbons, in which both zinc and CO_2 are simultaneously incorporated, must be a fascinating reaction in the view points of the preparation of organozinc compounds as well as the CO_2 fixation chemistry (Scheme 4-1, *path b*). Nevertheless, to date, there is no precedent for the carboxyzincation of C–C multiple bonds including alkynes, while the catalytic hydrocarboxylation[5] and alkylative or arylative carboxylation reactions[6,7] of unsaturated hydrocarbon compounds employing organozinc reagents in the presence of nickel or copper catalysts were reported.

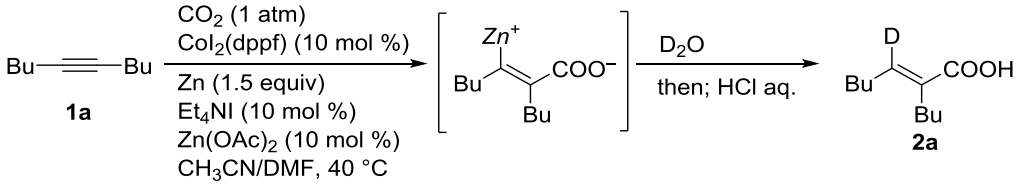
Recently, cobalt catalysts have shown their activity for C–C bond-forming CO_2 incorporating reactions.[8,9] On the other hand, they also have a capability to promote catalytic zincation of aryl halides with metallic Zn as a zinc source.[10] Thus, the author anticipated that cobalt catalyst should have the possibility to promote incorporation of both CO_2 and zinc atom into organic compounds. Herein, a cobalt-catalyzed carboxyzincation of alkynes employing CO_2 and metallic Zn powder is described (Scheme 4-1, *path b*). Noteworthy is that the zinc atom as well as carboxyl moiety could be incorporated into the product, giving the β-zincated acrylic derivatives. Moreover,

resulting alkenylzinc species possess sufficient reactivity and following transformation reactions with various electrophiles afforded the multi-functionalized olefins in a high stereoselective manner.

4-2. Results and Discussion

Catalytic carboxyzincation of 5-decyne (**1a**) smoothly proceeded in the presence of CoI_2(dppf) (10 mol %), zinc powder (1.5 equiv), Et_4NI (10 mol %) and $Zn(OAc)_2$ (10 mol %) in CH_3CN and DMF (0.55 mL, v/v = 10/1) under 1 atm pressure of CO_2 at 40 °C (Table 4-1). After the reaction, treatment with D_2O (>99% D) afforded the deuterocarboxylated product **2a** in 80% yield that was determined by ^1H NMR analysis. From the reaction mixture, 73% yield of **2a** could be isolated with high deuterium incorporation ratio (94% D) (entry 1). (*E*)-Configuration of **2a** was determined by NOE measurements. The catalyst *in situ* generated from CoI_2 and dppf also worked well and afforded the product in 74% yield (entry 2). The use of Zn powder (1.2 equiv) also gave the product in 70% yield. Cobalt catalyst was indispensable for this reaction (entry 3). Without Et_4NI, $Zn(OAc)_2$, or DMF, the yield of **2a** was reduced (entries 4–6). The use of dppf as a ligand was critical for this system and other phosphine ligands or 2,2'-bipyridine did not afford the product (entries 7 and 8). In the present reaction, nickel catalyst did not work well (entry 9).

Table 4-1. Cobalt-Catalyzed Carboxyzincation of **1a**[a]

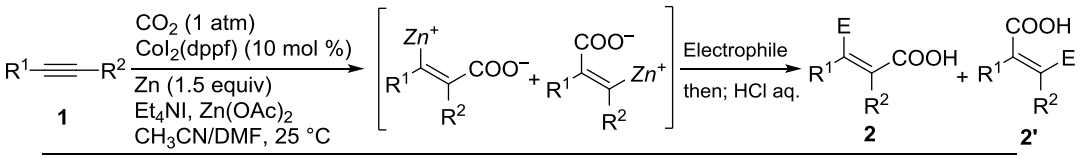


Entry	Changes from standard condition	Yield of **2a**[b]
1	None	80 (73)[c]
2	CoI_2 and dppf in place of CoI_2(dppf)	74
3	Without CoI_2(dppf)	0
4	Without Et_4NI	43
5	Without $Zn(OAc)_2$	53
6	Without DMF	42
7	CoI_2(dppe) in place of CoI_2(dppf)	<5
8	CoI_2(bpy) in place of CoI_2(dppf)	0
9	$NiCl_2$(dppf) in place of CoI_2(dppf)	0

[a]Reaction conditions; **1a** (0.25 mmol), CoI_2(dppf) (10 mol%), Zn powder (1.5 equiv), Et_4NI (10 mol %), $Zn(OAc)_2$ (10 mol %) under CO_2 (1 atm) in CH_3CN/DMF (0.55 mL, v/v = 10/1) at 40 °C for 20 h. [b]Determined by ^1H NMR analysis. [c]Isolated yield of **2a**.

Having identified the optimal reaction conditions, carboxyzincation of various alkynes, and subsequent reaction with electrophiles were examined (Table 4-2). 4-Octyne (**1b**) also afforded the products in good yields (entries 1 and 2). Resulting alkenyl zinc species could be smoothly trapped by I_2, giving the corresponding (*Z*)-*β*-iodo-acrylic acid derivative in good isolated yield (entry 3). After carboxyzincation reaction, by adding a palladium catalyst and an aryl bromide, Negishi coupling reaction proceeded and the corresponding tetra-substituted olefin was furnished in 56% isolated yield in two steps (entry 4). Allylation with a copper catalyst also afforded the corresponding product in 54% overall yield (entry 5). As unsymmetrical aryl alkyl alkynes, 1-phenyl-1-hexyne (**1c**) furnished a mixture of regioisomers in 82% combined yield with good regioselectivity (**2c**/**2c'** = 84/16). Gratifyingly, from the reaction mixture, the *β*-phenylacrylic acid derivative **2c** could be separated by silica gel chromatography, and obtained in 66% isolated yield (entry 6). This regioselectivity is opposite to copper-catalyzed bora- and silacarboxylations that mainly afford *α*-arylacrylic acid derivatives.[11] The present reaction compensates these heterocarboxylation reactions of alkynes. Transformation of *in situ* generated alkenyl zinc species with a benzyl chloride afforded the coupled product **2c-Bn** with the aid of a palladium catalyst (entry 7). Alkynes bearing an electron-rich or electron-deficient aryl ring (**1d-h**) gave the corresponding *β*-carboxylated products (entries 8–14). A bromo functionality which can be led to further functionalization remained intact (entries 13). The carboxyzincation of 4-(*N*,*N*-dimethylamino)phenyl substituted alkyne **1h** proceeded with high regioselectivity (entry 14). After derivatization to the corresponding methyl ester with trimethylsilyldiazomethane ($TMSCHN_2$), **Me-2h** was isolated in 69% yield. An acetyl moiety could be tolerated in the present catalyst system (entry 15). 2-Thiophene or 1-naphthalene substituted alkynes (**1j** and **1k**) also afforded the corresponding products in high yields with excellent regioselectivity (entries 16–19). In place of the butyl group on alkyne moiety, a secondary cyclohexyl group substituted alkyne (**1l**) also gave the product **2l** in 60% yield (entry 20). It is noted that a trimethylsilyl (TMS) group substituted alkyne **1m** afforded the desired product **2m** in 52% yield with perfect regioselectivity (entry 21). With some selected substrates, further transformations of the alkenyl zinc species could be accomplished with diverse electrophiles (entries 9, 10, 17 and 19). Unfortunately, diaryl alkynes and terminal alkynes such as diphenylacetylene gave a trace amount of carboxylated products.

Table 4-2. Cobalt-Catalyzed Carboxyzincation of Alkynes[a]



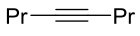
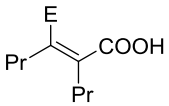
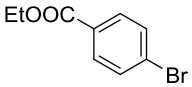
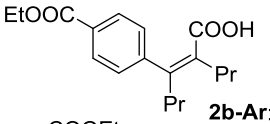
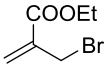
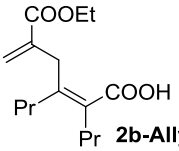
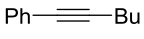
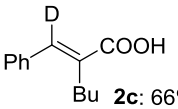
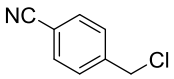
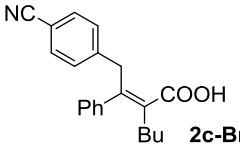
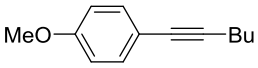
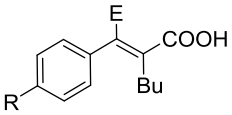
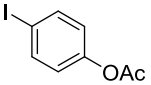
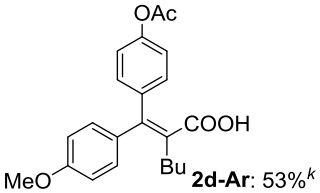
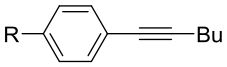
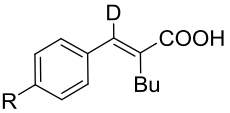
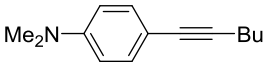
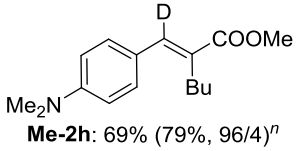
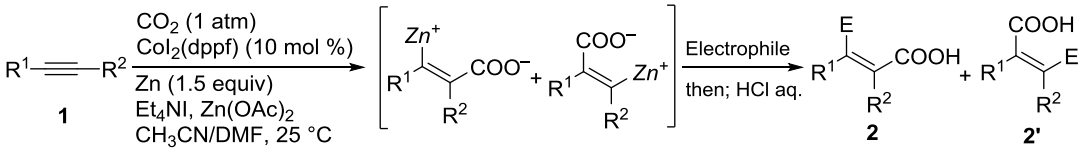
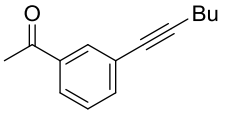
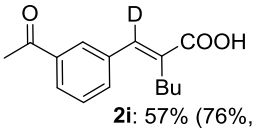
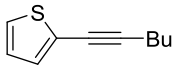
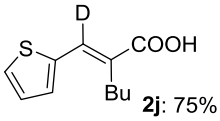
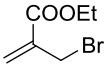
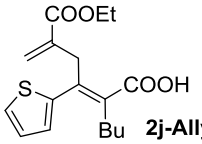
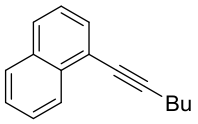
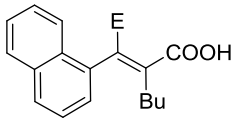
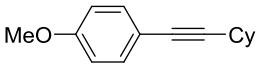
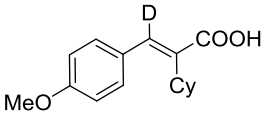
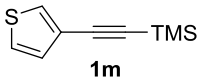
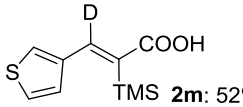
Entry	Substrate **1**	Electrophiles	Product **2**[b,c,d]
	 **1b**		
1[e,f]		D_2O	E = D, **2b**: 75% (80%)
2[e,f]		H_2O	E = H, **2b-H**: 77%
3[e,f]		I_2	E = I, **2b-I**: 68%[g]
4[e,f]	**1b**		 **2b-Ar**: 56%[h]
5[e,f]	**1b**		 **2b-Allyl**: 54%[i]
6[e]	 **1c**	D_2O	 **2c**: 66% (82%, 84/16)
7[e]	**1c**		 **2c-Bn**: 49%[j]
			
8[f]	**1d**	D_2O	E = D, **2d**: 68% (85%, 88/12)
9[k]		I_2	E = I, **2d-I**: 66%[g]
10[f]	**1d**		 **2d-Ar**: 53%[k]
			
11	**1e**: R = OAc	D_2O	**2e**: 57% (82%, 82/18)
12[l]	**1f**: R = CF_3		**2f**: 53%[m] (77%, 82/18)
13	**1g**: R = Br		**2g**: 50% (70%, 83/17)
14[f]	 **1h**	D_2O	 **Me-2h**: 69% (79%, 96/4)[n]

Table 4-2. Cobalt-Catalyzed Carboxyzincation of Alkynes (continued)[a]

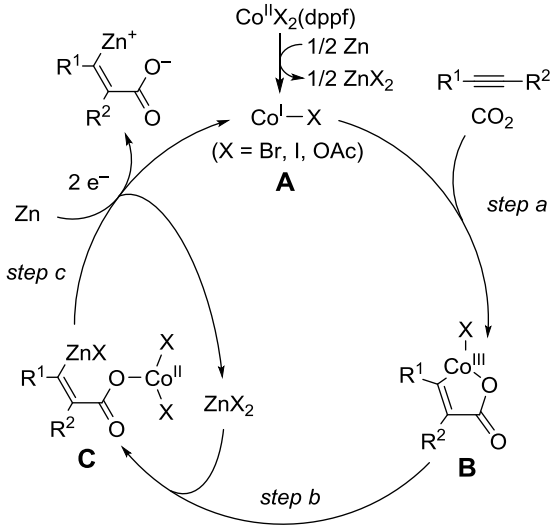


Entry	Substrate **1**	Electrophiles	Product **2**[b,c,d]
15[f]	 **1i**	D_2O	 **2i**: 57% (76%, 81/19)
16[o]	 **1j**	D_2O	 **2j**: 75% (80%, >95/5)
17[o]	**1j**		 **2j-Allyl**: 48%[i]
18[e,o]	 **1k**	D_2O	 E = D, **2k**: 82% (89%, >95/5)
19[e,o]		I_2	E = I, **2k-I**: 73%[g]
20[e,f]	 **1l**	D_2O	 **2l**: 60% (81%, 88/12)
21[k,p]	 **1m**	D_2O	 **2m**: 52% (60%, >99/1)

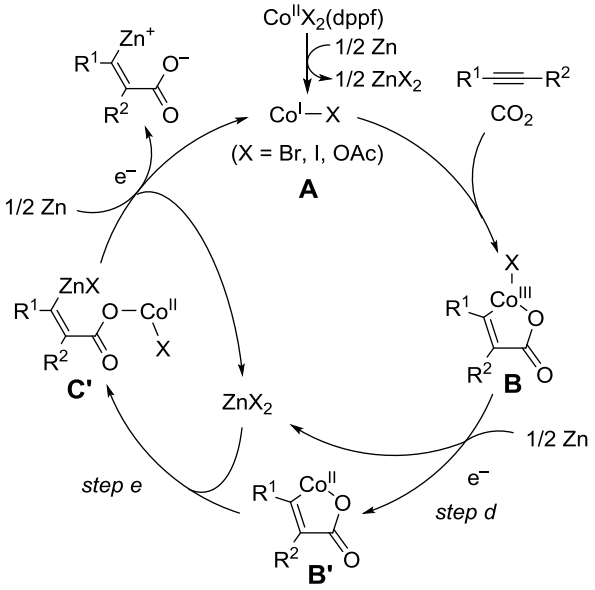
[a]Reaction conditions; alkyne (**1**), CoI_2(dppf) (10 mol%), Zn powder (1.5 equiv), Et_4NI (10 mol %), $Zn(OAc)_2$ (10 mol %) under CO_2 (1 atm) in CH_3CN/DMF (0.55 mL, v/v = 10/1) at 25 °C for 20 h. [b]Isolated yield. Total yield and ratio of **2** and **2'** determined by ^1H NMR analysis are shown in parentheses. [c]Isomeric purity >95%. [d]Deuterium incorporation ratio >92%. [e]At 40 °C. [f]$CoBr_2$(dppf) (10 mol%) was used as a catalyst. [g]Obtained after reaction with I_2 (1.5 equiv). [h]Obtained after reaction with an aryl bromide (1.2 equiv) catalyzed by $Pd(PPh_3)_4$ (2.0 mol %) at 70 °C. [i]Obtained after reaction with na allyl bromide (2.0 equiv) catalyzed by CuCN·2LiCl (20 mol%), at –15 °C to rt. [j]Obtained after reaction with a benzyl chloride (1.5 equiv) catalyzed by $PdCl_2(PPh_3)_2$ (2.0 mol %) at 70 °C. [k]Obtained after reaction with an aryl iodide (1.5 equiv) catalyzed by $PdCl_2(PPh_3)_2$ (2.0 mol %) at 70 °C. [l]CH_3CN/DMF (v/v = 1/1). [m]Isomeric purity was 93%. [n]Determined after derivatization into its methyl ester by esterification with trimethylsilyldiazomethane ($TMSCHN_2$). [o]CH_3CN/DMF (v/v = 1/4). [p]At 50 °C.

A plausible reaction mechanism is depicted in Scheme 4-2. At first, Co(II) precursor would be reduced to Co(I) species **A** with Zn powder. Oxidative cyclization of **A** with alkyne and CO_2 affords a Co(III) metalalactone intermediate **B** (*step a*). Transmetalation of **B** with Zn(II) salt would give the alkenyl zinc species with carboxylate-Co(III) moiety **C** (*step b*). Finally, release of product and two electron reduction of Co(III) to Co(I) with Zn powder complete the catalytic cycle (*step c*). On the other hand, it was reported that a Ni(II) metalalactone could be reduced with Zn powder, giving Ni(I) intermediate.[12] Consequently, the author cannot exclude another reaction pathway (Scheme 4-3) that one electron reduction of **B** to Co(II) species **B'** occurs (*step d*) followed by transmetallation between **B'** and Zn(II) salt (*step e*).[13]

Scheme 4-2. Putative Reaction Mechanism



Scheme 4-3. Alternative Reaction Mechanism



4-3. Conclusion

The author discovered a cobalt-catalyzed carboxyzincation of alkynes employing CO_2 (1 atm) and Zn powder where simultaneous formation of C–C and C–Zn bonds affords *β*-zincated acrylic derivatives. Following transformation of the *in situ* generated alkenyl zinc species with various electrophiles gave highly stereodefined multi-functionalized olefins.

4-4. Experimental Section

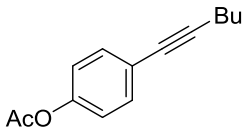
4-4-1. Instrumentation and Chemicals

THF and toluene were dried and purified by usual procedures.[14] CH_3CN and DMF were distilled with CaH_2 and stored over activated MS-4A. Zn powder was activated by washing with HCl aq. and stored under a nitrogen atmosphere. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. IR spectra were obtained on a SHIMADZU IRTracer-100 spectrometer. ^1H and ^{13}C NMR spectra were measured with a Bruker AVANCE-500 spectrometer or a JEOL ECX-400P spectrometer. The ^1H NMR chemical shifts are reported relative to tetramethylsilane (TMS, 0.00 ppm). The ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ (77.0 ppm). High-resolution mass spectra (EI-HRMS and ESI-HRMS) were obtained with JEOL JMX-SX102A (EI-HRMS) and Thermo Fisher Scientific Exactive LC-MS spectrometers (ESI-HRMS). Column chromatography was carried out on silica gel (Kanto N60, spherical, neutral, 40–50 μm or 63–210 μm). Medium pressure liquid chromatography (MPLC) was performed on a Biotage Isorera One with a silica-gel column (Biotage SNAP Ultra 10 g, HP-Sphere 25 μm). Preparative recycling gel permeation chromatography (GPC) was performed with a SHIMADZU LC-20AP system. TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck Silica gel $60F_{254}$. $CoBr_2$(dppf),[15] CoI_2(dppe), and CoI_2(bpy)[8b] were prepared according to the literature procedure. CoI_2(dppf) was also prepared with the same procedure for the preparation of $CoBr_2$(dppf). **1d**,[16] **1g**,[17] **1j**,[15] and **1k**[18] were prepared according to the literature procedure.

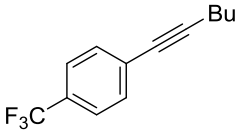
4-4-2. Preparation of Alkynes

General procedure for the preparation of Alkynes

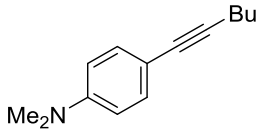
The reaction was performed under an argon atmosphere. A 100 mL round-bottled flask was charged with a palladium catalyst, CuI and an aryl halide. To this flask, degassed NEt_3 (15 mL) and an alkyne were added via syringe. The resulting mixture was stirred at indicated temperature for indicated time. Then, the reaction was quenched by adding EtOAc (40 mL) and water (10 mL). The organic layer was subsequently washed with saturated NH_4Cl aq., 1 M HCl aq. and brine, and dried over $MgSO_4$. After removal of all volatiles, the residue was purified by silica gel chromatography.



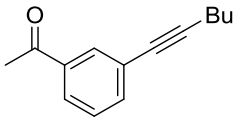
1e: 4-Iodophenyl acetate (1.8 g, 7.0 mmol), 1-hexyne (0.96 mL, 8.4 mmol), $Pd(PPh_3)_4$ (0.20 g, 0.17 mmol, 2.5 mol %), CuI (67 mg, 0.35 mmol, 5.0 mol %), at 50 °C, for 15 h. Yellow oil (1.4 g, 6.3 mmol, 90%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 8.5 Hz, 2H), 7.01 (d, J = 8.9 Hz, 2H), 2.39 (t, J = 7.0 Hz, 2H), 2.28 (s, 3H), 1.61-1.55 (m, 2H), 1.51-1.44 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.2, 149.9, 132.6, 121.9, 121.5, 90.5, 79.8, 30.8, 22.0, 21.1, 19.1, 13.6. All the resonances in ^{1}H and ^{13}C NMR spectra were consistent with reported values.[19]



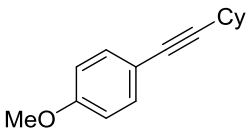
1f: THF (20 mL) was added as a co-solvent. 1-Bromo-4-trifluoromethylbenzene (0.69 mL, 5.0 mmol), 1-hexyne (0.85 mL, 7.5 mmol), $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol, 3.0 mol %), CuI (27 mg, 0.14 mmol, 2.8 mol %), at 70 °C, for 18 h. Pale yellow oil (1.1 g, 4.7 mmol, 95%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.53 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 2.43 (t, J = 7.0 Hz, 2H), 1.63-1.57 (m, 2H), 1.52-1.45 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 131.7, 129.2 (q, J = 32.4 Hz), 128.0, 125.1 (q, J = 3.8 Hz), 124.0 (q, J = 271.3 Hz), 93.3, 79.5, 30.6, 22.0, 19.1, 13.6. All the resonances in ^{1}H and ^{13}C NMR spectra were consistent with reported values.[20]



1h: Piperidine (15 mL) was used instead of NEt_3. 4-Bromo-*N*,*N*-dimethylaniline (1.0 g, 5.0 mmol), 1-hexyne (0.85 mL, 7.5 mmol), $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol, 3.0 mol %), CuI (27 mg, 0.14 mmol, 2.8 mol %), at 80 °C, for 64 h. Because the desired product and remaining aryl bromide could not be separated by silica gel chromatography, the mixture was again purified by preparative recycling gel permeation chromatography. Orange oil (0.36 g, 1.8 mmol, 36%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, J = 9.8 Hz, 2H), 6.61 (d, J = 8.9 Hz, 2H), 2.95 (s, 6H), 2.39 (t, J = 7.0 Hz, 2H), 1.60-1.55 (m, 2H), 1.51-1.43 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.7, 132.5, 112.0, 111.3, 87.7, 81.0, 40.3, 31.2, 22.0, 19.2, 13.7. All the resonances in ^{1}H and ^{13}C NMR spectra were consistent with reported values.[21]



1i: 3-Bromoacetophenone (0.66 mL, 5.0 mmol), 1-hexyne (0.86 mL, 7.5 mmol), $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol, 3.0 mol %), CuI (27 mg, 0.14 mmol, 2.8 mol %), at 70 °C, for 48 h. Brown oil (0.87 g, 4.3 mmol, 87%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 2.59 (s, 3H), 2.43 (t, J = 7.0 Hz, 2H), 1.66-1.57 (m, 2H), 1.54-1.44 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 137.0, 135.8, 131.5, 128.5, 127.1, 124.7, 91.7, 79.6, 30.7, 26.6, 22.0, 19.0, 13.6. EI-HRMS (*m/z*): $[M]^+$ calcd for $C_{14}H_{16}O$, 200.1196; found, 200.1199.



1l: 4-Iodoanisole (1.6 g, 7.0 mmol), cyclohexylacetylene (1.1 mL, 8.4 mmol), $Pd(PPh_3)_4$ (0.20 g, 0.17 mmol, 2.5 mol %), CuI (67 mg, 0.35 mmol, 5.0 mol %), at 50 °C, for 20 h. Yellow oil (1.0 g, 4.9 mmol, 69%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 3.79 (s, 3H), 2.58-2.53 (m, 1H), 1.89-1.86 (m, 2H), 1.78-1.72 (m, 2H), 1.57-1.49 (m, 3H), 1.37-1.30 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.9, 132.9, 116.3, 113.8, 92.9, 80.2, 55.3, 32.9, 29.7, 26.0, 25.0. All the resonances in ^{1}H and ^{13}C NMR spectra were consistent with reported values.[22]

4-4-3. Experimental Procedures

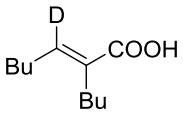
General procedure for carboxyzincation of 1a (Table 4-1)

A 20 mL Schlenk flask was charged with Zn powder (25 mg, 0.38 mmol) and dried with a heating-gun under vacuum. Then, the flask was charged with CoI_2(dppf) (22 mg, 0.025 mmol), Et_4NI (6.4 mg, 0.025 mmol) and $Zn(OAc)_2$ (4.6 mg, 0.025 mmol). The flask was evacuated and refilled with CO_2. This sequence was repeated five times. Then, CH_3CN (0.50 mL), DMF (50 μL) and **1a** (45 μL, 0.25 mmol) were added via airtight syringes, and the resulting mixture was stirred at 40 °C for 20 h. After the reaction, D_2O (50 μL) was added via airtight syringe and the resulting mixture was stirred for 10 min. Then, fluorene (17 mg, 0.10 mmol) as an internal standard, Et_2O (5.0 mL), and 1 M HCl aq. (3.0 mL) were added to the reaction mixture, and the resulting biphasic solution was stirred for further 10 min. A part of organic layer was separated and dried in vacuum. Then, the residue was dissolved in $CDCl_3$ and ^{1}H NMR spectrum of the resultant solution was measured to determine the yield of **2a**.

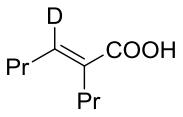
General procedure for carboxyzincation of alkynes 1 (Table 2)

A 20 mL Schlenk flask was charged with Zn powder (25 mg, 0.38 mmol) and dried with a heating-gun under vacuum. Then, the flask was charged with CoI_2(dppf) (22 mg, 0.025 mmol), Et_4NI (6.4 mg, 0.025 mmol) and $Zn(OAc)_2$ (4.6 mg, 0.025 mmol). The flask was evacuated and refilled with CO_2. This sequence was repeated five times. Then, CH_3CN (0.5 mL), DMF (0.050 mL) and alkyne **1** (0.25 mmol) were added via airtight syringes, and the resulting mixture was stirred at 40 °C for 20 h. After the reaction, D_2O (50 μL) was added via airtight syringe and the resulting mixture was stirred for 10 min. Then, fluorene (17 mg, 0.10 mmol) as an internal standard, Et_2O (5.0 mL), and 1 M HCl aq. (3.0 mL) were added to the reaction mixture, and the resulting biphasic solution was stirred for 10 min. A part of organic layer was separated and dried in vacuum. Then, the residue was dissolved in $CDCl_3$ and ^{1}H NMR spectrum of the resultant solution was measured to determine the total yield of products and the ratio of **2** and **2'**. Remaining reaction mixture was extracted with Et_2O (5 mL × 5). The collected organic layer and the NMR sample were combined and dried over anhydrous $MgSO_4$. After removal of volatiles, the residue was purified by silica gel chromatography (eluent: hexane/EtOAc or hexane/acetone) or MPLC

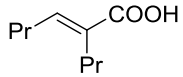
(eluent: hexane/EtOAc). When unsymmetric alkyne was employed as a substrate, isomeric purity of the major isomer in the isolated product was higher than 95%, unless otherwise noted.



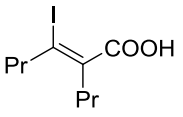
2a: The reaction was performed on 0.50 mmol scale. The product was purified by silica gel chromatography using hexane/EtOAc as an eluent. Pale yellow oil (67 mg, 73%); The deuterium incorporation ratio (94%) was determined by ^{1}H NMR.^{1}H NMR (500 MHz, $CDCl_3$): δ 2.28 (t, J = 7.5 Hz, 2H), 2.20 (t, J = 7.3 Hz, 2H), 1.46-1.31 (m, 8H), 0.94-0.90 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 145.1 (t, $J_{C–D}$ = 23.4 Hz), 131.8, 31.5, 30.8, 28.3, 26.1, 22.7, 22.5, 13.93, 13.87. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{11}H_{18}DO_2$, 184.1453; found, 184.1451. IR (neat): 3000-2800 (br), 1685.8, 1627.9, 1465.9, 1417.7, 1379.1, 1280.7, 1217.1, 1184.3, 1105.2, 943.2 cm^{-1}.



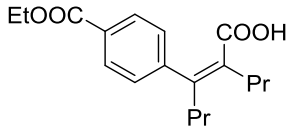
2b: The reaction was performed on 0.50 mmol scale. The product was purified by silica gel chromatography using hexane/EtOAc as an eluent. Pale yellow oil (59 mg, 75%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.27 (t, J = 7.8 Hz, 2H), 2.19 (t, J = 7.3 Hz, 2H), 1.52-1.41 (m, 4H), 0.97-0.90 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.9, 145.2 (t, $J_{C–D}$ = 23.4 Hz), 131.7, 30.7, 28.3, 22.4, 22.0, 13.94, 13.90. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_9H_{14}DO_2$, 156.1140; found, 156.1136. IR (neat): 3000-2800 (br), 1681.9, 1626.0, 1417.7, 1234.4, 1184.3, 925.8, 746.5 cm^{-1}.



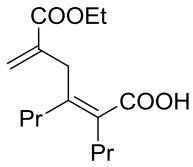
2b-H: The reaction was quenched with H_2O instead of D_2O. The product was purified by silica gel chromatography using hexane/EtOAc as an eluent. Pale yellow oil (60 mg, 77%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (t, J = 7.5 Hz, 1H), 2.27 (t, J = 7.8 Hz, 2H), 2.19 (q, J = 7.4 Hz, 2H), 1.51-1.42 (m, 4H), 0.97-0.90 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8, 145.5, 131.8, 30.8, 28.4, 22.4, 22.0, 14.0, 13.9. All the resonances in ^{1}H and ^{13}C NMR spectra were consistent with reported values.[23]



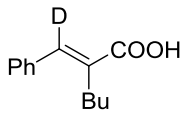
2b-I: The reaction was performed on 0.50 mmol scale. After the reaction, I_2 (0.75 mmol) was added to the reaction mixture and it was stirred for 30 min. The product was purified by silica gel chromatography using hexane/EtOAc as an eluent. Brown oil (96 mg, 68%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.60 (t, J = 7.5 Hz, 2H), 2.40 (t, J = 7.8 Hz, 2H), 1.65-1.58 (m, 2H), 1.54-1.48 (m, 2H), 0.98-0.93 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.9, 140.1, 107.5, 43.3, 33.4, 22.6, 21.9, 13.7, 13.0. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_9H_{14}IO_2$, 281.0044; found, 281.0040. IR (neat): 3000-2800 (br), 1697.4, 1456.3, 1284.6, 1226.7, 1155.4, 912.3, 740.7 cm^{-1}.



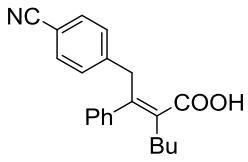
2b-Ar: After the reaction, ethyl 4-bromobenzoate (48 μL, 0.30 mmol, 1.2 equiv) and the solution of $Pd(PPh_3)_4$ (5.8 mg, 0.0050 mmol, 2.0 mol %) dissolved in toluene (0.50 mL) were added to the reaction mixture via airtight syringe. Resulting solution was stirred at 70 °C for 20 h. The product was purified by silica gel chromatography using hexane/EtOAc as an eluent. Brown oil (42 mg, 56%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.44-2.40 (m, 4H), 1.53-1.46 (m, 2H), 1.39 (t, J = 7.2 Hz, 3H), 1.29-1.22 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.6, 166.5, 148.2, 147.3, 131.2, 129.3, 129.1, 127.4, 60.9, 36.7, 31.9, 22.2, 20.8, 14.3, 13.9, 13.8. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{18}H_{23}O_4$, 303.1602; found, 303.1599. IR (neat): 3000-2800 (br), 1716.7, 1689.6, 1608.6, 1456.3, 1367.5, 1273.0, 1178.5, 1099.4, 1020.3, 910.4, 858.3, 781.2, 733.0, 711.7 cm^{-1}.



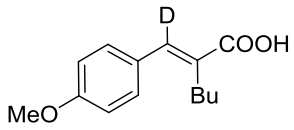
2b-Allyl: After the reaction, CuCN·2LiCl (50 μL of 1.0 M THF solution, 0.050 mmol, 20 mol %) was added to the reaction mixture via airtight syringe at –15 °C and the resulting solution was stirred for 5 min. Then, Ethyl 2-(bromomethyl)acrylate (70 μL, 0.50 mmol, 2.0 equiv) was added and the resulting mixture was stirred at –20 °C for 1 h. Later, the reaction mixture was allowed to warm to room temperature and stirred 20 h additionally. The product was purified by silica gel chromatography using hexane/acetone as an eluent. Pink-colored oil (36 mg, 54%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.25 (s, 1H), 5.57 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.37 (s, 2H), 2.34 (t, J = 7.8 Hz, 2H), 2.06-2.03 (m, 2H), 1.49-1.39 (m, 4H), 1.31 (t, J = 7.2 Hz, 3H), 0.95-0.91 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.8, 167.8, 145.1, 137.8, 131.7, 126.6, 61.3, 36.0, 34.5, 31.9, 22.4, 21.6, 14.3, 14.1, 13.9. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{15}H_{23}O_4$, 267.1602; found, 267.1601. IR (neat): 3000-2800 (br), 1716.7, 1681.9, 1629.9, 1404.2, 1273.0, 1246.0, 1143.8, 1111.0, 1028.1, 943.2, 817.8, 746.5 cm^{-1}.



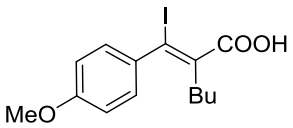
2c: The reaction was performed on 0.50 mmol scale. The product was purified by MPLC using hexane/EtOAc as an eluent. White solid (68 mg, 66%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-7.34 (m, 5H), 2.55 (t, J = 7.9 Hz, 2H), 1.62-1.55 (m, 2H), 1.45-1.37 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.5, 140.6 (t, $J_{C–D}$ = 23.4 Hz), 135.5, 132.8, 129.5, 128.7, 128.5, 31.3, 27.0, 22.9, 13.9. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{13}H_{14}DO_2$, 204.1140; found, 204.1137. IR (neat): 3000-2800 (br), 1672.3, 1469.8, 1446.6, 1421.5, 1340.5, 1319.3, 1282.7, 1217.1, 1166.9, 914.3, 763.8, 733.0 cm^{-1}.



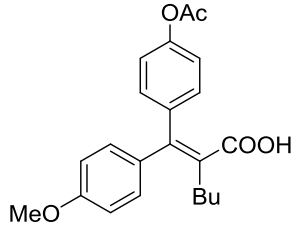
2c-Bn: After the reaction, the solution of 4-cyanobenzyl chloride (57 mg, 0.38 mmol, 1.5 equiv) and $Pd(PPh_3)_4$ (5.8 mg, 0.0050 mmol, 2.0 mol %) dissolved in THF (0.50 mL) was added to the reaction mixture via airtight syringe. Resulting solution was stirred at 70 °C for 20 h. The product was purified by silica gel chromatography using hexane/acetone as an eluent. Yellow oil (39 mg, 49%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, J = 8.2 Hz, 2H), 7.28-7.20 (m, 5H), 6.87 (dd, J = 7.8, 1.7 Hz, 2H), 4.08 (s, 2H), 2.18 (t, J = 7.9 Hz, 2H), 1.43-1.37 (m, 2H), 1.22-1.15 (m, 2H), 0.77 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.0, 147.7, 144.1, 140.1, 131.94, 131.92, 130.0, 128.2, 127.6, 127.5, 119.0, 110.0, 42.5, 31.3, 30.9, 22.4, 13.7. ESI-HRMS (*m/z*): $[M–H]^–$ calcd for $C_{21}H_{20}NO_2$, 318.1500; found, 318.1494. IR (neat): 3000-2800 (br), 2229.7, 1687.7, 1606.7, 1504.5, 1413.8, 1313.5, 1278.8, 1217.1, 1159.2, 1022.3, 858.3, 837.1, 819.8, 731.0 cm^{-1}.



2d: The reaction was performed on 0.50 mmol scale. The product was purified by silica gel chromatography using hexane/acetone as an eluent. White solid (80 mg, 68%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 8.2 Hz, 2H), 3.85 (s, 3H), 2.57 (t, J = 7.9 Hz, 2H), 1.62-1.55 (m, 2H), 1.47-1.40 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.7, 160.1, 140.2 (t, $J_{C–D}$ = 22.9 Hz), 131.4, 130.4, 127.9, 114.0, 55.2, 31.1, 26.9, 22.9, 13.9. ESI-HRMS (*m/z*): $[M–H]^–$ calcd for $C_{14}H_{16}DO_3$, 234.1246; found, 234.1244. IR (neat): 3000-2800 (br), 1670.4, 1602.9, 1510.3, 1456.3, 1435.0, 1423.5, 1338.6, 1317.4, 1296.2, 1255.7, 1217.1, 1178.5, 1165.0, 1031.9, 839.0, 823.6, 796.6, 761.9, 733.0 cm^{-1}.

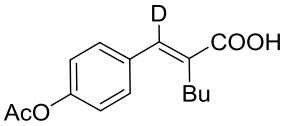


2d-I: After the reaction, I_2 (0.75 mmol) was added to the reaction mixture and it was stirred for 30 min. The product was purified by silica gel chromatography using hexane/acetone as an eluent. White solid (59 mg, 66%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 3.83 (s, 3H), 2.29 (t, J = 7.9 Hz, 2H), 1.46-1.39 (m, 2H), 1.26-1.18 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.5, 159.4, 142.5, 135.5, 129.2, 113.7, 99.3, 55.4, 32.4, 30.6, 22.2, 13.7. ESI-HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{14}H_{17}IO_3Na$, 383.0115; found, 383.0112. IR (neat): 3000-2800 (br), 1687.7, 1606.7, 1506.4, 1462.0, 1440.8, 1402.3, 1290.4, 1271.1, 1249.9, 1224.8, 1174.7, 1153.4, 1111.0, 1080.1, 1026.1, 823.6, 814.0, 798.5, 767.7, 731.0 cm^{-1}.

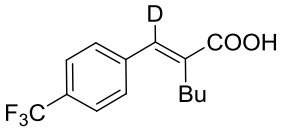


2d-Ar: After the reaction, 4-iodophenyl acetate (57 μL, 0.38 mmol, 1.5 equiv) and the suspension of $PdCl_2(PPh_3)_2$ (3.5 mg, 0.0050 mmol, 2.0 mol %) in toluene (0.50 mL) were added to the reaction mixture via airtight syringe. Resulting solution was stirred at 70 °C for 20 h. The product was purified by silica gel chromatography using

hexane/acetone as an eluent. White solid (49 mg, 53%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.9 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 3.81 (s, 3H), 2.38 (t, J = 8.1 Hz, 2H), 2.27 (s, 3H), 1.53-1.47 (m, 2H), 1.34-1.27 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.6, 169.3, 159.2, 150.1, 146.3, 139.9, 133.1, 132.5, 130.5, 129.8, 121.0, 113.5, 55.2, 32.1, 31.1, 22.6, 21.1, 13.8. ESI-HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{24}O_5Na$, 391.1516; found, 391.1508. IR (neat): 3000-2800 (br), 1757.2, 1674.2, 1608.6, 1512.2, 1369.5, 1321.2, 1249.9, 1197.8, 1147.7, 1033.9, 910.4, 835.2, 815.9, 738.7 cm^{-1}.

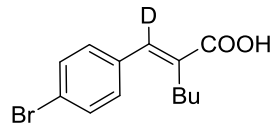


2e: The product was purified by silica gel chromatography using hexane/acetone as an eluent. White solid (38 mg, 57%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H), 2.54 (t, J = 7.9 Hz, 2H), 2.32 (s, 3H), 1.61-1.54 (m, 2H), 1.45-1.37 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 169.2, 150.8, 139.4 (t, J_{C-D} = 23.8 Hz), 133.0, 132.8, 130.6, 121.7, 31.2, 26.9, 22.8, 21.1, 13.8. ESI-HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{17}DO_4Na$, 286.1160; found, 286.1158. IR (neat): 3000-2800 (br), 1762.9, 1681.9, 1506.4, 1421.5, 1369.5, 1307.7, 1282.6, 1257.6, 1193.9, 1020.3, 912.3, 860.3, 814.0, 796.6, 731.0 cm^{-1}.



2f: The reaction was performed on 0.50 mmol scale. The product was purified by MPLC using hexane/EtOAc as an eluent. White solid (72 mg, 53%); Isomeric purity was 93%, determined by ^{1}H NMR of isolated product. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 2.51 (t, J = 8.1 Hz, 2H), 1.60-1.54 (m, 2H), 1.43-1.36 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.0, 139.0, 138.9 (t, J_{C-D} = 24.8 Hz), 135.0, 130.4 (q, J = 32.7 Hz), 129.5, 125.5 (q, J = 3.8 Hz), 124.0 (q, J_{C-F} = 272.1 Hz,), 31.3, 27.0, 22.8, 13.8. ESI-HRMS (*m/z*): $[M-H]^-$ calcd for $C_{14}H_{13}DF_3O_2$, 272.1074; found, 272.1013. IR (neat): 3000-2800 (br), 1685.8, 1612.5, 1423.5, 1327.0, 1303.9, 1280.7, 1217.1, 1159.2, 1111.0, 1089.8, 1066.6, 1016.5, 949.0, 850.6, 796.6, 733.0 cm^{-1}.

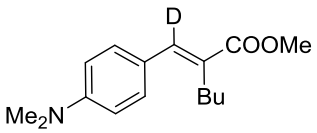
2f': This product was not isolated. Diagnostic resonances observed in ^{1}H NMR spectrum of mixture with the major product was listed. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, J = 7.9 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 2.11 (t, J = 7.3 Hz, 2H), 1.46-1.35 (m, 2H), 1.33-1.25 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H).



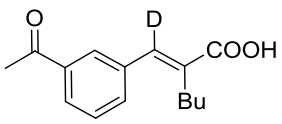
2g: The reaction was performed on 0.50 mmol scale. The product was purified by MPLC using hexane/EtOAc as an eluent. Pale yellow solid (72 mg, 50%); Isomeric purity was 95%, determined by ^{1}H NMR of isolated product. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 2.50 (t, J = 7.9 Hz, 2H), 1.58-1.52 (m, 2H), 1.43-1.36 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.2, 139.3 (t, J_{C-D} = 24.3 Hz), 134.3, 133.5, 131.8, 130.9, 123.0,

31.2, 27.0, 22.9, 13.8. ESI-HRMS (*m/z*): $[M–H]^-$ calcd for $C_{13}H_{13}DBrO_2$, 282.0245; found, 282.0245 (exact same mass was found). IR (neat): 3000-2800 (br), 1683.9, 1610.6, 1487.1, 1419.6, 1309.7, 1280.7, 1215.2, 1166.9, 1072.4, 1006.8, 792.7, 729.1 cm^{-1}.

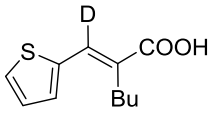
2g': This product was not isolated. Diagnostic resonances observed in ^1H NMR spectrum of mixture with the major product was listed. ^1H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 2.10 (t, J = 7.5 Hz, 2H), 1.44-1.34 (m, 2H), 1.32-1.24 (m, 2H), 0.85 (t, J = 7.3 Hz, 3H).



Me-2h: After the reaction, D_2O (50 μL) was added via airtight syringe and the resulting mixture was stirred for 10 min. Then, 1 M HCl aq. (0.3 mL), water (2 mL), and Et_2O (5 mL) were added, and the mixture was extracted with Et_2O (5 mL × 7). The collected organic layer was combined and dried over anhydrous $MgSO_4$. After removal of solvent under reduce pressure, the residue was treated with $TMSCHN_2$ (0.63 mL of 2.0 M Et_2O solution, 1.3 mmol, 5.0 equiv) in Et_2O/MeOH as a solvent. After 1h, all volatiles were removed under reduced pressure and the residue was purified by silica gel chromatography using hexane/EtOAc as an eluent. Orange oil (45 mg, 69%); ^1H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J = 8.9 Hz, 2H), 6.70 (d, J = 8.9 Hz, 2H), 3.78 (s, 3H), 2.99 (s, 6H), 2.58 (t, J = 8.1 Hz, 2H), 1.58-1.52 (m, 2H), 1.47-1.40 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.7, 150.4, 138.8 (t, $J_{C–D}$ = 23.4 Hz), 131.3, 128.4, 123.4, 111.7, 51.6, 40.1, 31.2, 27.3, 22.9, 13.9. ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{23}DNO_2$, 263.1864; found, 263.1860. IR (neat): 1701.2, 1599.0, 1521.8, 1433.1, 1361.7, 1263.4, 1199.7, 1134.1, 1087.9, 1062.8, 947.1, 910.4, 827.5, 798.5, 733.0 cm^{-1}.

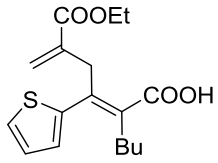


2i: The reaction was performed on 0.50 mmol scale. The product was purified by silica gel chromatography using hexane/acetone as an eluent. White solid (70 mg, 57%); ^1H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 2.64 (s, 3H), 2.55 (t, J = 7.8 Hz, 2H), 1.64-1.58 (m, 2H), 1.47-1.39 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 197.7, 173.7, 139.2 (t, $J_{C–D}$ = 22.9 Hz), 137.3, 135.9, 134.1, 133.7, 129.1, 128.8, 128.3, 31.3, 27.0, 26.5, 22.8, 13.8. ESI-HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{15}H_{17}DO_3Na$, 270.1211; found, 270.1209. IR (neat): 3000-2800 (br), 1683.9, 1670.4, 1608.6, 1573.9, 1417.7, 1361.7, 1338.6, 1317.4, 1267.2, 1217.1, 1165.0, 956.7, 898.8, 814.0, 794.7, 709.8 cm^{-1}.

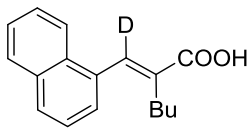


2j: The reaction was performed on 0.50 mmol scale. The product was purified by silica gel chromatography using hexane/acetone as an eluent. Pale yellow solid (79 mg, 75%); ^1H NMR (500 MHz, $CDCl_3$): δ 7.50 (dd, J = 5.0, 1.1 Hz, 1H), 7.29 (dd, J = 3.7, 0.9 Hz, 1H), 7.10 (dd, J = 5.2, 3.7 Hz, 1H), 2.69 (t, J = 8.1 Hz, 2H), 1.59-1.44 (m, 4H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.4, 138.3,

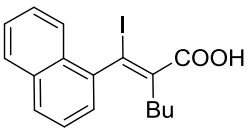
133.1 (t, J_{C-D} = 23.8 Hz), 132.9, 129.7, 128.9, 127.3, 30.4, 27.7, 23.1, 14.0. ESI-HRMS (*m/z*): $[M-H]^-$ calcd for $C_{11}H_{12}DO_2S$, 210.0705; found, 210.0703. IR (neat): 3000-2800 (br), 1660.7, 1604.8, 1415.8, 1313.5, 1296.2, 1253.7, 1222.9, 1161.2, 1057.0, 916.2, 858.3, 846.8 cm^{-1}.



2j-Allyl: After the reaction, CuCN·2LiCl (50 μL of 1.0 M THF solution, 0.050 mmol, 20 mol %) was added to the reaction mixture via airtight syringe at –15 °C and the resulting solution was stirred for 5 min. Then, ethyl 2-(bromomethyl)acrylate (70 μL, 0.50 mmol, 2.0 equiv) was added and the resulting mixture was stirred at –20 °C for 1 h. The reaction mixture was allowed to warm to room temperature and stirred 20 h additionally. The product was purified by silica gel chromatography using hexane/acetone as an eluent. Pink-colored oil (38 mg, 48%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, J = 5.2 Hz, 1H), 6.98 (dd, J = 5.2, 3.7 Hz, 1H), 6.83 (d, J = 3.4 Hz, 1H), 6.17 (s, 1H), 5.56 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.62 (s, 2H), 2.41 (t, J = 7.9 Hz, 2H), 1.50-1.44 (m, 2H), 1.32-1.26 (m, 5H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.7, 167.9, 140.7, 136.43, 136.37, 135.2, 128.4, 126.8, 126.7, 125.7, 61.5, 39.8, 31.9, 31.3, 22.5, 14.0, 13.8. ESI-HRMS (*m/z*): $[M-H]^-$ calcd for $C_{17}H_{121}O_4S$, 321.1166; found, 321.1162. IR (neat): 3000-2800 (br), 1714.7, 1685.8, 1627.9, 1435.0, 1404.2, 1369.5, 1275.0, 1138.0, 1026.1, 943.2, 852.5, 815.9 cm^{-1}.

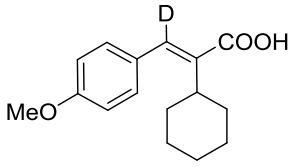


2k: The reaction was performed on 0.50 mmol scale. The product was purified by silica gel chromatography using hexane/acetone as an eluent. Pale yellow solid (0.10 g, 82%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94-7.85 (m, 3H), 7.55-7.49 (m, 3H), 7.42 (d, J = 7.0 Hz, 1H), 2.44 (t, J = 7.8 Hz, 2H), 1.55-1.49 (m, 2H), 1.30-1.23 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 139.5 (t, J_{C-D} = 21.9 Hz), 135.0, 133.4, 132.9, 131.5, 128.8, 128.5, 126.4, 126.2, 126.1, 125.1, 124.6, 31.6, 27.3, 22.7, 13.7. ESI-HRMS (*m/z*): $[M-H]^-$ calcd for $C_{17}H_{16}DO_2$, 254.1297; found, 254.1297 (exact same mass was found). IR (neat): 3000-2800 (br), 1674.2, 1417.7, 1313.5, 1273.0, 1219.0, 1184.3, 1161.2, 1105.2, 916.2, 790.8, 775.4, 748.4, 729.1, 713.7 cm^{-1}.

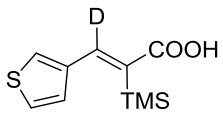


2k-I: After the reaction, I_2 (0.75 mmol) was added to the reaction mixture and it was stirred for 30 min. The product was purified by silica gel chromatography using hexane/acetone as an eluent. Yellow oil (69 mg, 73%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.53 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 7.0 Hz, 1H), 2.20-2.15 (m, 1H), 2.08-2.02 (m, 1H), 1.39-1.33 (m, 2H), 1.12-1.07 (m, 2H), 0.66 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 144.4, 139.7, 133.7, 129.1, 128.8, 128.4, 126.53, 126.51, 125.3, 125.1, 124.7, 96.6, 32.6, 30.3, 22.0, 13.5. ESI-HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{17}IO_2Na$, 403.0165; found, 403.0164. IR (neat): 3000-2800 (br), 1697.4

(brs), 1506.4, 1392.6, 1275.0, 1205.5, 1149.6, 798.5, 775.4, 731.0 cm^{-1}.



2l: The product was purified by silica gel chromatography using hexane/acetone as an eluent. White solid (39 mg, 60%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.9 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 3.85 (s, 3H), 2.84 (t, J = 11.9 Hz, 1H), 2.04 (q, J = 12.2 Hz, 2H), 1.78 (d, J = 10.4 Hz, 2H), 1.69-1.61 (m, 3H), 1.30-1.21 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.0, 159.8, 139.9 (t, $J_{C–D}$ = 24.3 Hz), 135.7, 130.9, 128.1, 113.9, 55.3, 38.4, 30.6, 26.7, 25.9. ESI-HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{19}DO_3Na$, 284.1367; found, 284.1366. IR (neat): 3000-2800 (br), 1668.4, 1604.8, 1508.3, 1419.6, 1321.2, 1292.3, 1255.7, 1226.7, 1178.5, 1163.1, 1116.8, 1031.9, 956.7, 842.9, 833.3, 802.4, 781.2 cm^{-1}.



2m: The reaction was performed on 0.50 mmol scale. The product was purified by silica gel chromatography using hexane/acetone as an eluent. Pale brown solid (59 mg, 52%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (dd, J = 4.9, 2.7 Hz, 1H), 7.26 (dd, J = 3.1, 1.2 Hz, 1H), 7.07 (dd, J = 4.9, 1.2 Hz, 1H), 0.15 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.6, 148.6 (t, $J_{C–D}$ = 23.8 Hz), 138.4, 136.0, 128.3, 125.7 (two peaks overlap absolutely, confirmed with the HMQC and HMBC spectra), 0.2. ESI-HRMS (*m/z*): $[M–H]^–$ calcd for $C_{10}H_{12}DO_2SSi$, 226.0474; found, 226.0472. IR (neat): 3000-2800 (br), 1662.6, 1577.8, 1406.1, 1273.0, 1247.9, 841.0, 788.9, 761.9, 717.5 cm^{-1}.

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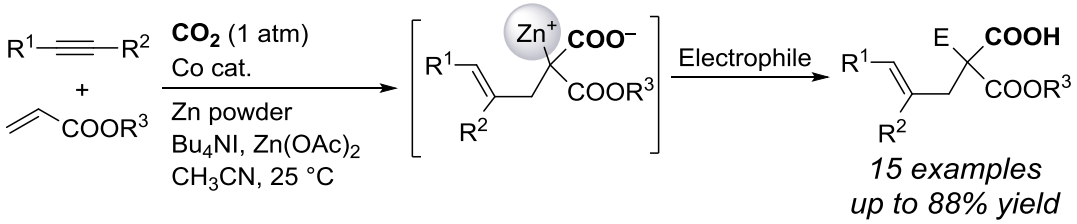
Chapter 5

Cobalt-Catalyzed Carboxylative Coupling Reaction of Alkyne and Acrylate Employing Carbon Dioxide and Zinc Powder

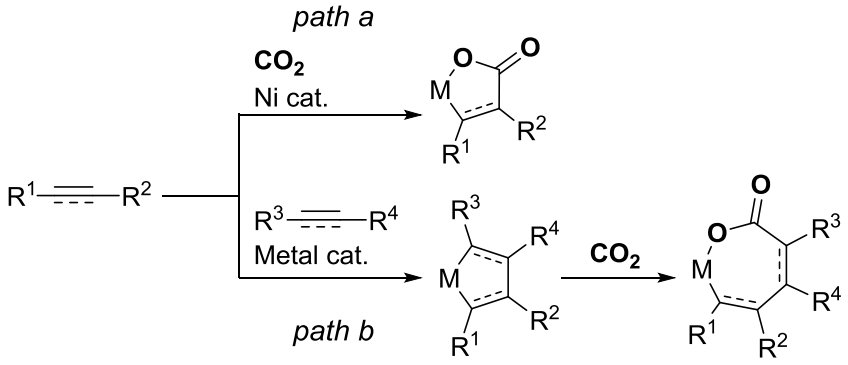
The cobalt-catalyzed carboxylative coupling reaction of alkyne and acrylate employing CO_2 (1 atm) and Zn powder as a reducing reagent is described. Utilized Zn was also incorporated and totally four-component coupled compounds were formed with perfect regio- and stereoselectivity. Subsequent reaction with electrophiles furnished stereodefined α,α-disubstituted malonic acid monoesters in good to high yields.



5-1. Introduction

Carbon dioxide (CO_2) is an inexpensive, non-toxic, abundant and easily accessible C1 synthon and utilization of CO_2 as a chemical feedstock would provide significant progress in both scientific and industrial societies.[1,2] The oxidative cyclization of low-valent transition metal species with unsaturated hydrocarbons and CO_2 is one of the most promising processes for carboxylation reactions with CO_2. To date, some Ni(0)-mediated systems have been investigated (Scheme 5-1, *path a*).[3,4] In the reaction of an alkyne, a nickelalactone intermediate can be catalytically converted to various α,β-unsaturated carboxylic acids by using organozinc reagent,[4c,d] alcohol,[4a] or CO_2[4b]. Another prospective protocol regarding an oxidative cyclization event is the insertion of CO_2 into the metalacycle intermediate constructed by the reaction of two carbon–carbon unsaturates and a low-valent transition metal (Scheme 5-1, *path b*).[5] Nonetheless, few examples for this type of reaction have been explored except co-oligomerization of 1,3-diene and CO_2.[6,7] Although Mori, Sato and co-workers reported the nickel-mediated or catalyzed carboxylative cyclization reaction of α,ω-enynes,[8] this process was limited to intramolecular reaction. To the best of the author's knowledge, no precedent for CO_2 fixation reaction through intermolecular cross oxidative cyclization has been available.

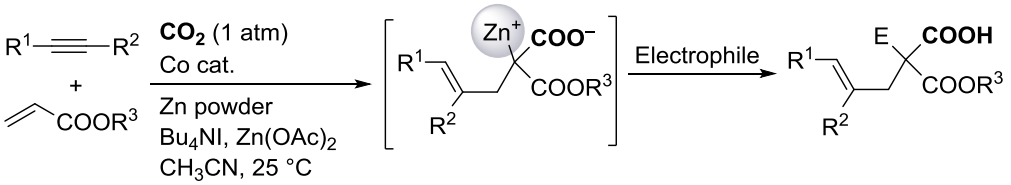
Scheme 5-1. CO_2 Incorporation Reactions through Oxidative Cyclization



To achieve this type of reaction, the author focused his attention on the use of low-valent cobalt catalyst. Cheng and co-workers reported the reductive coupling reactions of alkynes and activated alkenes in the presence of Zn powder and H_2O.[9,10] In these reactions, they proposed that cross oxidative cyclization with a low-valent cobalt, an alkyne, and an alkene would be an important initial step. Meanwhile, cobalt catalysts also have shown catalytic activity for the C–C bond forming CO_2 incorporation process, as described in Chapters 2–4.[11,12] Thus, the author anticipated that cobalt catalysts potentially enable cross oxidative cyclization followed by incorporation of CO_2, affording the multi-component coupled products.

In this Chapter, the cobalt-catalyzed carboxylative coupling reaction of alkyne and acrylate employing CO_2 (1 atm) and Zn powder as a reducing reagent is presented. Interestingly, Zn atom as well as carboxyl moiety were introduced onto the same carbon atom derived from acrylate, and the following reaction with electrophiles afforded α,α-disubstituted malonic acid monoesters in good to high yields with perfect regioselectivity (Scheme 5-2).

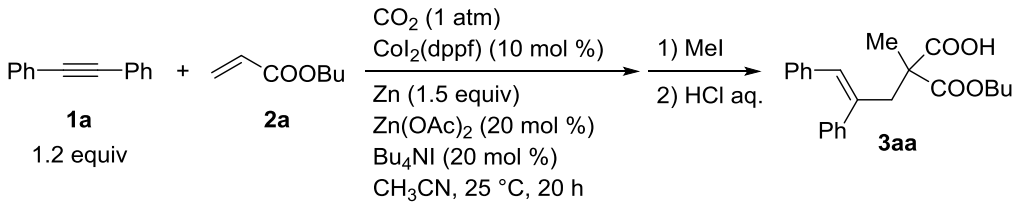
Scheme 5-2. Cobalt-Catalyzed Carboxylative Coupling Reaction of Alkyne and Acrylate along with the Incorporation of Zinc Moiety



5-2. Results and Discussion

Studies were initiated with diphenylacetylene (**1a**) and butyl acrylate (**2a**) as model substrates (Table 5-1). The carboxylative coupling reaction of **1a** and **2a** was carried out utilizing 10 mol % of CoI_2(dppf) as a catalyst in the presence of Zn powder (1.5 equiv), $Zn(OAc)_2$ (20 mol %), and tetrabutyl ammonium iodide (Bu_4NI, 20 mol %), in CH_3CN under 1 atm pressure of CO_2 at 25ºC. After a treatment with iodomethane as an electrophile, α-methyl malonic acid monoester **3aa** was given in 91% yield which was determined by ^1H NMR analysis. From the reaction mixture, **3aa** could be isolated in 88% yield (entry 1). This result indicates that not only CO_2 but also zinc atom are introduced onto the same α-carbon atom of **3aa**. (*Z*)-Configuration of the alkenyl moiety in **3aa** was determined by NOE measurements. The cobalt catalyst was indispensable (entry 2), and in the absence of Bu_4NI or $Zn(OAc)_2$, the yield of **3aa** was slightly decreased (entries 3 and 4). Although other phosphine ligands instead of dppf afforded the product in moderate yields, bipyridine as the ligand did not show catalytic activity at all (entries 5–7). A choice of solvent was also important and a use of DMF or THF decreased the yield of the product (entries 8 and 9). In this reaction, nickel catalyst did not afford the product although it is known as a highly efficient catalyst for the CO_2 fixation reaction as described above (entry 10).[3–8]

Table 5-1. Optimization of Reaction Conditions[a]

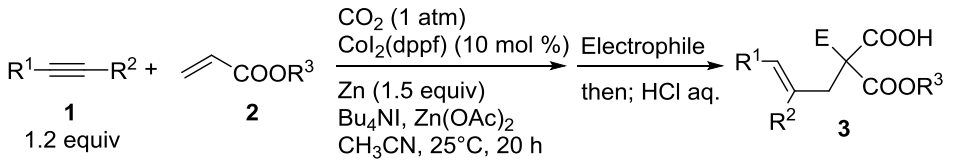


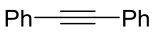
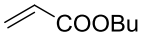
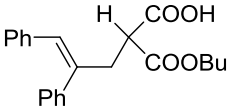
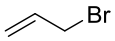
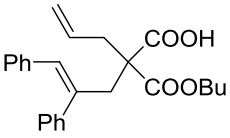
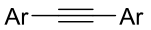
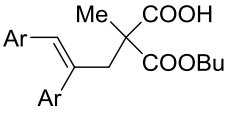
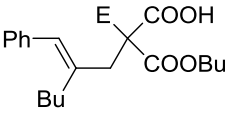
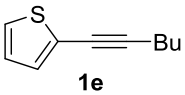
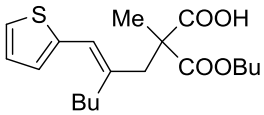
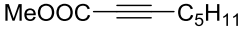
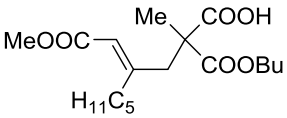
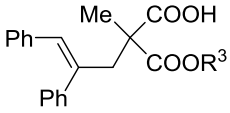
Entry	Catalytic System	Yield of **3aa** (%)[b]
1	Standard condition	91 (88)[c]
2	Without CoI_2(dppf)	0
3	Without $Zn(OAc)_2$	82
4	Without Bu_4NI	73
5	$CoI_2(PPh_3)_2$ (in place of CoI_2(dppf))	42
6	CoI_2(dppe)	49
7	CoI_2(bpy)	0
8	DMF (in place of CH_3CN)	30
9	THF	74
10	$NiI_2(PPh_3)_2$ (in place of CoI_2(dppf))	0

[a]Reaction conditions; **1a** (0.30 mmol), **2a** (0.25 mmol). CoI_2(dppf) (10 mol %), Zn powder (1.5 equiv), $Zn(OAc)_2$ (20 mol %), Bu_4NI (20 mol %), CO_2 (1 atm), in CH_3CN (0.50 mL), at 25 °C for 20 h. [b]Determined by ^1H NMR analysis. [c]Isolated yield of **3aa**.

Having identified the optimal reaction conditions, the author explored the scope of substrates (Table 5-2). Employing H_2O or allyl bromide instead of iodomethane, α-protonated (**3aa-H**) or α-allylated (**3aa-allyl**) products were obtained by the carboxylative coupling reaction with **1a** and **2a** (entries 1 and 2). Chloro or trifluoromethyl (CF_3) functionalities was intact under the reaction condition (entries 3 and 4). It is noteworthy that the carboxylative coupling reaction of unsymmetrical internal aryl alkyl alkynes (**1d** or **1e**) and **2a** proceeded in a perfectly regioselective manner (entries 5–8). Deuterium could also be installed onto α-position of the product utilizing deuterium oxide as an electrophile, while rapid H/D exchange during isolation process decreased the deuterium incorporation ratio to 60% (entry 7). Methyl alkynoate **1f** also gave a regiocontrolled product **3fa** in 65% yield (entry 9). This reaction proceeded with several acrylates such as methyl, ethyl, and *t*-butyl esters (**2b–d**), affording the coupled products in moderate to high yields (entries 10–12).

Table 5-2. Scope of Alkynes and Acrylates[a]

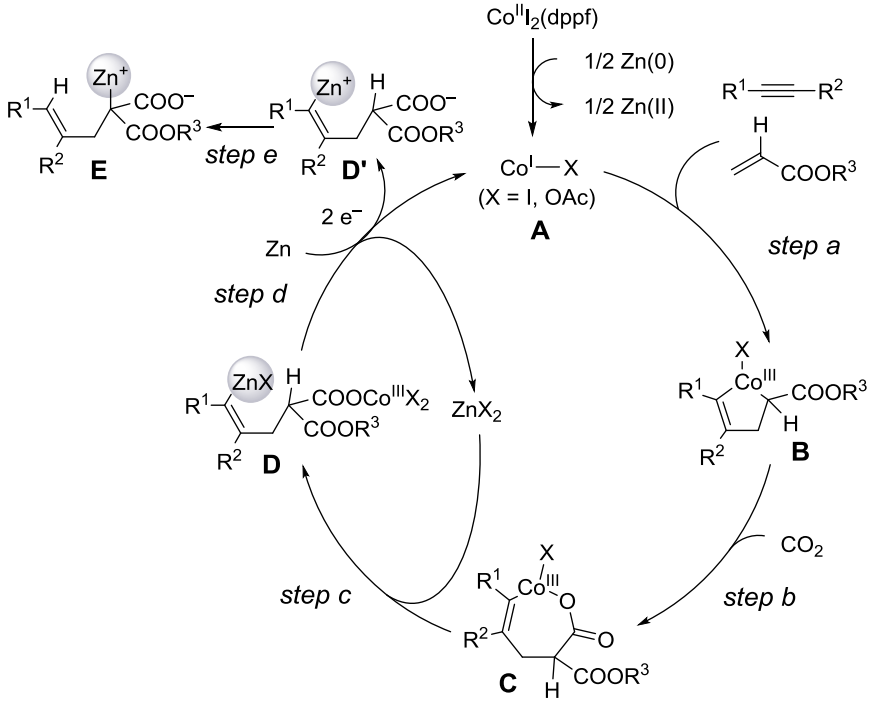


Entry	Alkyne **1**	Acrylate **2**	Electrophiles	Product **3**[b]
1	 **1a**	 **2a**	H_2O	 **3aa-H**: 85%
2	**1a**	**2a**		 **3aa-Allyl**: 74%
		**2a**	MeI	
3	Ar = 4-ClC_6H_4 (**1b**)			**3ba**: 55%
4	Ar = 3-$F_3CC_6H_4$ (**1c**)			**3ca**: 57%
	 **1d**	**2a**		
5			MeI	**3da**: 54%
6			H_2O	**3da-H**: 70%
7			D_2O	**3da-D**: 58% (60% D)
8	 **1e**	**2a**	MeI	 **3ea**: 50%
9	 **1f**	**2a**	MeI	 **3fa**: 65%
	1a		MeI	
10		**2b**: R^3 = Me		**3ab**: 47%
11		**2c**: R^3 = Et		**3ac**: 59%
12		**2d**: R^3 = *t*Bu		**3ad**: 74%

[a]Reaction conditions; **1** (0.30 mmol), **2** (0.25 mmol), CoI_2(dppf) (10 mol %), Zn powder (1.5 equiv), $Zn(OAc)_2$ (20 mol %), Bu_4NI (20 mol %), CO_2 (1 atm), in CH_3CN (0.50 mL), at 25 °C for 20 h. [b]Isolated yield of **3**.

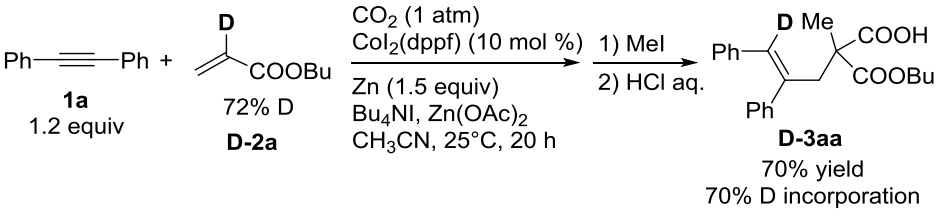
A plausible reaction mechanism is depicted in Scheme 5-3. At first, Co(II) precursor is reduced to Co(I) species **A** by one electron transfer from Zn powder. The oxidative cyclization of **A** with an alkyne and an acrylate occurs selectively, giving the corresponding metallacycle intermediate **B** (*step a*).[10d] Then, CO_2 insertion into C–Co bond derived from acrylate furnishes a seven membered metallalactone **C** (*step b*). Transmetalation of **C** with Zn(II) salt would afford the alkenyl zinc species **D** (*step c*),[13] and subsequent two electron reduction would give Co(I) and the product **D'** (*step d*). The formal acid-base reaction between the alkenyl zinc moiety and acidic proton would furnish the α-zincated malonate product **E** (*step e*).

Scheme 5-3. Plausible Mechanism of the Carboxylative Coupling Reaction of Alkyne and Acrylate



To gain insights into the *step e* in Scheme 5-3, the reaction utilizing α-deuterated butyl acrylate **D-2a** (72% D) was carried out. After the reaction, the coupling product **D-3aa** was isolated in 70% yield with the 70% of deuterium incorporation at the alkenyl position of **D-3aa** (Scheme 5-4).

Scheme 5-4. Carboxylative Coupling Reaction with α-Deuterated Acrylate



To expand the scope of electron-deficient alkenes further, the author tested acrylamide **4** in place of acrylate. While the desired carboxylative coupling reaction also smoothly proceeded, interestingly, subsequent treatment with D_2O followed by methylesterification with $TMSCHN_2$ afforded a product **5-D** in 61% isolated yield with 62% deuterium incorporation at the alkenyl position. (Scheme 5-5). This result suggests that part of zinc moiety was retained at the alkenyl position as opposite to that of acrylate depicted in Table 5-2.

Scheme 5-5. Carboxylative Coupling Reaction with Acrylamide

5-3. Conclusion

The first example of the cobalt-catalyzed carboxylative coupling reaction of alkyne and acrylate employing CO_2 (1 atm) and metallic Zn powder is described in this Chapter. During the course of the reaction, an introduction of zinc atom derived from Zn powder also proceeded to furnish totally four-component coupled products.

5-4. Experimental Section

5-4-1. Instrumentation and Chemicals

THF was dried and purified by usual procedures.[14] CH_3CN and DMF were distilled with CaH_2 and stored over activated MS-4A. Zn powder was activated by washing with HCl aq. and stored under a nitrogen atmosphere. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. IR spectra were obtained on a SHIMADZU IRTracer-100 spectrometer. ^1H and ^{13}C NMR spectra were measured with a Bruker AVANCE-500 spectrometer or a JEOL ECX-400P spectrometer. The ^1H NMR chemical shifts are reported relative to tetramethylsilane (TMS, 0.00 ppm). The ^{13}C NMR chemical shifts are reported relative to $CDCl_3$ (77.0 ppm). High-resolution mass spectra (ESI-HRMS) were obtained with Thermo Fisher Scientific Exactive LC-MS spectrometers. Column chromatography was carried out on silica gel (Kanto N60, spherical, neutral, 40–50 μm or 63–210 μm). TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck Silica gel $60F_{254}$. $CoI_2(dppf)$ was prepared according to a published method for $CoBr_2(dppf)$.[15] $CoI_2(PPh_3)_2$, $CoI_2(dppe)$ and $CoI_2(bpy)$, were also prepared according to the literature procedure.[11b] **1b**,[16] **1c**[17] and **1e**[18] were prepared according to the literature procedure.

5-4-2. Preparation of Substrates

Preparation of α-deuterated butyl acrylate (D-2a)

D-2a was prepared by similar procedure for the preparation of α-deuterated ethyl acrylate.[19] Butyl acrylate (7.1 mL, 50 mmol) was added to a solution of DABCO (2.8 g, 25 mmol) in D_2O (5 mL), and the mixture was vigorously stirred for 3 h. Then, the organic phase was separated from D_2O, and added to other solution of DABCO (2.8 g, 25 mmol) in D_2O (5 mL), and the reaction mixture was again vigorously stirred for 3 h. The organic phase was separated, dried over $MgSO_4$, filtered. Distillation of the residue with CaH_2 under reduced pressure (30 Torr, 60 °C) gave α-deuterated ethyl acrylate (**D-2a**). Colorless oil (1.5 g, 12 mmol, 24%). The deuterium incorporation ratio (72%) was determined by ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.41-6.38 (m, 1H), 6.12 (dd, J = 17.4, 10.4 Hz, 0.28H), 5.82-5.80 (m, 1H), 4.16 (t, J = 6.7 Hz, 2H), 1.69-1.62 (m, 2H), 1.45-1.37 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 166.3, 130.2, 128.4 (t, J_{C-D} = 25.3 Hz), 64.38, 30.6, 19.1, 13.7 (the signals of butyl acrylate **2a** were also resolved: δ 130.4, 128.6, 64.39).

5-4-3. Experimental Procedures

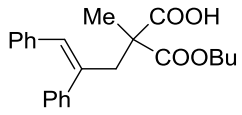
General procedure for the carboxylative coupling reaction of 1a and 2a (Table 5-1)

A 20 mL Schlenk flask was charged with Zn powder (25 mg, 0.38 mmol) and dried with a heating-gun under vacuum. Then, the flask was charged with CoI_2(dppf) (22 mg, 0.025 mmol), Bu_4NI (19 mg, 0.050 mmol), and $Zn(OAc)_2$ (9.2 mg, 0.050 mmol). The flask was evacuated and refilled with CO_2. This sequence was repeated five times. Then, CH_3CN (0.50 mL), alkyne **1a** (0.30 mmol), and acrylate **2a** (0.25 mmol) were added via airtight syringes, and the resulting mixture was stirred at 25 °C for 20 h. After the reaction, iodomethane (78 μL, 1.3 mmol) and DMF (0.50 mL) were added via airtight syringe and the resulting mixture was stirred at room temperature for 4 h. Then, 1,3,5-trimethoxybenzene (17 mg, 0.10 mmol) as an internal standard, Et_2O (5.0 mL), and 1 M HCl aq. (3.0 mL) were added to the reaction mixture, and the resulting biphasic solution was stirred for 10 min. A part of organic layer was separated and dried in vacuum. Then, the residue was dissolved in $CDCl_3$ and ^{1}H NMR spectrum of resultant solution was measured to determine the yield of **3aa**.

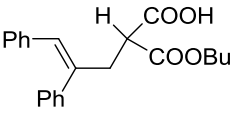
General procedure for the carboxylative coupling reaction of 1 and 2 (Table 5-2)

A 20 mL Schlenk flask was charged with Zn powder (25 mg, 0.38 mmol) and dried with a heating-gun under vacuum. Then, the flask was charged with CoI_2(dppf) (22 mg, 0.025 mmol), Bu_4NI (19 mg, 0.050 mmol), and $Zn(OAc)_2$ (9.2 mg, 0.050 mmol). The flask was evacuated and refilled with CO_2. This sequence was repeated five times. Then, CH_3CN (0.50 mL), alkyne **1** (0.30 mmol), and acrylate **2** (0.25 mmol) were added via airtight syringes, and the resulting mixture was stirred at 25 °C for 20 h. After the reaction, 1 M HCl aq. (3 mL) and Et_2O (5 mL) were added,

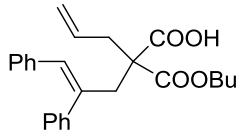
and the mixture was extracted with Et_2O (5 mL × 5). The collected organic layer was combined and dried over anhydrous $MgSO_4$. After removal of all volatiles, the residue was purified by silica gel chromatography using hexane/EtOAc as an eluent unless otherwise noted.



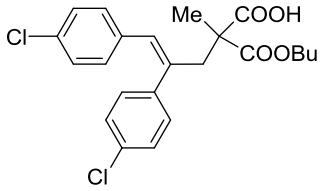
3aa: After the reaction, iodomethane (78 μL, 1.3 mmol, 5.0 equiv) and DMF (0.50 mL) were added via airtight syringe and the resulting mixture was stirred for 4 h at room temperature. The product was purified by silica gel chromatography using hexane/EtOAc as an eluent. Pale brown solid (81 mg, 88%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24-7.19 (m, 3H), 7.13 (d, J = 6.4 Hz, 2H), 7.06 (d, J = 6.4 Hz, 3H), 6.88-6.87 (m, 2H), 6.52 (s, 1H), 3.84-3.80 (m, 1H), 3.75-3.70 (m, 1H), 3.28 (d, J = 13.7 Hz, 1H), 3.14 (d, J = 13.7 Hz, 1H), 1.52-1.47 (m, 2H), 1.41 (s, 3H), 1.32-1.26 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.3, 172.0, 139.5, 137.3, 136.7, 131.5, 129.3, 129.0, 128.2, 127.8, 127.3, 126.6, 65.4, 53.5, 45.4, 30.2, 20.4, 19.0, 13.6. ESI-HRMS (*m/z*): $[M–H]^–$ calcd for $C_{23}H_{25}O_4$, 365.1758; found, 365.1754. IR (neat): 3100-2900 (br), 1753.3, 1730.2, 1705.1, 1508.3, 1280.7, 1182.4, 1124.5, 1099.4, 775.4, 758.0 cm^{-1}.



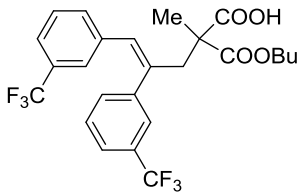
3aa-H: Yellow oil (75 mg, 85%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.27 (m, 3H), 7.17-7.15 (m, 2H), 7.07-7.05 (m, 3H), 6.89-6.87 (m, 2H), 6.52 (s, 1H), 4.13-4.09 (m, 2H), 3.46 (t, J = 7.6 Hz, 1H), 3.16-3.08 (m, 2H), 1.62-1.57 (m, 2H), 1.38-1.31 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.5, 168.9, 139.2, 138.2, 136.6, 129.2, 129.0, 128.8, 128.7, 127.8, 127.5, 126.6, 65.5, 50.4, 39.7, 30.4, 19.0, 13.6. ESI-HRMS (*m/z*): $[M–H]^–$ calcd for $C_{22}H_{23}O_4$, 351.1602; found, 351.1598. IR (neat): 3100-2800 (br), 1735.9, 1712.8, 1599.0, 1492.9, 1300-1150 (br), 1026.1, 918.1, 777.3, 758.0 cm^{-1}.



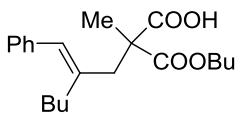
3aa-allyl: After the reaction, allyl bromide (0.11 mL, 1.3 mmol, 5.0 equiv) and DMF (0.50 mL) were added via airtight syringe and the resulting mixture was stirred for 20 h at room temperature. The product was purified by silica gel chromatography using hexane/acetone as an eluent. Pale yellow oil (72 mg, 74%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.23 (m, 3H), 7.12 (d, J = 7.0 Hz, 2H), 7.05 (br s, 3H), 6.85 (d, J = 4.9 Hz, 2H), 6.54 (s, 1H), 5.63-5.55 (m, 1H), 5.09-5.02 (m, 2H), 3.82-3.77 (m, 1H), 3.55-3.50 (m, 1H), 3.27 (d, J = 13.7 Hz, 1H), 3.16 (d, J = 14.0 Hz, 1H), 2.79 (dd, J = 13.6, 6.9 Hz, 1H), 2.59 (dd, J = 13.6, 7.8 Hz, 1H), 1.51-1.44 (m, 2H), 1.34-1.27 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.1, 173.2, 139.3, 136.8, 136.5, 131.7, 131.6, 129.4, 129.1, 128.3, 127.8, 127.4, 126.6, 119.6, 65.8, 57.7, 44.3, 39.5, 30.1, 19.0, 13.6. ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{29}O_4$, 393.2060; found, 393.2049. IR (neat): 3100-2900 (br), 1749.4, 1732.1, 1708.9, 1288.5, 1197.8, 910.4, 773.5, 758.0, 733.0 cm^{-1}.



3ba: After the reaction, iodomethane (78 μL, 1.3 mmol, 5.0 equiv) and DMF (0.50 mL) were added via airtight syringe and the resulting mixture was stirred for 4 h at room temperature. The product was purified by silica gel chromatography using hexane/EtOAc as an eluent. Pale yellow solid (60 mg, 55%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 8.2 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 6.48 (s, 1H), 3.86-3.76 (m, 2H), 3.24 (d, J = 14.0 Hz, 1H), 3.11 (d, J = 14.0 Hz, 1H), 1.53-1.47 (m, 2H), 1.41 (s, 3H), 1.34-1.26 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.9, 172.1, 137.6, 136.9, 134.8, 133.5, 132.6, 131.0, 130.7, 130.3, 128.7, 128.2, 65.7, 53.4, 45.2, 30.3, 20.6, 19.0, 13.7. ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{25}Cl_2O_4$, 435.1124; found, 435.1119. IR (neat): 3300-3100 (br), 2962.7, 1751.4, 1697.4, 1489.1, 1292.3, 1190.1, 1176.6, 1091.7, 1014.6, 887.3, 814.0, 763.8, 727.2 cm^{-1}.

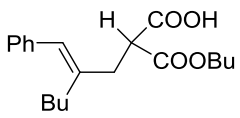


3ca: After the reaction, iodomethane (78 μL, 1.3 mmol, 5.0 equiv) and DMF (0.50 mL) were added via airtight syringe and the resulting mixture was stirred for 4 h at room temperature. The product was purified by silica gel chromatography using hexane/EtOAc as an eluent. Yellow oil (60 mg, 55%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.6 Hz, 1H), 7.39-7.33 (m, 3H), 7.27 (d, J = 7.9 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.05 (s, 1H), 6.99 (d, J = 7.9 Hz, 1H), 6.62 (s, 1H), 3.76 (t, J = 6.7 Hz, 2H), 3.32 (d, J = 14.0 Hz, 1H), 3.18 (d, J = 14.0 Hz, 1H), 1.50-1.44 (m, 5H), 1.31-1.24 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.8, 171.8, 139.8, 138.0, 136.8, 132.8, 132.1, 131.4, 131.0 (q, J = 32.4 Hz), 130.5 (q, J = 32.4 Hz), 129.0, 128.5, 126.0 (q, J = 3.5 Hz), 125.8 (q, J = 3.8 Hz), 124.5 (q, J = 3.8 Hz), 123.82 (q, J = 272.4 Hz), 123.79 (q, J = 272.4 Hz), 123.65 (q, J = 3.8 Hz), 65.7, 53.4, 44.8, 30.2, 20.5, 18.9, 13.5. ESI-HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{25}H_{24}F_6O_4Na$, 525.1471; found, 525.1461. IR (neat): 3000-2800 (br), 1732.1, 1714.7, 1329.0, 1205.5, 1165.0, 1124.5, 1074.4, 910.4, 808.2, 729.1 cm^{-1}.

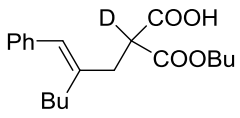


3da: After the reaction, iodomethane (78 μL, 1.3 mmol, 5.0 equiv) and DMF (0.50 mL) were added via airtight syringe and the resulting mixture was stirred for 4 h at room temperature. The product was purified by silica gel chromatography using hexane/acetone as an eluent. Yellow oil (47 mg, 54%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 7.3 Hz, 1H), 7.15 (d, J = 7.3 Hz, 2H), 6.30 (s, 1H), 4.21-4.12 (m, 2H), 2.91 (d, J = 14.0 Hz, 1H), 2.79 (d, J = 14.0 Hz, 1H), 2.19-2.07 (m, 2H), 1.67-1.61 (m, 2H), 1.52 (s, 3H), 1.45-1.34 (m, 4H), 1.27-1.20 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.5, 173.1, 138.2, 137.8, 130.1, 128.6, 128.1, 126.3, 65.8, 53.7, 42.0, 30.7, 30.41, 30.37, 22.6, 20.7, 19.0, 13.8, 13.6. ESI-HRMS

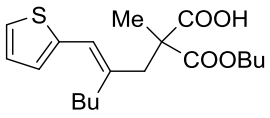
(*m/z*): $[M+H]^+$ calcd for $C_{21}H_{31}O_4$, 347.2217; found, 347.2212. IR (neat): 3000-2800 (br), 1708.9, 1460.1, 1300-1200 (br) 1114.9, 914.3, 734.9 cm^{-1}.



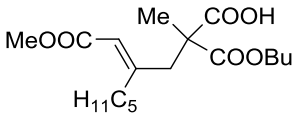
3da-H: Yellow oil (57 mg, 70%); ^1H NMR (500 MHz, $CDCl_3$): δ 7.29 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.3 Hz, 1H), 7.15 (d, J = 7.6 Hz, 2H), 6.33 (s, 1H), 4.16 (t, J = 6.6 Hz, 2H), 3.71 (t, J = 7.6 Hz, 1H), 2.80 (d, J = 7.3 Hz, 2H), 2.26-2.19 (m, 2H), 1.65-1.59 (m, 2H), 1.48-1.42 (m, 2H), 1.38-1.26 (m, 4H), 0.91-0.86 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.8, 169.0, 138.7, 137.7, 128.6, 128.1, 127.6, 126.3, 65.6, 50.7, 35.9, 30.5, 30.3, 30.0, 22.7, 19.0, 13.8, 13.6. ESI-HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{20}H_{28}O_4Na$, 355.1880; found, 355.1876. IR (neat): 3000-2800 (br), 1800-1700 (br), 1454.3, 1350-1100 (br), 1064.7, 1026.1, 918.1, 839.0, 748.4 cm^{-1}.



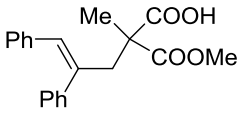
3da-D: After the reaction, D_2O (50 μL) was added via airtight syringe and the resulting mixture was stirred for 10 min. The product was rapidly purified by silica gel chromatography using hexane/acetone as an eluent. Yellow oil (49 mg, 58%); The deuterium incorporation ratio (60%) was determined by ^1H NMR. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 7.2 Hz, 2H), 6.33 (s, 1H), 4.16 (t, J = 6.6 Hz, 2H), 3.71 (t, J = 7.9 Hz, 0.40H), 2.83-2.75 (m, 2H), 2.27-2.18 (m, 2H), 1.65-1.58 (m, 2H), 1.47-1.27 (m, 6H), 0.91-0.85 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 174.7, 169.0, 138.7, 137.7, 128.6, 128.1, 127.6, 126.3, 65.6, 50.6, 35.8, 30.5, 30.3, 30.0, 22.7 19.0, 13.8, 13.6 (the C–D coupling could not be resolved, the signal of **3da-H** was also resolved: δ 35.9). HRMS measurement of **3da-D** did not succeed due to fast H/D exchange and only the signal of **3da-H** was found. ESI-HRMS (*m/z*): $[M-H]^-$ calcd for $C_{20}H_{27}O_4$, 331.1915; found, 331.1914.



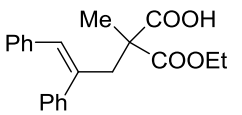
3ea: After the reaction, iodomethane (78 μL, 1.3 mmol, 5.0 equiv) and DMF (0.50 mL) were added via airtight syringe and the resulting mixture was stirred for 4 h at room temperature. The product was purified by silica gel chromatography using hexane/EtOAc as an eluent. Brown oil (44 mg, 50%); ^1H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, J = 4.9 Hz, 1H), 6.97 (t, J = 4.3 Hz, 1H), 6.89 (d, J = 3.7 Hz, 1H), 6.37 (s, 1H), 4.17 (td, J = 6.6, 2.3 Hz, 2H), 2.93 (d, J = 14.0 Hz, 1H), 2.77 (d, J = 14.0 Hz, 1H), 2.36-2.24 (m, 2H), 1.67-1.61 (m, 2H), 1.50-1.35 (m, 9H), 0.94-0.91 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.7, 172.7, 140.1, 137.2, 127.1, 126.6, 124.6, 122.9, 65.8, 53.9, 43.0, 32.2, 30.4, 30.0, 23.0, 20.6, 19.1, 13.9, 13.6. ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{19}H_{29}O_4S$, 353.1781; found, 353.1775. IR (neat): 3000-2800 (br), 1732.1, 1707.0, 1456.3, 1288.5, 1242.2, 1209.4, 1114.9, 910.4, 733.0 cm^{-1}.



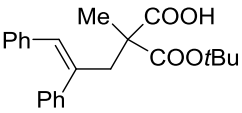
3fa: After the reaction, iodomethane (78 μL, 1.3 mmol, 5.0 equiv) and DMF (0.50 mL) were added via airtight syringe and the resulting mixture was stirred for 4 h at room temperature. The product was purified by silica gel chromatography using hexane/EtOAc as an eluent. Yellow oil (56 mg, 65%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.63 (s, 1H), 4.20-4.14 (m, 2H), 3.68 (s, 3H), 2.89 (d, J = 14.3 Hz, 1H), 2.75 (d, J = 14.3 Hz, 1H), 2.57-2.46 (m, 2H), 1.67-1.61 (m, 2H), 1.46-1.30 (m, 11H), 0.93 (t, J = 7.3 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.9, 171.9, 166.2, 159.0, 118.9, 65.9, 53.4, 50.9, 42.5, 32.6, 31.9, 30.3, 28.3, 22.4, 20.3, 19.0, 13.9, 13.5. ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{18}H_{31}O_6$, 343.2115; found, 343.2108. IR (neat): 3100-2800 (br), 1716.6, 1456.3, 1435.0, 1222.9, 1192.0, 1153.4, 1112.9, 1026.1, 918.1, 877.6, 835.2, 734.9 cm^{-1}.



3ab: After the reaction, iodomethane (78 μL, 1.3 mmol, 5.0 equiv) and DMF (0.50 mL) were added via airtight syringe and the resulting mixture was stirred for 4 h at room temperature. The product was purified by silica gel chromatography using hexane/EtOAc as an eluent. White solid (38 mg, 47%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24-7.19 (m, 3H), 7.13 (d, J = 7.6 Hz, 2H), 7.07 (d, J = 4.6 Hz, 3H), 6.89-6.87 (m, 2H), 6.52 (s, 1H), 3.38 (s, 3H), 3.30 (d, J = 13.7 Hz, 1H), 3.13 (d, J = 13.7 Hz, 1H), 1.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.1, 172.4, 139.4, 137.1, 136.6, 131.7, 129.3, 129.1, 128.2, 127.8, 127.3, 126.6, 53.3, 52.4, 45.5, 20.4. ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{20}H_{21}O_4$, 325.1434; found, 325.1427. IR (neat): 3100-2800 (br), 1745.6, 1710.9, 1456.3, 1446.6, 1404.2, 1290.4, 1267.2, 1201.7, 1182.4, 1124.5, 1101.4, 918.1, 771.5, 756.1, 734.9 cm^{-1}.

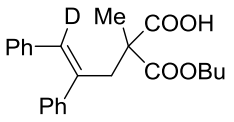


3ac: After the reaction, iodomethane (78 μL, 1.3 mmol, 5.0 equiv) and DMF (0.50 mL) were added via airtight syringe and the resulting mixture was stirred for 4 h at room temperature. The product was purified by silica gel chromatography using hexane/acetone as an eluent. Pale yellow solid (52 mg, 62%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24-7.20 (m, 3H), 7.13 (dd, J = 7.6, 1.5 Hz, 2H), 7.08-7.05 (m, 3H), 6.88-6.86 (m, 2H), 6.52 (s, 1H), 3.85-3.77 (m, 2H), 3.29 (d, J = 13.7 Hz, 1H), 3.14 (d, J = 13.7 Hz, 1H), 1.45 (s, 3H), 1.14 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.1, 172.1, 139.5, 137.3, 136.7, 131.6, 129.3, 129.0, 128.2, 127.8, 127.3, 126.6, 61.6, 53.4, 45.4, 20.5, 13.7. ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{23}O_4$, 339.1591; found, 339.1584. IR (neat): 3000-2800 (br), 1753.3, 1712.8, 1280.7, 1251.8, 1182.4, 1124.5, 1101.4, 1022.3, 773.5, 756.1 cm^{-1}.

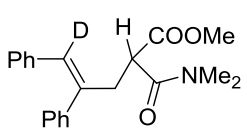


3ad: After the reaction, iodomethane (78 μL, 1.3 mmol, 5.0 equiv) and DMF (0.50 mL) were added via airtight syringe and the resulting mixture was stirred for 4 h at room temperature. The product was purified by silica gel chromatography using hexane/EtOAc as an eluent. White solid (68 mg, 74%); ^{1}H NMR (500

MHz, $CDCl_3$): δ 7.22 (t, J = 6.4 Hz, 3H), 7.15 (d, J = 7.6 Hz, 2H), 7.07-7.03 (m, 3H), 6.87-6.85 (m, 2H), 6.50 (s, 1H), 3.22 (d, J = 14.0 Hz, 1H), 3.14 (d, J = 14.3 Hz, 1H), 1.39 (s, 9H), 1.34 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.5, 171.4, 140.1, 137.7, 136.8, 131.1, 129.2, 129.0, 128.3, 127.8, 127.3, 126.5, 82.4, 54.3, 45.2, 27.7, 20.8. ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{27}O_4$, 367.1904; found, 367.1894. IR (neat): 3300-3100 (br), 1749.4, 1705.1, 1371.4, 1288.5, 1257.6, 1190.1, 1180.4, 1132.2, 1099.4, 783.1, 704.0 cm^{-1}.



D-3aa: α-deuterated butyl acrylate was used instead of butyl acrylate. After the reaction, iodomethane (78 μL, 1.3 mmol, 5.0 equiv) and DMF (0.50 mL) were added via airtight syringe and the resulting mixture was stirred for 4 h at room temperature. The product was purified by silica gel chromatography using hexane/acetone as an eluent. Pale yellow solid (64 mg, 65%); The deuterium incorporation ratio (70%) was determined by ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24-7.18 (m, 3H), 7.13 (dd, J = 7.5, 1.4 Hz, 2H), 7.08-7.05 (m, 3H), 6.88-6.86 (m, 2H), 6.52 (s, 0.30H), 3.85-3.71 (m, 2H), 3.28 (d, J = 13.7 Hz, 1H), 3.14 (d, J = 13.7 Hz, 1H), 1.52-1.47 (m, 2H), 1.41 (s, 3H), 1.33-1.26 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H). All ^{1}H NMR resonances except alkenyl region were in good agreement with **3aa**. ^{13}C NMR (126 MHz, $CDCl_3$): δ 177.2, 172.1, 139.5, 137.2, 136.6, 131.2 (t, J_{C-D} = 21.9 Hz), 129.3, 129.0, 128.2, 127.8, 127.3, 126.6, 65.5, 53.5, 45.4, 30.2, 20.4, 19.0, 13.6 (the signals of **3aa** were also resolved: δ 137.3, 136.7, 131.5). ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{23}H_{26}DO_4$, 368.1967; found, 368.1960. IR (neat): 3000-2800 (br), 1753.3, 1728.2, 1705.1, 1489.1, 1280.7, 1246.0, 1182.4, 1155.4, 1122.6, 1103.3, 918.1, 763.8 cm^{-1}.



5-D: *N*,*N*-demethylacrylamide (**4**, 26 μL, 0.25 mmol) was used instead of acrylate. After the reaction, D_2O (50 μL) was added via airtight syringe and the resulting mixture was stirred for 10 min. Then, 1 M HCl aq. (1 mL) and Et_2O (5 mL) was added, and the mixture was extracted with Et_2O (5 mL × 7). The collected organic layer was combined and dried over anhydrous $MgSO_4$. After removal of solvent under reduce pressure, the residue was treated with $TMSCHN_2$ (0.63 mL of 2.0 M Et_2O solution, 1.3 mmol, 5.0 equiv) in Et_2O/MeOH as a solvent. After 1 h, all volatiles were removed under reduced pressure and the residue was purified by silica gel chromatography using hexane/acetone as an eluent. Yellow oil (51 mg, 61%); The deuterium incorporation ratio (62%) was determined by ^{1}H NMR. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.24 (m, 3H), 7.16-7.15 (m, 2H), 7.09-7.05 (m, 3H), 6.91 (dd, J = 7.5, 2.0 Hz, 2H), 6.56 (s, 0.38H), 3.68 (s, 3H), 3.63 (t, J = 7.3 Hz, 1H), 3.22-3.11 (m, 2H), 2.92 (s, 3H), 2.78 (s, 3H). All ^{1}H NMR resonances except alkenyl region were in good agreement with **5**. ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.9, 167.9, 139.6, 138.5, 136.7, 129.01, 128.8, 128.6, 127.7, 127.3, 126.4, 52.3, 47.0, 39.7, 37.3, 35.9 (the C–D coupling in the alkenyl region could not be resolved, the signals of **5** were also resolved: δ 138.6, 136.8, 129.03, 39.8).

ESI-HRMS (*m/z*): $[M+H]^+$ calcd for $C_{21}H_{23}DNO_3$, 339.1813; found, 339.1803. IR (neat): 1741.7, 1687.7, 1651.1, 1491.0, 1440.8, 1313.5, 1269.2, 1215.2, 1161.2, 1024.2, 920.1, 837.1, 756.1 cm^{-1}.

5 was prepared by similar procedure for **5-D** followed by proton quench. ^1H NMR (500 MHz, $CDCl_3$): δ 7.31-7.24 (m, 3H), 7.15 (d, J = 7.0 Hz, 2H), 7.09-7.05 (m, 3H), 6.91 (dd, J = 7.5, 1.7 Hz, 2H), 6.56 (s, 1H), 3.69 (s, 3H), 3.63 (t, J = 7.2 Hz, 1H), 3.20 (dd, J = 14.3, 7.0 Hz, 1H), 3.13 (dd, J = 14.2, 7.8 Hz, 1H), 2.92 (s, 3H), 2.78 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.9, 167.9, 139.7, 138.7, 136.9, 129.1, 128.8, 128.7, 127.8, 127.3, 126.4, 52.3, 47.0, 39.8, 37.3, 35.9.

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List of Publications

The present Thesis is composed of the following papers.

Chapter 1

(1) Nickel-Catalyzed Carboxylation of Aryl and Vinyl Chlorides Employing Carbon Dioxide
Tetsuaki Fujihara, Keisuke Nogi, Tinghua Xu, Jun Terao, Yasushi Tsuji
J. Am. Chem. Soc. **2012**, *134*, 9106–9109.

Chapter 2

(2) Cobalt- and Nickel-Catalyzed Carboxylation of Alkenyl and Sterically Hindered Aryl Triflates Utilizing CO_2
Keisuke Nogi, Tetsuaki Fujihara, Jun Terao, Yasushi Tsuji
J. Org. Chem. **2015**, *80*, 11618–11623.

Chapter 3

(3) Cobalt-catalyzed carboxylation of propargyl acetates with carbon dioxide
Keisuke Nogi, Tetsuaki Fujihara, Jun Terao, Yasushi Tsuji
Chem. Commun. **2014**, *50*, 13052–13055.

Chapter 4

(4) Cobalt-Catalyzed Carboxyzincation of Alkynes Utilizing Carbon Dioxide and Zinc Powder
Keisuke Nogi, Tetsuaki Fujihara, Jun Terao, Yasushi Tsuji
In preparation.

Chapter 5

(5) Cobalt-Catalyzed Carboxylative Coupling Reaction of Alkyne and Acrylate Employing Carbon Dioxide and Zinc Powder
Keisuke Nogi, Tetsuaki Fujihara, Jun Terao, Yasushi Tsuji
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