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Doctoral Dissertation

Studies on Nickel-Mediated and -Catalyzed
Hydrocarboxylation of Ynamides with Carbon Dioxide

(ニッケル錯体を用いた量論的および触媒的なイナ
ミドのヒドロカルボキシ化反応に関する研究)

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Sapporo, August 2017

Iman Abdullah

Abbreviations

acac	: acetylacetonate
aq.	: aqueous solution
atm	: atmosphere
BAr ^F	: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	: benzyl
bpy	: 2,2'-bipyridine
°C	: degrees Celsius
cat.	: catalytic
cm ⁻¹	: wave number(s)
cod	: 1,5-cyclooctadiene
COSY	: correlation spectroscopy
Cy	: cyclohexyl
DIBAL-H	: diisobutylaluminium hydride
DBU	: 1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	: dichloromethane
DMF	: <i>N,N</i> -dimethylformamide
dppb	: 1,4-bis(diphenylphosphino)butane
<i>ee</i>	: enantiomeric excess
EI	: electron ionization
equiv	: equivalent(s)
ESI	: electrospray ionization
Et	: ethyl
EWG	: electron withdrawing group
glyme	: 1,2-dimethoxyethane
h	: hour(s)
HOBt	: 1-hydroxybenzotriazole
HPLC	: high performance liquid chromatography
HRMS	: high resolution mass spectroscopy

IMes	: 1,3-bis(2,4,6-trimethylphenyl)-imidazolium
IPA	: isopropanol
ⁱ Pr	: isopropyl
IPr	: 1,3-bis-(2,6-diisopropylphenyl)imidazolium
IR	: infrared absorption spectrometry
Ln	: ligand
LRMS	: low resolution mass spectroscopy
Me	: methyl
min	: minute(s)
MOM	: methoxymethyl
Ms	: methanesulfonyl
MS	: molecular sieve
<i>n</i>	: normal
ⁿ Bu	: normal butyl
nbd	: 2,5-norbornadiene
NBS	: N-bromosuccinimide
ND	: not detected
NMR	: nuclear magnetic resonance
NOE	: nuclear Overhauser effect
PGME	: phenylglycine methyl ester
Ph	: phenyl
phen	: 1,10-phenanthroline
PhMe	: toluene
PhOH	: phenol
PTLC	: preparative thin-layer chromatography
PyBOP	: benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
quant.	: quantitative yield
R	: substituent
rt	: room temperature
sat.	: saturated

<i>t</i>	: tertiary
TBAB	: tetrabutylammonium bromide
TBAF	: tetrabutylammonium fluoride
TBS	: <i>tert</i> -butyldimethylsilyl
^t Bu	: tertiary butyl
^t BuOH	: tertiary butanol
TFE	: trifluoroethanol
THF	: tetrahydrofuran
TLC	: thin-layer chromatography
TMEDA	: tetramethylethylenediamine
TMS	: trimethylsilyl or tetramethylsilane
Ts	: <i>p</i> -toluenesulfonyl

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General Introduction

CO₂ is a nontoxic, inexpensive, and abundant renewable carbon source in nature. Therefore, utilization of CO₂ in organic synthesis such as in carboxylation reaction of various types of substrates has attracted great interest for a couple of decades (Figure 1).¹ However, low reactivity of CO₂ hampers its broad utilization. In most cases, transition metal such as nickel is required in order to activate CO₂ and works as a catalyst/mediator in carboxylation reaction.

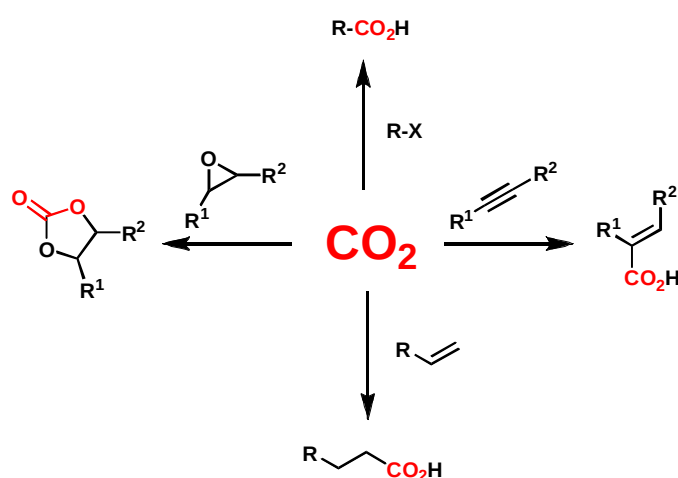


Figure 1. Utilization of CO₂ as carbon source in the synthesis of fine chemicals.

It is well known that CO₂ coordinates to transition metals such as nickel complex. The first isolated and structurally characterized Ni-CO₂ complex was reported by Aresta in 1975, in which the complex was synthesized by treating Ni(PCy₃)₃ with CO₂ in toluene.² In this complex, CO₂ possesses a bent geometry and is coordinated to nickel through carbon atom and one of the oxygen atom (Figure 2). Later on, the interaction between CO₂ and metal complex has been investigated intensively through stoichiometric experimental studies.^{3,4} As shown in Figure 2, there are several coordination modes between CO₂ and transition metals.⁵ In complex **I**, CO₂ coordinates directly via σ bonding of the metal to carbon atom. Formation of this complex is feasible for electron rich metal center via electron transfer from the metal to carbon atom of CO₂. In complex **II**, CO₂ coordinates via σ bonding of oxygen to the metal center. However, this complex is more difficult to obtain due to the weak interaction between lone electron pair of the only one oxygen atom with the metal

center. In complex **III**, CO₂ acts as a bidentate ligand to an electron-deficient metal center. Complex **IV** is a combination of complex **I** and **II**, in which electron transfer could proceed from metal to carbon and from oxygen to metal to afford a three-membered metallacycle. Aresta's Ni-CO₂ complex belongs to this type of coordination. The last possible coordination of CO₂ to metal center is via π coordination of one C=O bond to the metal center as shown in complex **V**. Among all of those possible metal-CO₂ coordination modes, type **I** and **IV/V** are the most common and the most convenient in term of catalysis.^{1a}

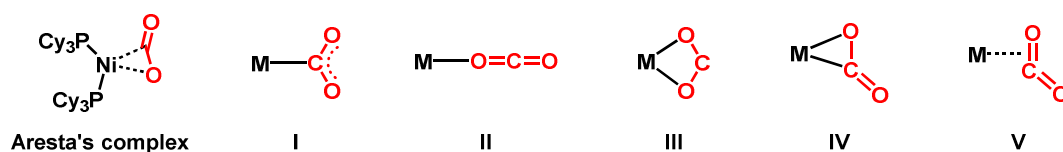
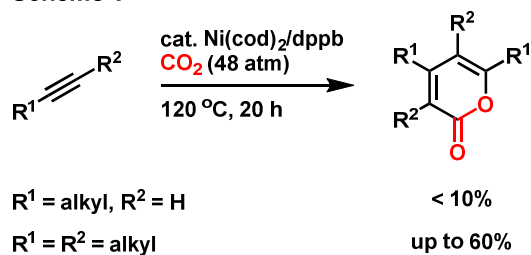


Figure 2. Structure of Aresta's complex and coordination modes of CO₂ with transition metals.

Nickel is a relatively electropositive transition metal.⁶ Therefore it tends to undergo a facile oxidative addition which results in loss of electron density around nickel. In addition, nickel also has a number of readily available oxidation states which allows different type of reactivity and reaction mechanism. Many transformations catalyzed by nickel are based on Ni(0)/Ni(II), Ni(I)/Ni(III), or Ni(0)/Ni(I)/Ni(II) cycles.⁶ Compared to other group 10 metals such as Pd, nickel has smaller atomic radius, thus the Ni-ligand bonds are often relatively short. Those important properties together with lower cost of nickel in its elemental form, have prompted the development of nickel catalyst in various organic reactions including carboxylation of unsaturated C–C bonds with CO₂.

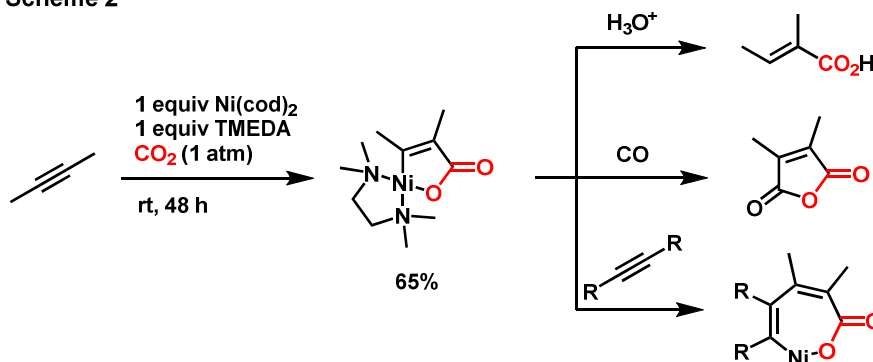
The first example of fixation of CO₂ into unsaturated C–C bond of alkyne catalyzed by nickel was reported in 1977 by Inoue.⁷ The reaction was conducted using Ni(cod)₂ and phosphine bidentate ligand under high pressure of CO₂ to afford α -pyrone as the carboxylated product. Due to a competing [2+2+2] cocyclization reaction of alkyne, α -pyrone was obtained in low yields (less than 10%). Later in 1980, the same author reported that the use of disubstituted alkyne improved the yield of the carboxylated product up to 60% yield (Scheme 1).⁸

Scheme 1



In 1982, Hoberg reported a ground-breaking discovery of formation of nickelalactone complex via oxidative cyclization of alkyne and CO_2 into Ni(0) center.⁹ The complex was obtained by coupling reaction of 2-butyne with CO_2 in the presence of a stoichiometric amounts of $Ni(cod)_2$ and TMEDA (Scheme 2). Protonolysis of the complex led to an α,β -unsaturated carboxylic acid, while reaction with carbon monoxide gave dimethylmaleic anhydride. Later on, Hoberg found that the nickelalactone reacted with alkynes to afford oxanickelacycloheptadienones, which was the intermediate in the Ni-catalyzed synthesis of α -pyrones reported earlier by Inoue. The structure of the oxanickelacycloheptadienone complex was also characterized by X-Ray crystallography analysis.¹⁰ Other type of unsaturated C-C bonds such as alkene,¹¹ allene,¹² and 1,3-diene¹³ were also reported to form nickelalactone intermediate.

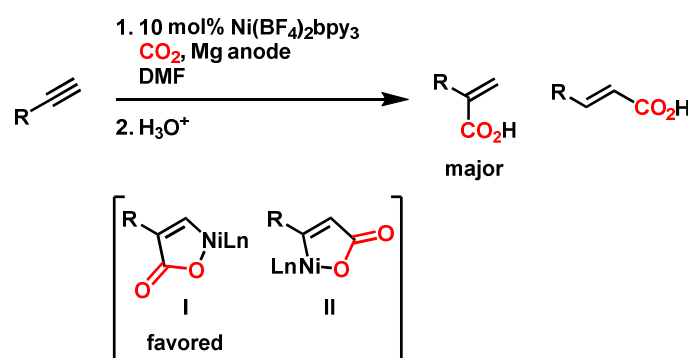
Scheme 2



In 1988, the first Ni-catalyzed hydrocarboxylation of alkynes was reported by Duñach for electrochemical carboxylation of terminal alkynes in the presence of $Ni(BF_4)_2bpy_3$ as a catalyst precursor and Mg anode in DMF solvent.¹⁴ Nickel(0) as the active catalyst was generated by electrochemical reduction method. Then in 1991, they reported the development of their method for hydrocarboxylation of both terminal and internal alkynes including the investigation of mechanistic study.¹⁵ In

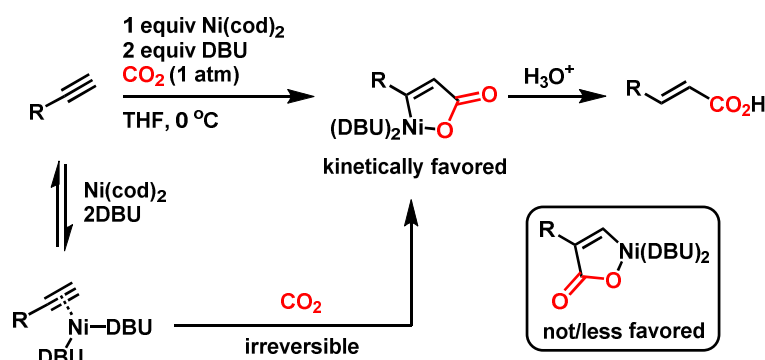
these reports, the authors suggested that two nickelalactone intermediates might exist which correspond to the formation of regioisomeric mixture of the products. In case of terminal alkynes, an intermediate such as intermediate **I** in which the metal occupied the less hindered site of the metallacycle, would be favoured, thus giving the α -carboxylation product as a major product (Scheme 3). In case of unsymmetrically internal alkynes, both steric and electronic effects play significant roles in regioselectivity of the reaction.

Scheme 3



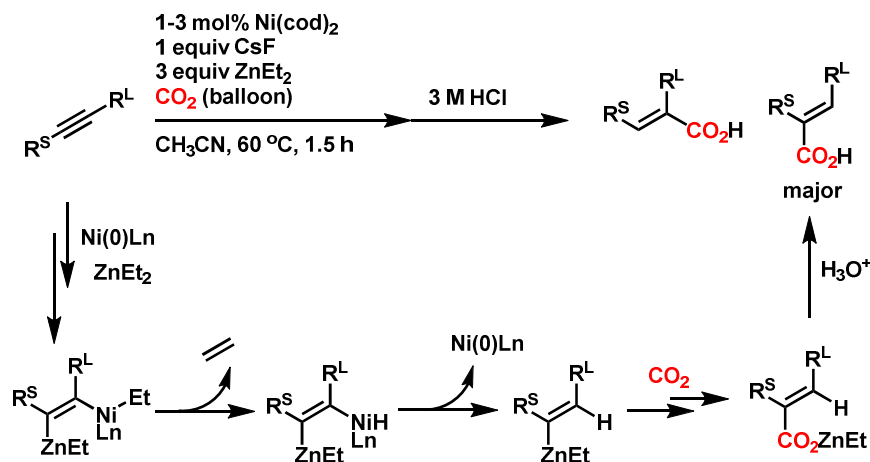
In 1999, by using Hoberg's method for the synthesis of nickelalactone, Yamamoto developed a procedure for the regio- and chemoselective synthesis of α,β -unsaturated carboxylic acids from terminal alkynes using a stoichiometric amount of $Ni(cod)_2$ and DBU under mild conditions.¹⁶ The regioselectivity of CO_2 incorporation in their method was in contrast to that of the previous report by Duñach. CO_2 attacked the less sterically hindered carbon atom of terminal alkyne to form a nickelalactone intermediate. Thus, products of carboxylation at β -position were obtained as sole or major products. They assumed that the choice of ligand played an important role in regioselectivity. In the presence of DBU, the Ni-alkyne complex will be more reactive towards CO_2 , and react rapidly and irreversibly to give nickelalactone (Scheme 4).

Scheme 4



Later on, another pathway for Ni-catalyzed hydrocarboxylation of alkynes has also been proposed by Ma¹⁷ in 2011. This pathway takes place when the reaction is conducted in the presence of diethylzinc reagent. The reaction is believed to proceed via hydrozincation followed by CO₂ insertion (Scheme 5). Hydrozincation product would be obtained after β -hydride elimination followed by reductive elimination. Then insertion of CO₂ would generate zinc carboxylate, and finally acidic work up would generate the desired carboxylated product.

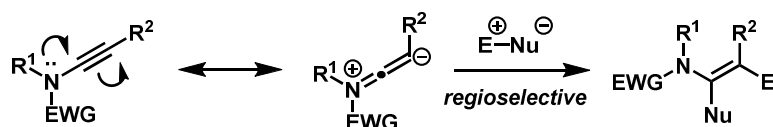
Scheme 5



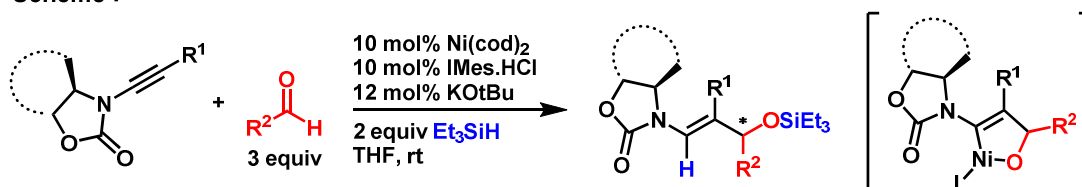
Although carboxylations of alkynes mediated- or catalyzed by Ni(0) have been studied extensively, the scopes were limited to relatively simple terminal- or internal alkynes. The reactivity of the electronically biased alkynes such as ynamides has been remained elusive. Ynamide is a polarized alkyne due to delocalization property of the unshared electron pair of nitrogen atom to the alkyne moiety (Scheme 6). The presence of electron withdrawing group (EWG) on nitrogen atom gives several effects

on the chemistry of ynamide by stabilization and by being a directing group. In some cases, ynamide having a chiral auxiliary would undergo an enantioselective reaction. Compared to ynamine, ynamide has better stability toward hydrolysis and can be isolated in pure form. In addition, electronic property would render ynamide a regioselective transformation upon reaction with nucleophile/electrophile.¹⁸ For example, in 2008 Sato's group reported an example of ynamide transformation catalyzed by Ni(0).¹⁹ Oxazolidinone-derived ynamide was coupled with aldehyde and silane to afford functionalized enamides via formation of oxanickelacycle intermediate. At the oxanickelacycle formation stage, the reaction proceeded through C-C bond formation between the negatively polarized carbon at β -position of ynamide with the positive carbonyl carbon of aldehyde. Consequently, only β -alkylated enamide was obtained as a single isomer. Then in 2011, by utilizing ynamide having chiral auxiliary, the diastereoselective coupling reaction was successfully achieved to give γ -siloxyenamide derivatives (Scheme 7).²⁰

Scheme 6



Scheme 7



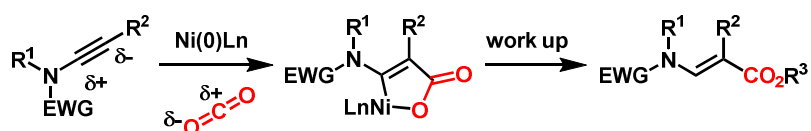
In summary, nickel has been well known as CO₂ activator as well as catalyst in carboxylation of various unsaturated compounds. Although carboxylations of alkynes mediated or catalyzed by nickel complex have been studied extensively, the substrate scope remains limited to relatively simple alkynes. Therefore, exploration of carboxylation reaction of alkynes having electronic bias property such as ynamides would be obviously attractive and important, especially those concerning the regioselectivity of the reaction.

Chapter 1. Nickel(0)-Mediated Hydrocarboxylation of Ynamides and Asymmetric Hydrogenation

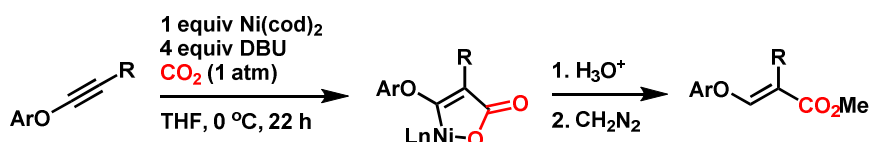
1.1 Introduction

Considering the electronic property of ynamide and previous report, I hypothesized that oxidative cyclization of ynamide and CO₂ to the Ni(0) center would regio- and stereo-selectively proceed via C–C bond formation between negatively charged β-carbon atom of ynamide and electrophilic carbon of CO₂ to give a nickelalactone. Thus, hydrolysis of the nickelalactone would generate the corresponding β-amino acrylic acid derivative which is a useful precursor for the synthesis of unnatural optically active β-amino acid derivative via asymmetric hydrogenation (Scheme 8).²¹ This strategy for regioselective hydrocarboxylation of ynamides is similar to the previous report on oxidative cyclization of aryl ynol ether and CO₂ to the Ni(0) (Scheme 9).²² Although copper-catalyzed alkylative carboxylation of oxazolidinone/carbamate-derived ynamides is reported by Hou²³ (Scheme 10), there is no example of coupling of ynamides with CO₂ mediated or catalyzed by Ni(0). Herein, the Ni(0)-mediated hydrocarboxylation of ynamides with CO₂ is presented.

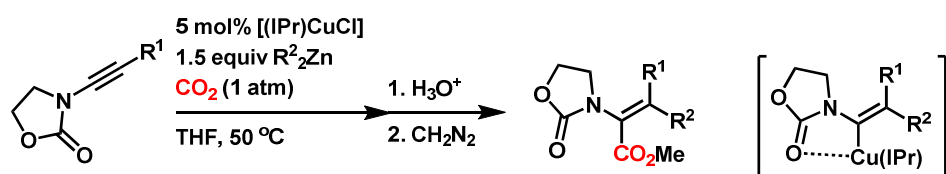
Scheme 8



Scheme 9

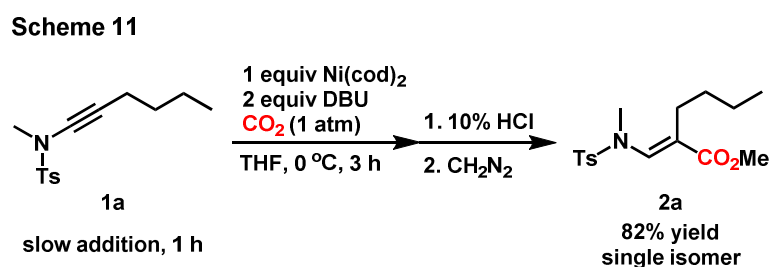


Scheme 10

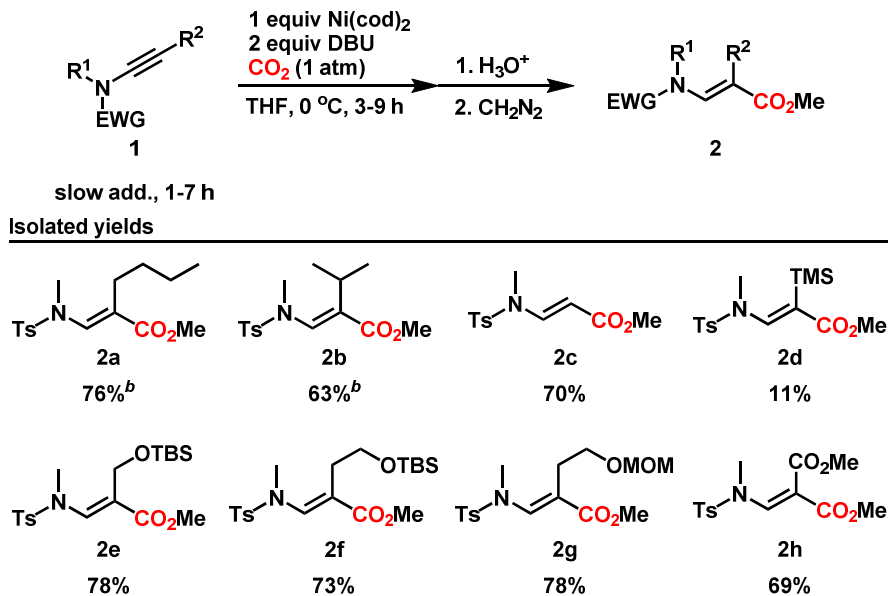


1.2 Hydrocarboxylation of ynamides with CO₂

At first, nickel-mediated hydrocarboxylation of ynamides was investigated by using ynamide **1a** as substrate in the presence of a stoichiometric amount of Ni(cod)₂ and DBU under CO₂ atmosphere, which is the same method to that reported by Yamamoto et al in 1999 for Ni-mediated regioselective hydrocarboxylation of terminal alkynes.¹⁶ After acidic work up followed by methylation with diazomethane, the corresponding β -carboxylated **2a** was obtained in 82% yield as a sole product (Scheme 11).²⁴

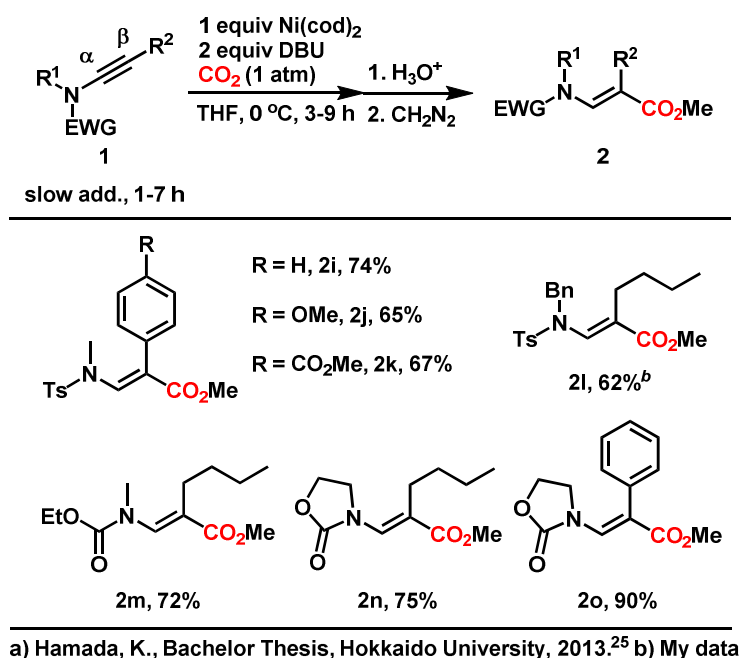


Based on the above result, nickel-mediated hydrocarboxylation of various ynamides was investigated. The results were summarized in Scheme 12 and 13. Carboxylation of *i*Pr-substituted ynamide **1b** proceeded well to give β -carboxylated **2b** in 63% yield as a single regio- and stereoisomer. A similar result was obtained for ynamide having terminal alkyne **1c**. On the other hand, carboxylation of TMS-substituted ynamide **1d** produced the desired product in a low yield. Next, ynamides having oxygen functionality such as OTBS (**1e** and **1f**), OMOM (**1g**) and methoxycarbonyl group (**1h**) were tested as substrate. As the result, the desired products were obtained in good yields.

Scheme 12^a

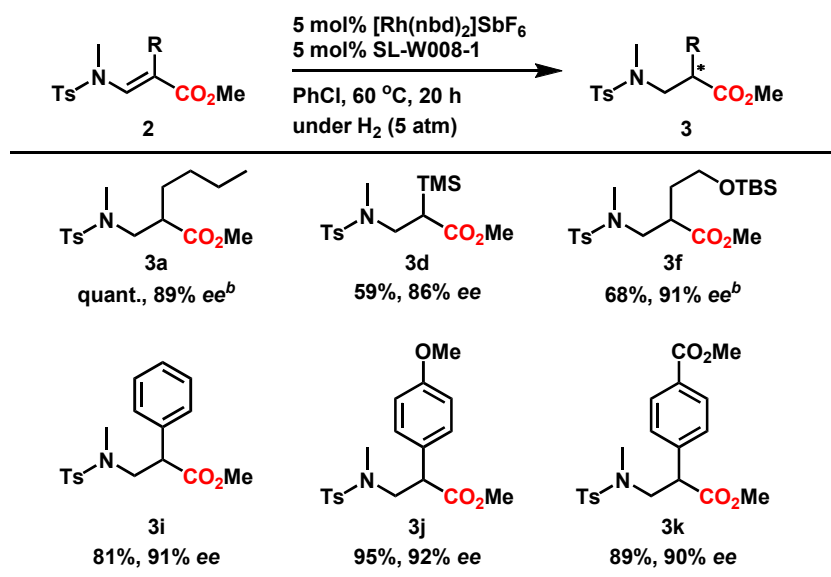
a) Hamada, K., Bachelor Thesis, Hokkaido University, 2013.²⁵ b) My data

Carboxylation of ynamides having aromatic ring **1i-1k** produced the corresponding targeted product in good yields. Ynamide having electron donating group **1j** or electron withdrawing group **1k** on aryl ring gave comparable result to ynamide **1i**. Carboxylation of ynamide having benzyl group on nitrogen atom **1l** also gave the desired product in good yield. The effect of EWG on nitrogen atom was also investigated. Carboxylation of carbamate-derived ynamide **1m** smoothly proceeded to give the desired product in 72% yield. Oxazolidinone-derived ynamides **1n** and **1o** were also applicable to the nickel-mediated carboxylation, the carboxylated products were obtained in good yields.

Scheme 13^a

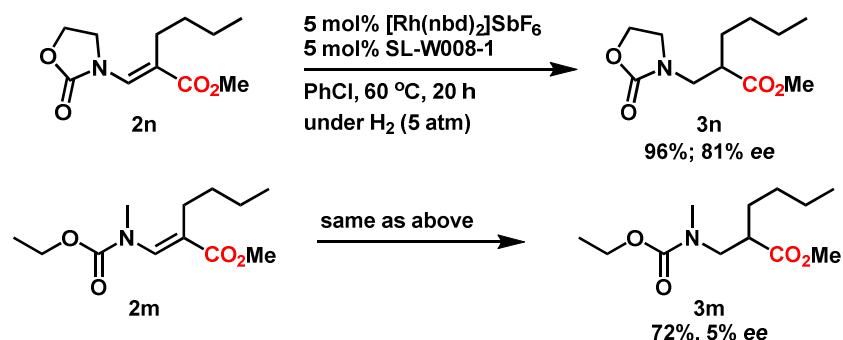
1.3 Asymmetric hydrogenation of enamides

Next, asymmetric hydrogenation of the carboxylated enamide was investigated. The reactions were conducted using similar condition to previous report on asymmetric hydrogenation of β -aryloxy- α,β -unsaturated esters by using Rh and Walphos ligand.^{22,26} As the result, various Ts-enamide substrates including an ether moiety, a silyl group as well as a substituted-aromatic ring were hydrogenated in high yields and high *ees* (Scheme 14).²⁷ The same result was observed for asymmetric hydrogenation of oxazolidinone-derived enamide: the product was obtained in high yield and high *ee*. Unfortunately, in case of asymmetric hydrogenation of carbamate-derived enamide, the product was obtained in a low *ee* (Scheme 15).

Scheme 14^a

a) Koyama, M., Master Thesis, Hokkaido University, 2013.²⁸ b) My data

Scheme 15

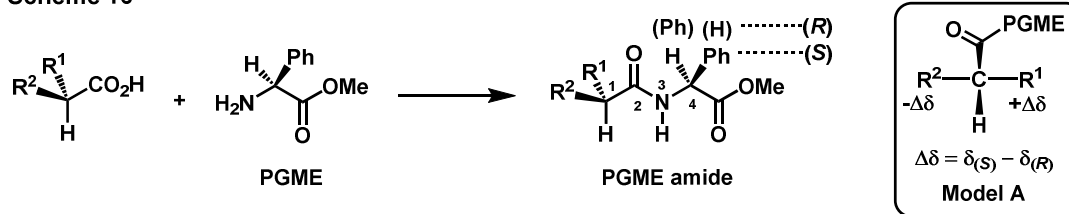


1.4 Determination of the absolute configuration

Next, determination of the absolute configuration at C2 position of the product was examined using an NMR method introduced by Kusumi.²⁸ In this method, a chiral α,α -disubstituted carboxylic acid is reacted with both (*S*)- and (*R*)-phenylglycine methyl ester (PGME) to give the amide (Scheme 16). Coplanarity of the atoms from position 1 to position 4 in PGME amide is guaranteed due to the presence of *s-trans* amide linkage. In (*S*)-isomer, the benzene ring of PGME gives a diamagnetic anisotropic effect to the protons in R^2 substituent, while in (*R*)-isomer, the R^1 protons will get the same effect. Thus, the R^2 protons of (*S*)-isomer will have the more upfield chemical shift than those of the (*R*)-isomer. The same will stand for R^1 protons of (*R*)-isomer. Then, the absolute configuration of the carboxylic acid can be determined by analyzing the positive and negative distribution patterns of the

chemical shift differences between (*S*)- and (*R*)-isomer using model **A** as shown in Scheme 17.

Scheme 16



To apply Kusumi's PGME method, the methyl ester group of **3f** was hydrolyzed to give carboxylic acid **4f**, and then reacted with both (*S*)- and (*R*)-PGME to give the corresponding amide (*S*)-**5f** and (*R*)-**5f**. Then, differences between the chemical shift of (*S*)-**5f** and (*R*)-**5f** in the 500 MHz ^1H NMR spectra were calculated. By mapping the positive and negative values according to Kusumi's PGME method, the configuration at the C_2 position of **3f** was assigned to be *R*. The absolute configuration of the C_2 position of **3a** was also assigned to be *R* in a similar manner (Figure 3).

Scheme 17

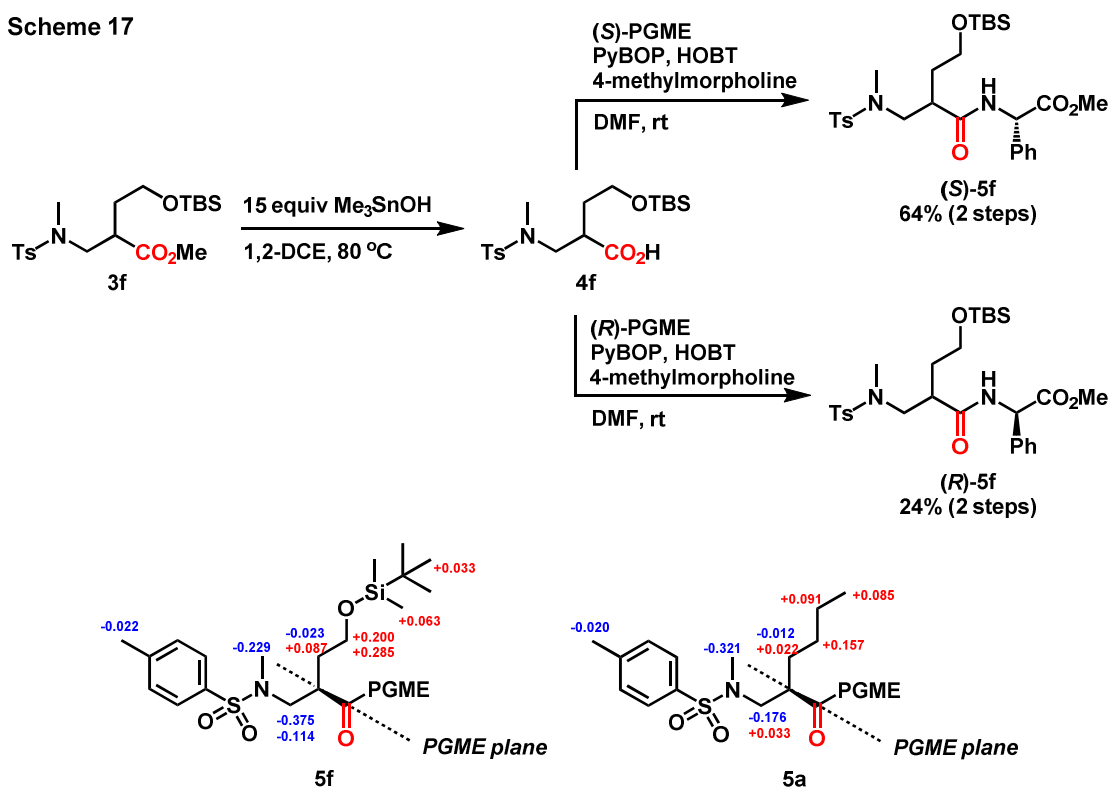


Figure 3. Chemical shift differences ($\Delta\delta = \delta_{(S)} - \delta_{(R)}$) in **5f** and **5a**, revealing the *R* configuration at C_2 position both in **3f** and **3a**.

1.5 Summary of chapter 1

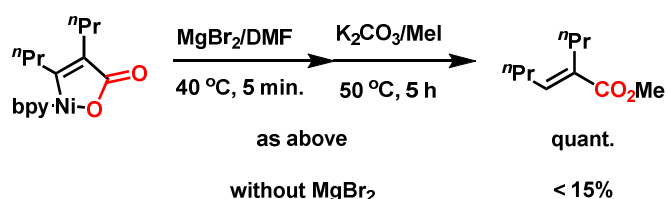
In summary, nickel-mediated hydrocarboxylation of ynamides proceeded to give the corresponding α -substituted β -aminoacrylate derivatives as a single regio- and stereoisomer. Then, subsequent Rh-catalyzed asymmetric hydrogenation provided the corresponding α -substituted β -amino acid derivatives in high yields and high *ees*. The absolute configuration at C2 position of the asymmetric hydrogenation product was assigned to be *R* by using Kusumi's PGME method.

Chapter 2. Nickel-Catalyzed Hydrocarboxylation of Ynamides

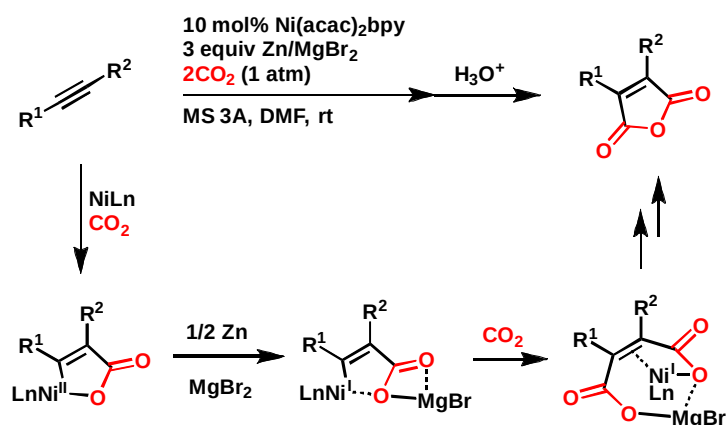
2.1 Introduction

As described in Chapter 1, the Ni-mediated hydrocarboxylation of ynamides using a stoichiometric amount of Ni(0) complex proceeded via nickelalactone formation. In order to perform the reaction with a catalytic amount of Ni(0) complex, the nickelalactone intermediate must be cleaved to facilitate regeneration of Ni(0) as the active species. According to previous report by Duñach and Perichon in 1991,¹⁵ the addition of MgBr₂ would cleave the Ni-O bond of nickelalactone to give an alkenyl nickel species. They provided some experimental evidences which support the role of MgBr₂ in ring opening of nickelalactone. At first, they isolated a nickelalactone complex prepared from 4-octyne substrate, then treated the complex with anhydrous MgBr₂ in DMF and followed with direct methylation with MeI/K₂CO₃. As the result, the corresponding methyl ester was obtained in a quantitative yield. On the other hand, treatment of the complex using the same procedure in the absence of MgBr₂ afforded the ester only in less than 15% yield (Scheme 18). Thus, it was confirmed that MgBr₂ played an important role in cleaving the Ni-O bond of nickelalactone. In addition, Tsuji *et al.*²⁹ in 2014 also reported the importance of MgBr₂ along with Zn as reducing agent in Ni-catalyzed double carboxylation of alkynes in the presence of molecular sieves (Scheme 19). They reported that nickelalactone complex underwent one electron reduction by zinc assisted with MgBr₂ to give a nickel(I) species. Then second insertion of CO₂ into Ni^I-C bond proceeded to give a double carboxylated product. This pathway required the least energy among other two possible paths as examined by DFT calculation.

Scheme 18

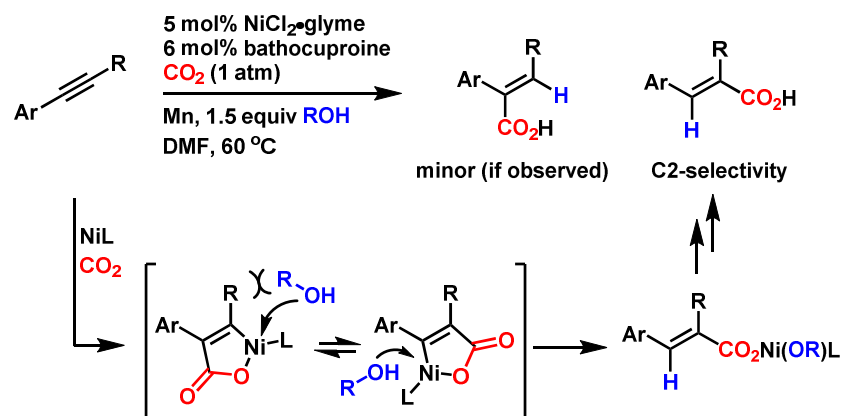


Scheme 19



In 2015, Martin group reported the use of simple alcohol as a proton sources in regioselective hydrocarboxylation of aryl alkynes catalyzed by nickel complex (Scheme 20).³⁰ In addition to its role as proton source, Martin *et al.* suggested that the simple alcohol might also act as a reagent that interacted with intermediates within catalytic cycle. They speculated that an equilibrium would exist between two possible nickelalactones derived from alkynes and CO₂ and that steric repulsion between an alkyl group and alcohol would be a key factor in regioselectivity.

Scheme 20



Considering previous reports, the strategy for Ni-catalyzed hydrocarboxylation of ynamides was planned as shown in Figure 4. Magnesium bromide would cleave the Ni-O bond of nickelalactone to give an alkenyl nickel species. Then subsequent reduction by Zn in the presence of water as proton source would generate magnesium carboxylate salt along with regeneration of Ni(0).

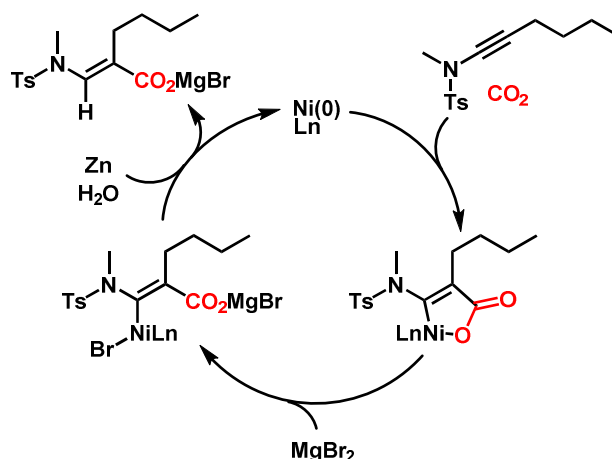
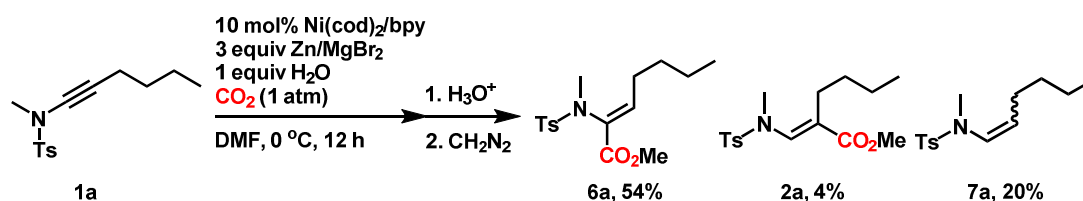


Figure 4. Strategy for Ni-catalyzed hydrocarboxylation of ynamide.

2.2 Ni-catalyzed hydrocarboxylation of ynamide

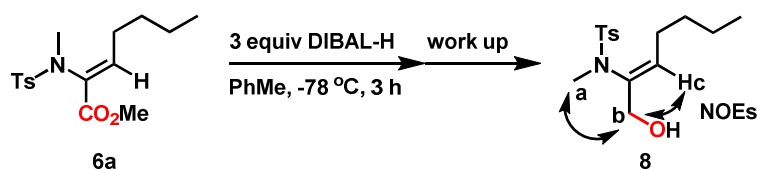
The catalytic hydrocarboxylation of ynamide **1a** was performed by use of 10 mol% of Ni(cod)₂/bpy, 3 equivalents of MgBr₂/Zn, and 1.0 equivalents of water as a proton source under CO₂ atmosphere. As the result, carboxylated product was obtained in 58% yield as a regioisomeric mixture of **2a** and **6a** along with formation of undesired hydrogenated **7a** in 20% yield. The regioselectivity of CO₂ incorporation was in contrast to that of the stoichiometric carboxylation. In this case, α-carboxylated product was obtained as a major product (Scheme 21).

Scheme 21



The structure of the α-carboxylated product was then elucidated by NOE experiment. At first, the ester group was transformed into hydroxyl group by reduction with DIBAL-H. After work up, the corresponding alcohol **8** was obtained in 90% yield. NOE analysis showed the correlation between protons **b** and **a**, and **b** and **c** (Scheme 22). Thus, it confirms the *Z* structure of the product, which was generated from *syn*-hydrocarboxylation reaction.

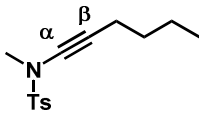
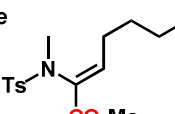
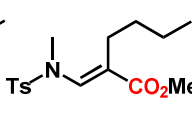
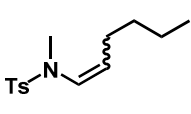
Scheme 22



2.3 Investigation of reaction conditions

Then I investigated the effects of proton source in this reaction. The results were shown in Table 1. Conducting the hydrocarboxylation reaction in the absence of water for 24 h produced the carboxylated product in a low yields (entry 1). Elongation of the reaction time from 24 h to 48 h improved the yield of the α -carboxylated product **6a** up to 40% (entry 2). Increasing the amount of water to 3 equivalents gave a comparable amount of carboxylated products along with higher amount of hydrogenated byproduct **7a** (entry 3). By reducing the amount of water to 0.5 equivalents, the yield of α/β -carboxylated product increased to 74% and 11% yield respectively (entry 5). Moreover, the generation of **7a** was reduced to 11%. The addition of substrate and proton source in a single portion gave an almost similar result (entry 6). On the other hand, simple alcohols such as methanol and ethanol also worked as a proton source although longer reaction time was needed (entries 7-9). Other alcohols having larger molecular size such as *tert*-butanol, trifluoroethanol and phenol were less effective (entries 10-13).

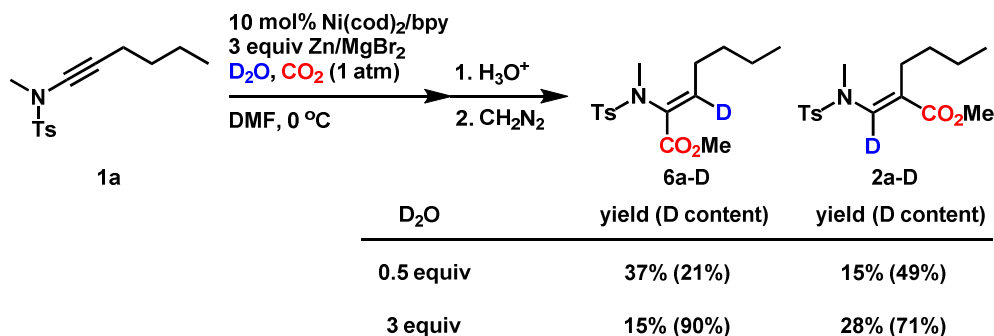
Table 1. The effects of proton source

 1a 1. 10 mol% Ni(cod)₂/bpy 3 equiv Zn/MgBr₂ CO₂ (1 atm), proton source DMF (0.07 M), 0 °C, time 2. H₃O⁺ 3. CH₂N₂  6a  2a  7a					
entry	proton source	time	6a	2a	7a
1	none	24 h	26	12	2
2	none	48 h	40	14	1
3 ^a	H ₂ O (3 equiv)	12 h	47	5	28
4 ^a	H ₂ O (1 equiv)	12 h	54	4	20
5 ^a	H ₂ O (0.5 equiv)	12 h	74	11	11
6	H ₂ O (0.5 equiv)	12 h	67	9	11
7	MeOH (1 equiv)	12 h	42	10	3
8	MeOH (1 equiv)	36 h	65	16	4
9	EtOH (1 equiv)	36 h	65	14	4
10	IPA (1 equiv)	36 h	53	11	3
11	^t BuOH (1 equiv)	36 h	35	11	trace
12	TFE (1 equiv)	36 h	41	16	3
13	PhOH (1 equiv)	47 h	41	15	3

^aSolution of proton sources and SM in DMF was added slowly for 7 h.

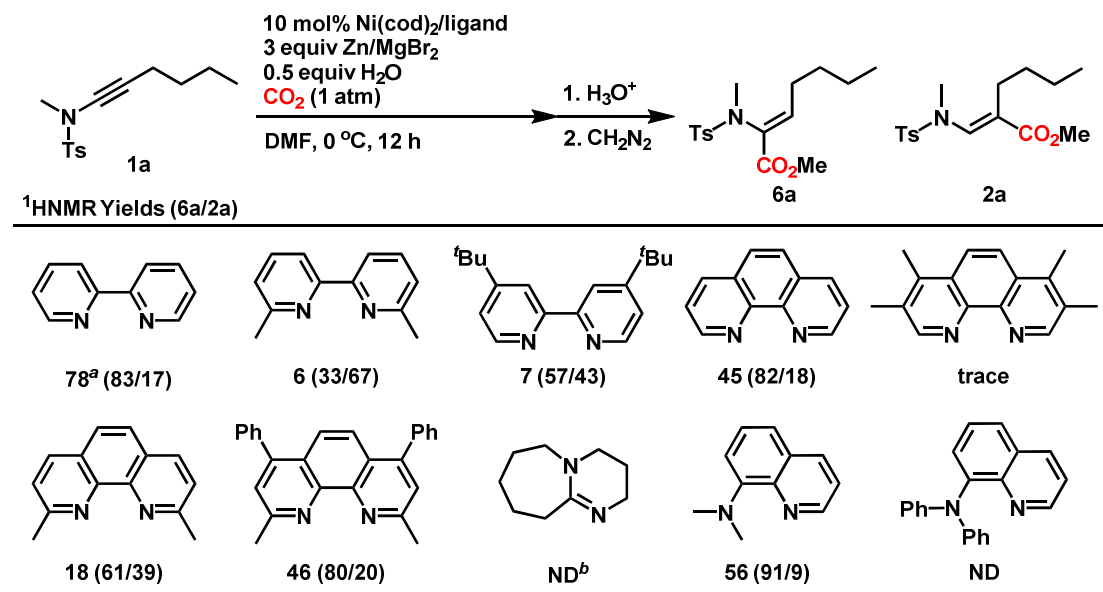
To confirm the role of water as proton source in the reaction, isotope labeling experiments were conducted by using D₂O. When hydrocarboxylation of **1a** was conducted in the presence of 0.5 equivalents of D₂O, the same amount to that in the optimum conditions, the D content for **6a** and **2a** was found to be 21% and 49% respectively (Scheme 23). The low value of D content in the carboxylated products indicates two possible things: 1) trace amount of water were still existed in the reaction mixture (which might come from magnesium salt or even the distilled DMF), 2) DMF itself worked as proton source, as reported by Dunach and Perichon.¹⁵ This result is also in line with the result of the reaction in the absence of water (Table 1 entries 1 and 2), in which the reaction still proceeded and gave a moderate yield after stirring for 48 h. Finally, in the presence of 3 equivalents of D₂O, the D content was observed at a satisfactory level, 90% in **6a** and 71% in **2a**. However, the regioselectivity was changed in which β-carboxylated product was obtained as major product in 28% yield.

Scheme 23



The effect of ligand in this reaction was also investigated (Scheme 24). While bpy is an effective ligand, its derivatives such as 6,6'-dimethyl-2,2'-bpy and 4,4'-ditert-butyl-2,2'-bpy were not. On the other hand, by replacing bpy with phenanthroline, the hydrocarboxylation reaction proceeded to give similar regioselectivity albeit in lower yield. Other phenanthroline derivatives such as 3,4,7,8-tetramethyl-1,10-phenanthroline and neocuproine (2,9-dimethyl-1,10-phenanthroline) were not effective in this hydrocarboxylation reaction. Meanwhile bathocuproine, another phenanthroline derivative which was a highly effective ligand in hydrocarboxylation of alkynes reported by Martin,³⁰ gave similar regioselectivity to bpy but in a lower yield. Indeed, I have also applied Martin's condition for ynamide substrate, but it did not work at all. Unlike in stoichiometric reaction, DBU did not work as effective ligand in this catalytic hydrocarboxylation. Surprisingly, *N,N*-dimethylquinolin-8-amine also worked as ligand, giving the carboxylated products in 56% yield with high α -selectivity. While its analog, *N,N*-diphenylquinolin-8-amine was not an effective ligand.

Scheme 24



^a isolated yield. ^b 20 mol% ligand was used.

Next, the effect of reductants and additives was investigated (Table 2). Zn powder was indispensable for this reaction. Other reductants such as Mn and Mg did not work effectively giving the carboxylated products in a low yield with low regioselectivity (entries 2-3). Hydrocarboxylation in the presence of MgCl₂ in place of MgBr₂ gave a comparable result, showing the importance of magnesium ion in this reaction (entry 4). In fact, replacing magnesium salt with other additives such as ZnBr₂, LiBr or tetrabutylammonium bromide (TBAB) was not effective (entries 5-7).

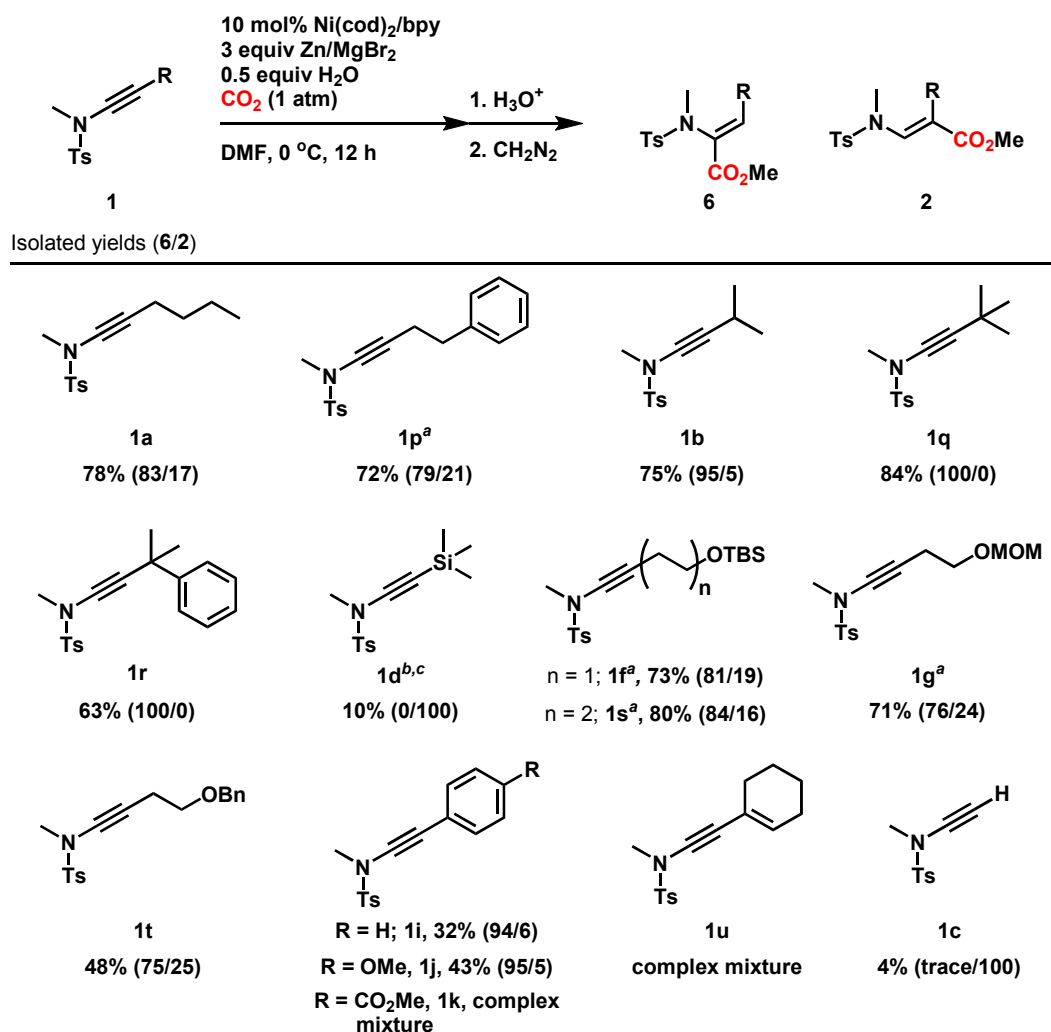
Table 2. The effects of reductant and additive

Entry	Reductant	Additive	6a	2a
1	Zn	MgBr ₂	65	13
2	Mn	MgBr ₂	16	13
3	Mg	MgBr ₂	7	4
4	Zn	MgCl ₂	65	6
5	Zn	ZnBr ₂	ND	trace
6	Zn	LiBr	3	10
7	Zn	TBAB	ND	trace

2.4 Substrate scope

With the optimum conditions, I checked the scope of the reaction. The results are shown in Scheme 25 and 26. Hydrocarboxylation of various alkyl-substituted ynamide gave good yields under this reaction conditions. The regioselectivity increased when ynamide bearing sterically hindered alkyl group was employed as a substrate. Especially, for ynamides having tertiary alkyl group **1q** and **1r**, the α -carboxylated product was generated as a single regioisomer. Unfortunately, hydrocarboxylation of TMS-substituted ynamide **1d** gave low yield with reverse regioselectivity. A desilylated of **2d** was also generated in 11% yield. Hydrocarboxylation of ynamides having oxygen functionality also gave the corresponding α/β -carboxylated products in good yields albeit a double amount of the nickel catalyst was needed. The hydrocarboxylation of ynamides having an aromatic ring **1i** and **1j** produced the targeted compound in a high α -selectivity. Electron withdrawing group on aryl ring affects the reactivity of ynamide **1k**. Ynamide having a cyclohexene moiety **1u** and a terminal alkyne **1c** were also not a suitable substrate.

Scheme 25. Substrate scope 1



^aTwenty mol% of catalyst was loaded. ^b¹H NMR yield. ^cDesilylation product **2d'** was also obtained in 11% yield.

Next, the effects of electron withdrawing and substituents on nitrogen atom were also investigated. Hydrocarboxylation of carbamate-derived ynamide **1m** gave the corresponding carboxylated product in a good yield and high selectivity while hydrocarboxylation of ynamide having mesyl group **1v** resulted in lower selectivity. In contrast, reverse regioselectivity was observed in hydrocarboxylation of oxazolidinone-derived ynamide **1n**. Various aryl or alkyl substituents on nitrogen atom were also tolerated in this hydrocarboxylation method, giving the carboxylated product in high to moderate yields with high selectivity, except for allyl substituent **1y**. The structure of α -carboxylated product **6l** obtained from hydrocarboxylation of **1l** was confirmed by X-Ray analysis (Figure 5).

Scheme 26. Substrate scope 2

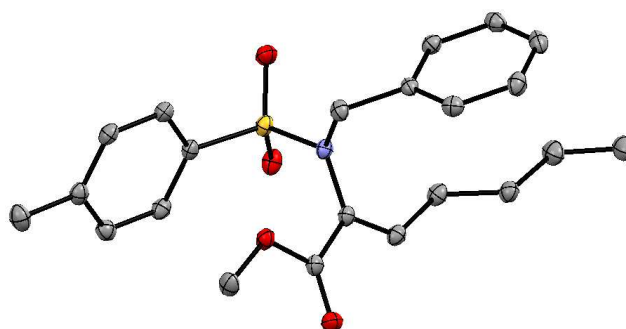
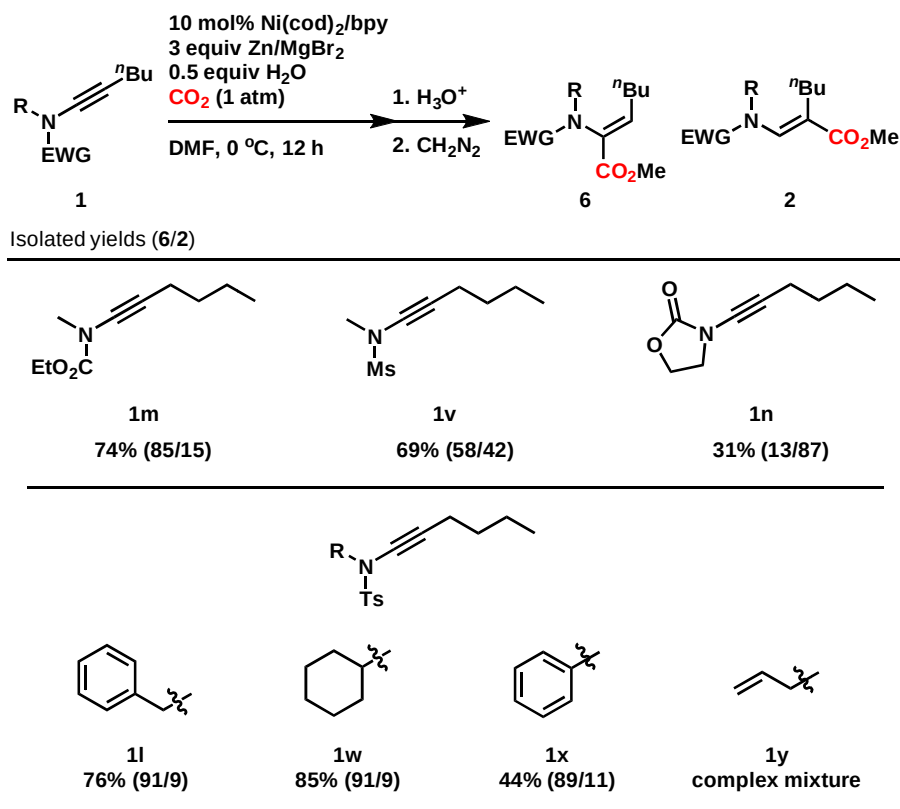


Figure 5. X-Ray structure of **6l**

2.5 Mechanistic study

To clarify key factors for regioselectivity switch, I conducted several control experiments. The results are shown in Table 3. Hydrocarboxylation using a stoichiometric amount of Ni(cod)₂ and bpy either in THF or DMF also gave β -carboxylated product **2a** as a sole product albeit in a low yield (entries 3 and 4), showing the same regioselectivity to that of the stoichiometric condition using a DBU ligand in THF (entry 2). These results suggest that neither ligand nor solvent affect the selectivity. The addition of 3 equivalents of zinc to the reaction mixture caused no effect on selectivity, while the addition of the same amount of magnesium bromide

produced α -carboxylated product **6a** in 2% (entries 5 and 6). When both zinc and magnesium bromide were added to the reaction mixture, the selectivity was drastically changed and α -carboxylated product **6a** was obtained as a major product, as observed in catalytic conditions (entry 7). This result reveals that both zinc and magnesium bromide plays an important role in the formation of an α -carboxylated product, and the regioselectivity does not depend on the amount of Ni(0) complex. Considering that Ni-mediated carboxylation of ynamides only afforded β -carboxylated product via nickelalactone formation, it seems that the presence of MgBr_2 and Zn suppressed this pathway and/or providing another pathway for formation of an α -carboxylated product.

Table 3. Investigation of key factor for selectivity

entry	reaction condition	6a	2a
1	10 mol% Ni(cod) ₂ /bpy, 3 equiv Zn/MgBr ₂ 0.5 equiv H ₂ O, DMF	65	13
2	1 equiv Ni(cod) ₂ ; 2 equiv DBU; THF	-	82
3	1 equiv Ni(cod) ₂ /bpy; THF	-	22
4	1 equiv Ni(cod) ₂ /bpy; DMF	-	31
5	1 equiv Ni(cod) ₂ /bpy; 3 equiv Zn; DMF	-	29
6	1 equiv Ni(cod) ₂ /bpy; 3 equiv MgBr ₂ ; DMF	2	27
7	1 equiv Ni(cod) ₂ /bpy; 3 equiv Zn/MgBr ₂ ; DMF	64	12

To gain insights into the reaction mechanism, nickelalactone **9** was prepared by treatment of *i*Pr-substituted ynamide **1b** with a stoichiometric amount of Ni(cod)₂/bpy under CO₂ in THF (Scheme 27). The structure of the resulting nickelalactone was successfully characterized by X-Ray crystallography (Figure 6). Then, the nickelalactone **9** was treated with the optimum conditions for hydrocarboxylation reaction using 3 equivalent of Zn/MgBr₂ and 0.5 equivalent of H₂O under CO₂ atmosphere. After acidic work-up, only the corresponding β -carboxylic acid **11** was obtained in 71%. It is noteworthy that no α -carboxylic acid **10** was observed at all (Scheme 28). This result suggests that nickelalactone only gave β -carboxylated

product, and that the α -carboxylated product might to be formed via different intermediate/pathway.

Scheme 27

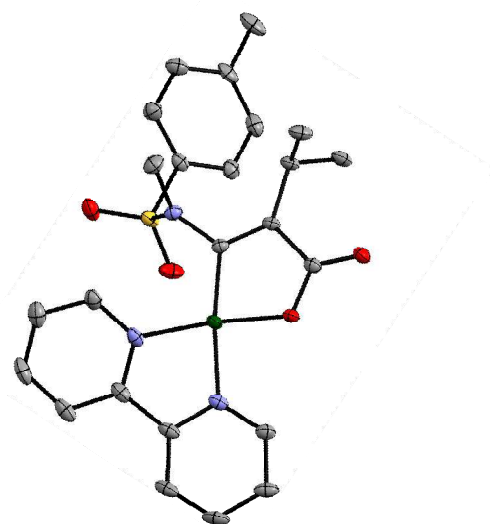
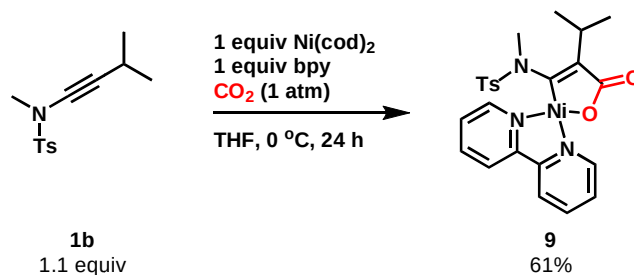
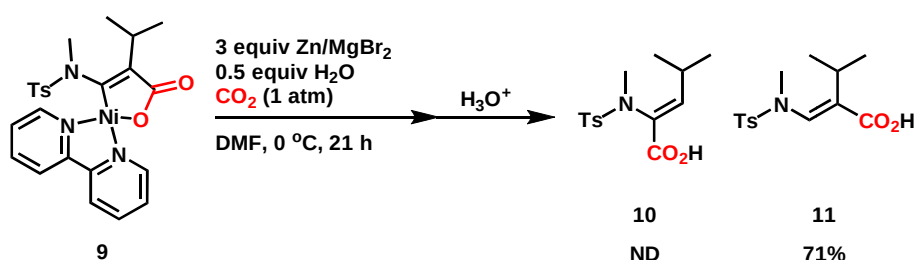


Figure 6. X-Ray structure of **9**

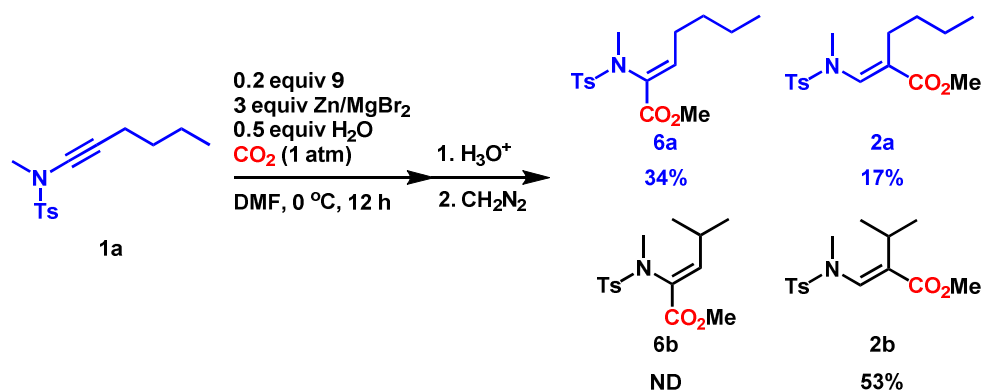
Scheme 28



In addition, nickelalactone **9** was also used as catalyst in hydrocarboxylation of n -Bu-substituted ynamide **1a** (Scheme 29). As the result, α - and β -carboxylated product **6a** and **2a** was obtained in 34 and 17% yield (based on ynamide **1a**) respectively. Meanwhile β -carboxylated product **2b** was obtained in 53% yield (based

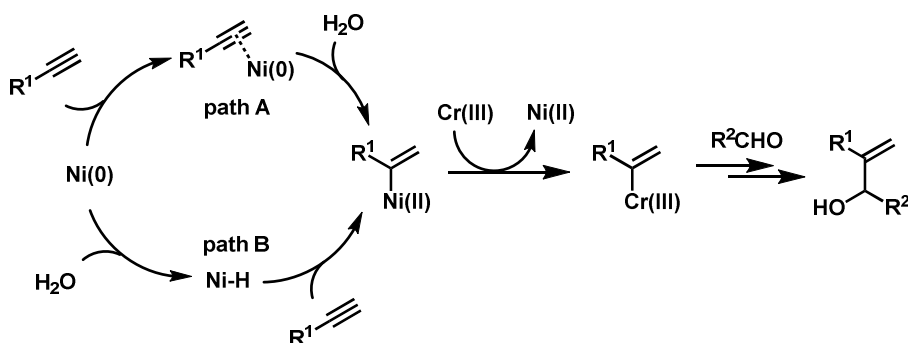
on nickelalactone **9**). The absence of the α -carboxylated product **6b**, again, indicates that nickelalactone always gave only β -carboxylated product, while α -carboxylated product might be formed via different pathway such as hydrometalation by Ni-H species.

Scheme 29



Regarding the involvement of Ni-H species in a reaction composition containing nickel complex and water, Takai³¹ in 2003 proposed that mechanism for Ni-catalyzed regioselective coupling of alkynes and aldehydes in the presence of CrCl₂ and water to form allylic alcohol. They proposed that the reaction proceeded through the formation of alkenyl chromium species generated by transmetalation from the alkenyl nickel species. They suggested that there are two possibilities for the formation of the alkenylnickel species, either by path A or B (Scheme 30). In path A, Ni(0) coordinates to alkyne followed by reaction with water, while in path B, Ni(0) reacts with water to form Ni-H species and then followed by the addition of Ni-H species to alkyne.

Scheme 30



Considering previous reports and the results of mechanistic study, the proposed reaction mechanism is shown in Figure 7. The reaction proceeded through the formation of alkenyl nickel **A** which is similar to that reported by Takai.³¹ At this stage, alkenyl nickel species **A** would be preferentially generated due to the coordination of X=O moiety on the nitrogen to nickel metal center and/or due to steric repulsion between a nickel complex and carbon substitution at the β -position at the addition step of a nickel hydride species to ynamide. Then, one electron reduction of **A** by Zn/MgBr₂ would generate Ni(I) species **B**, which would allow the insertion of CO₂ at α -position. Transmetalation of **C** with MgBr₂ would generate magnesium carboxylate **D** salt along with generation of another Ni(I) species. Finally, the Ni(0) would be regenerated by reduction with Zn.

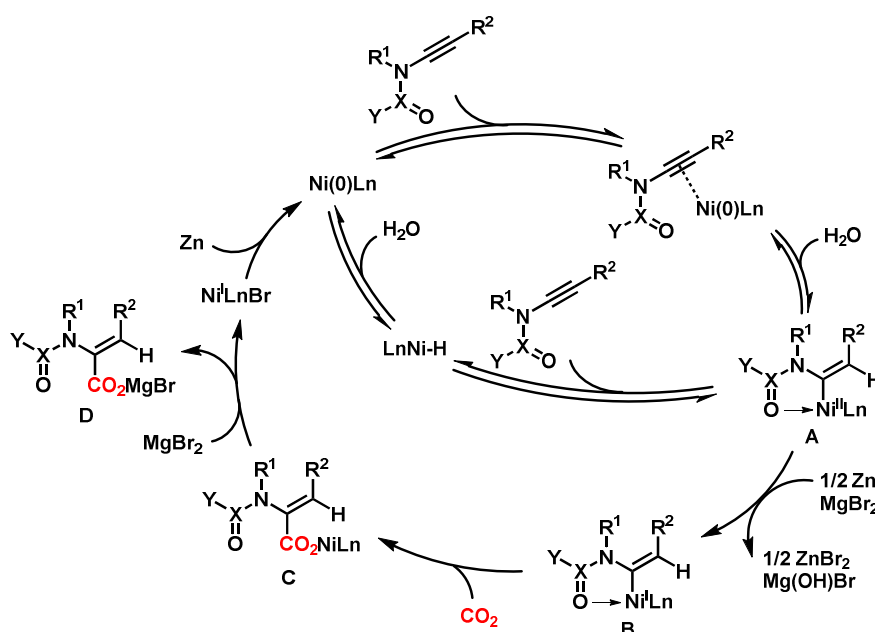
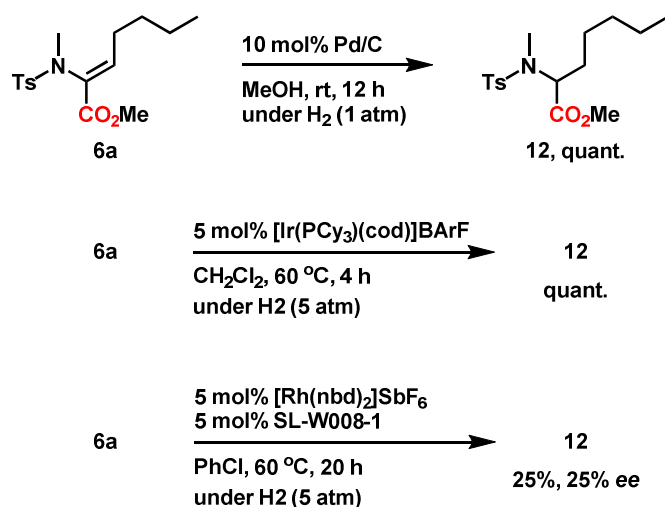


Figure 7. The proposed reaction mechanism for the formation of an α -carboxylated product.

2.6 Attempts for asymmetric hydrogenation

Although the α -carboxylated product **6a** was quantitatively hydrogenated with H₂ under racemic conditions in the presence of Pd/C or Crabtree's catalyst ([Ir(PCy₃)(cod)]BAR_F), the asymmetric hydrogenation by using the optimum conditions for β -carboxylated product **2a** did not proceed effectively. Both yield and enantioselectivity were low (Scheme 31).

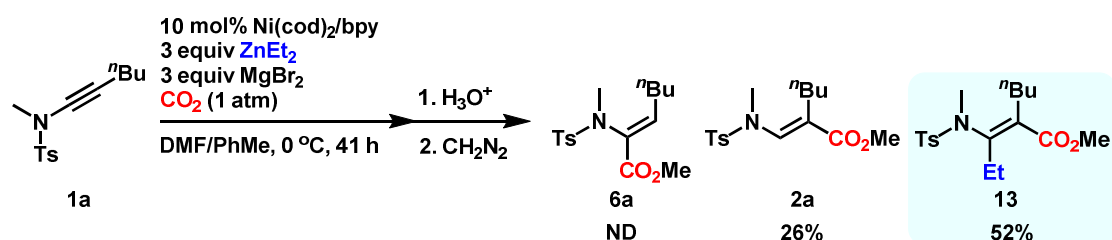
Scheme 31



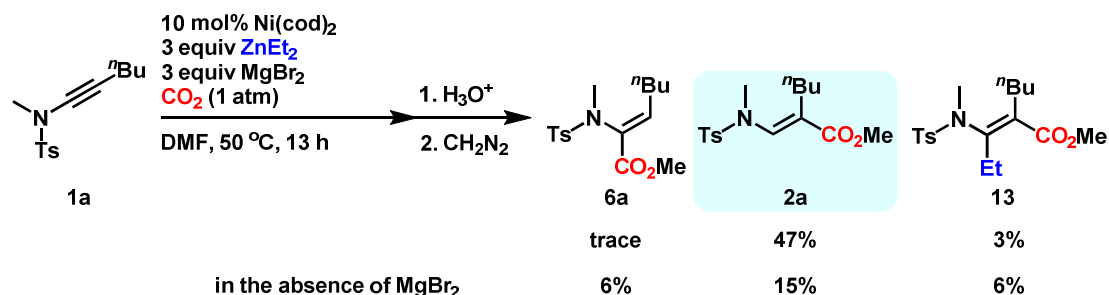
2.7 Attempts for Ni-catalyzed regioselective β -carboxylation

When zinc powder was replaced with diethyl zinc in the absence of water, surprisingly the carboxylation occurred only at β -position. The hydrocarboxylation product **2a** and carboxylation product **12a** having ethyl group were obtained in 26% and 52% yield, respectively (Scheme 32). By removing bpy from the reaction composition and increasing the reaction temperature to 50 °C, **2a** was afforded in 47% yield as a major product (Scheme 33). In the absence of MgBr₂, both yield and selectivity decreased, again showing the importance of the salt in this reaction. These result show high possibility to produce β -carboxylated product selectively in the presence of a catalytic amount of Ni(0).

Scheme 32



Scheme 33



Although the reaction mechanism is still unclear, it likely proceeds via formation of nickelalactone (Figure 8). Magnesium bromide accelerates the reaction by cleaving the Ni-O bond. Then the reaction with diethyl zinc followed by β -hydride elimination would generate an alkenyl-Ni-H species. Finally, reductive elimination would give magnesium carboxylate salt along with regeneration of Ni(0). It seems that the absence of ligand which strongly coordinate to nickel center such as bpy favor β -hydride elimination rather than direct reductive elimination, thus giving hydrocarboxylated product selectively. This can be explained by the easiness of β -hydrogen to approach the nickel center due to relatively low steric hindrance.³²

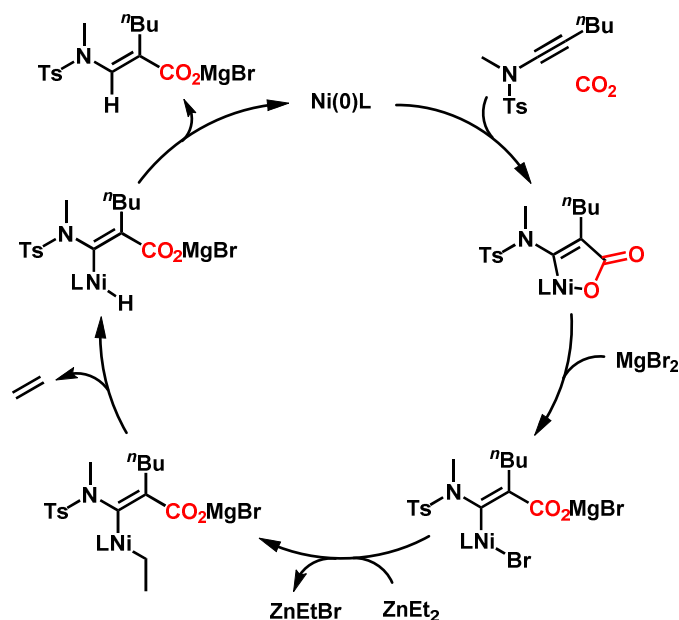


Figure 8. Plausible reaction mechanism for formation of β -carboxylated product.

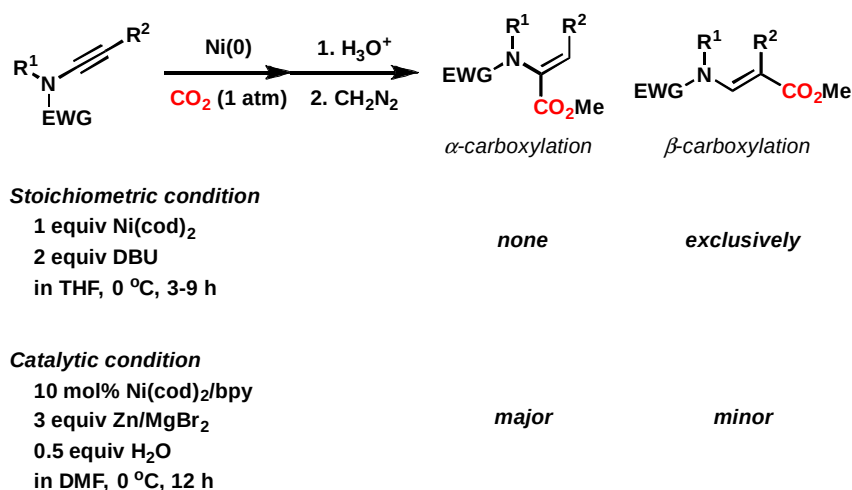
7. Summary of chapter 2

In summary, nickel-catalyzed hydrocarboxylation of ynamides with CO₂ and water has been developed under mild condition in the presence of Zn/MgBr₂. Contrary to previous study using a stoichiometric amount of Ni(0) complex as described in Chapter 1, this catalytic protocol mainly afforded α -carboxylated product as a major product. It is clarified that both zinc and magnesium bromide are the key factor for α -selectivity. This catalytic procedure is applicable to ynamides having various alkyl substituents and substituted aromatic ring on β -carbon, as well as some electron withdrawing groups on a nitrogen atom of ynamide.

Conclusions

Ni-mediated or -catalyzed fixation of CO₂ into unsaturated C-C bond is a promising method for one-carbon elongation reactions due to the inexpensiveness and abundance of CO₂. Hydrocarboxylation of ynamides in the presence of a stoichiometric amount of Ni(cod)₂ and DBU ligand in THF afforded α -substituted- β -aminoacrylate as a sole product. The reaction proceeded via oxidative cycloaddition of CO₂ and ynamide to Ni(0) to form nickelalactone intermediate in a regioselective manner. This method provides an easy access to the synthesis of unnatural optically active β -aminoacid derivatives after subsequent Rh-catalyzed asymmetric hydrogenation.³³

The catalytic protocol for regioselective hydrocarboxylation of ynamides was also developed by use of Ni(cod)₂/bpy as catalyst, magnesium bromide/zinc as additive/reducing agent and water as proton source. Interestingly, the selectivity of CO₂ incorporation was in contrast to that of the stoichiometric carboxylation. While hydrocarboxylation in stoichiometric condition gave β -carboxylated as a sole product, the catalytic protocol mainly afforded α -carboxylated product as a major product. Control experiments clarified the key factor for α -selectivity is a combination of zinc and magnesium bromide.³⁴



Experimental Section

General

All reactions were performed under an atmosphere of argon or nitrogen (1atm) unless otherwise stated. Solvents were purified under argon using The Ultimate Solvent System (Glass Counter Inc.) (THF, toluene, and DMF), and were distilled from CaH₂ (DMF). All other reagents were purified by standard procedures. Column chromatography was performed on silica gel 60 N (spherical, neutral, Kanto Chemical, Co. Inc., 45-50 μ m) with the indicated solvent as an eluent. Analytical thin-layer chromatography was performed on Silica gel 60 PF_{254u} (Merck).

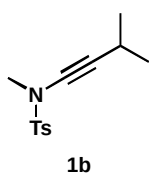
Infrared (IR) spectra were recorded on a JASCO FT/IR 4100 infrared spectrometer. ¹H NMR spectroscopy was recorded on JEOL ECA500 (500 MHz) or ECX400P (400 MHz) NMR spectrometer. Chemical shifts are reported in ppm from the solvent resonance as an internal standard (CDCl₃: δ = 7.26 ppm). NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. ¹³C NMR spectroscopy was recorded on JEOL ECA500 (125 MHz) or ECX400P (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from the internal reference (CDCl₃: δ = 77.00 ppm). Mass spectra were obtained on JEOL JMS-T100GCv mass spectrometer. Optical rotations were measured on a Jasco P-1030 digital polarimeter at the sodium D line (589 nm). Chiral HPLC analyses were carried out using a Jasco PU-980 and using indicated chiral column. Autoclave (Portable reactor, TVS-1, 10 cm³) was purchased from TAIATSU TECHNO.

Chapter 1

Preparation of ynamides

Ynamides except for new one **1b** were prepared by previously reported methods³⁵⁻³⁸.

Ynamide **1b**³⁶

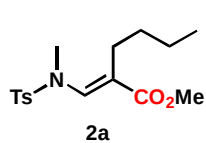


To a solution of CuCl_2 (135.4 mg; 1.0 mmol), N-methyltosylamide (4.66 g; 25.2 mmol), and Na_2CO_3 (1.07 g; 10.0 mmol) in toluene (45 mL) was added pyridine (0.81 mL; 10.0 mmol) at room temperature. The mixture was stirred under oxygen atmosphere and the temperature was raised to 70 °C. A solution of 3-methyl-1-butyne (0.52 mL; 5.0 mmol) in toluene (5 mL) was added slowly for over 4 hours at 70 °C, then the stirring was continued for 16 h at the same temperature. After cooled to room temperature, the reaction mixture was filtered through a pad of Celite and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give **1c** (1.075 g, 85%) as white solid. ^1H NMR (500 MHz, CDCl_3): δ 1.14 (d, J = 6.9 Hz, 6H), 2.46 (s, 3H), 2.58-2.64 (m, 1H), 3.00 (s, 3H), 7.35 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 20.3, 21.6, 23.1, 39.4, 73.9, 74.5, 127.9, 129.5, 133.0, 144.4; IR (film, CHCl_3): 2246, 2053, 1364, 1168 cm^{-1} ; EI-HRMS calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_2\text{S}$ 251.09800, found 251.09775.

Ni-mediated carboxylation of ynamides

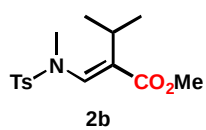
General procedure: $\text{Ni}(\text{cod})_2$ (99.0 mg, 0.360 mmol) was weighed into a flame-dried round bottom flask in a glove box (argon atmosphere). Then, the flask was taken out of the glove box, and THF (2.9 mL) and DBU (0.11 mL, 0.736 mmol) were added at 0 °C to the flask. After removal of argon gas in the flask by performing a freeze-pump-thaw procedure (3 times), the flask was backfilled with CO_2 gas using a balloon. To the resulting pale yellow suspension was slowly added a solution of ynamide **1a** (106.1 mg, 0.400 mmol) in THF (2.9 mL) over a period of 2 hours by a syringe pump at 0 °C. After addition of the solution of ynamide, the reaction mixture was stirred at the same temperature for 2 hours. To the mixture was added saturated 10% aqueous solution of HCl at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4 , and concentrated. The residue was treated with diazomethane, which was generated by treatment of 1-methyl-3-nitro-1-nitrosoguanidine with 40% aqueous KOH, in Et_2O at 0 °C. After the mixture had been concentrated, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 8/1) to afford **2a** (89.4 mg, 76%) as colorless oil.

Compound **2a** (Scheme 12)



^1H NMR (500 MHz, CDCl_3): δ 0.78 (t, J = 7.0 Hz, 3H), 1.16-1.26 (m, 4H), 2.28 (t, J = 7.5 Hz, 2H), 2.37 (s, 3H), 3.05 (s, 3H), 3.68 (s, 3H), 7.28 (d, J = 8.0 Hz, 2H), 7.52 (s, 1H), 7.63 (d, J = 8.0 Hz, 2H); ^{13}C NMR (500 MHz, CDCl_3) δ 13.8, 21.5, 22.6, 25.8, 32.1, 35.7, 51.8, 119.6, 127.2, 127.2, 129.9, 129.9, 134.2, 137.1, 144.3, 168.5; IR (film, CHCl_3) 2956, 1708, 1629 cm^{-1} ; EI-LRMS m/z 325 (M^+); EI-HRMS calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_4\text{S}$ 325.1348, found 325.1348.

Compound **2b** (Scheme 12)



Following the general procedure using $\text{Ni}(\text{cod})_2$ (55.0 mg, 0.200 mmol), DBU (60 μl , 0.401 mmol), and **1b** (51.7 mg, 0.206 mmol) in THF (3.0 ml) to afford **2b** (40.2 mg, 63%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 1.17 (d, J = 6.9 Hz, 6H), 2.43 (s, 3H), 2.96 (s, 3H), 3.03-3.09 (m, 1H), 3.72 (s, 3H), 6.97 (s, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 20.6, 21.5, 27.1, 37.7, 51.4, 127.5, 129.9, 132.9, 133.8, 136.5, 144.2, 167.1; IR (neat): 1714 cm^{-1} ; EI-HRMS calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_4\text{S}$ 311.11913, found 311.11880.

Compound **2l** (Scheme 13)

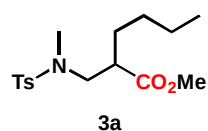
Following the general procedure using $\text{Ni}(\text{cod})_2$ (54.9 mg, 0.200 mmol), DBU (60 μl , 0.401 mmol), and **1l** (68.1 mg, 0.199 mmol) in THF (mL) to afford **2l** (49.9 mg, 62%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 0.74 (t, J = 7.4 Hz, 3H), 0.93-1.01 (m, 2H), 1.04-1.13 (m, 2H), 2.19 (t, J = 8.0 Hz, 2H), 2.44 (s, 3H), 3.71 (s, 3H), 4.47 (s, 2H), 7.07 (s, 1H), 7.19-7.30 (m, 5H), 7.33 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.8, 21.6, 22.7, 26.5, 31.2, 51.9, 53.2, 127.4, 127.7, 127.8, 128.6, 128.8, 129.9, 135.1, 135.2, 135.6, 144.2, 168.0; IR (film, CHCl_3): 1713 cm^{-1} ; ESI-HRMS calcd for $\text{C}_{22}\text{H}_{27}\text{O}_4\text{NNaS}$ 424.15530, found 424.15564.

Rh-catalyzed asymmetric hydrogenation

General procedure: $[\text{Rh}(\text{nbd})_2]\text{SbF}_6$ (0.4 mg, 0.765 μmol) and SL W008-1 (0.7 mg, 0.743 μmol) were added to a flame-dried 10 mL test tube. The test tube was purged with H_2 . Chlorobenzene (0.5 mL) was added to the test tube, and the resulting mixture stirred for 10 min under an atmosphere of H_2 (1 atm). To the mixture was added a solution of **13a** (24.3 mg, 0.075 mmol) in chlorobenzene

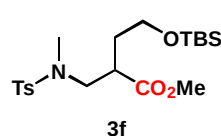
(0.8 mL). The test tube was placed in an autoclave and pressurized under an H₂ atmosphere (5 atm). The reaction mixture was stirred at 60 °C for 20 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to afford **16a** (25.0 mg, quant) as a colorless oil.

Compound **3a** (Scheme 14)



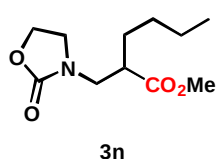
Following the general procedure using **2a** (15.6 mg, 0.046 mmol), [Rh(nbd)₂]SbF₆ (1.2 mg, 2.3 μmol), and SL W008-1 (2.2 mg, 2.3 μmol) in chlorobenzene (1.0 mL) to afford **3a** (mg, quant.) as colorless oil. The enantiomeric excess was determined to be 89% by HPLC analysis with a DAICEL CHIRALCEL AS-H [eluent: hexane/2-propanol = 95/5, flow rate: 0.5 mL/min, detector: UV (254 nm)]: *t_R*(major) = 23.2 min; *t_R*(minor) = 26.6 min. [α]_D²⁴ -14.5 (c 0.760, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.36-1.19 (m, 4H), 1.63-1.49 (m, 2H), 2.43 (s, 3H), 2.72 (s, 3H), 2.72 (m, 1H), 3.16-3.08 (m, 2H), 3.69 (s, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 13.8, 21.5, 22.5, 29.1, 29.7, 36.0, 45.1, 51.8, 52.1, 127.5 (2C), 129.7 (2C), 134.2, 143.4, 174.8; IR (neat) 1736, 1598, 1344, 1164 cm⁻¹; EI-LRMS *m/z* 172 [(M-Ts)⁺], 198, 155, 91; EI-HRMS calcd for C₉H₁₈NO₂ 172.13375, found 172.13385.

Compound **3f** (Scheme 14)



Following the general procedure using **13f** (15.6 mg, 0.046 mmol), [Rh(nbd)₂]SbF₆ (1.2 mg, 2.3 μmol), and SL W008-1 (2.2 mg, 2.3 μmol) in chlorobenzene (1.0 mL). The enantiomeric excess was determined to be 91% by HPLC analysis with a DAICEL CHIRALCEL AS-H [eluent: hexane/2-propanol = 98/2, flow rate: 0.5 mL/min, detector: UV (254 nm)]: *t_R*(major) = 14.7 min; *t_R*(minor) = 17.7 min. [α]_D²¹ -5.234 (c 0.564, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 0.03 (s, 6H), 0.87 (s, 9H), 1.90-1.76 (m, 2H), 2.43 (s, 3H), 3.71 (s, 3H), 2.89 (m, 1H), 3.11-3.20 (m, 2H), 3.59-3.66 (m, 2H), 3.68 (s, 3H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ -5.5 (2C), 18.3, 21.5, 25.9 (3C), 32.5, 35.6, 41.5, 51.8, 52.0, 60.5, 127.5 (2C), 129.7 (2C), 134.2, 143.4, 174.4; IR (neat) 1738, 1599, 1346, 1164 cm⁻¹; EI-LRMS *m/z* 372 [(M-^tBu)⁺], 198, 155, 91; EI-HRMS calcd for C₁₆H₂₆NO₅Si 372.13009, found 372.12979.

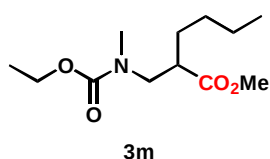
Compound **3n** (Scheme 15)



3n

Following the general procedure using **2n** (43.3 mg, 0.191 mmol), [Rh(nbd)₂]SbF₆ (5.0 mg, 9.6 μmol), and SL W008-1 (9.0 mg, 9.6 μmol) in chlorobenzene (2.7 mL) to give **3n** (42.0 mg, 96%) as a colorless oil. The enantiomeric excess was determined to be 81% by HPLC analysis with DAICEL CHIRALCEL OJ-H + OD-H [eluent: hexane/2-propanol = 95/5, flow rate: 0.4 mL/min, detector: UV (210 nm)]: $t_R(\text{major}) = 69.2$ min; $t_R(\text{minor}) = 75.2$ min. $[\alpha]_D^{24} -1.860$ (c 0.600, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 0.86 (t, $J = 7.0$ Hz, 3H), 1.21-1.34 (m, 4H), 1.42-1.51 (m, 1H), 1.55-1.56 (m, 1H), 2.69 (tt, $J = 8.6, 4.0$ Hz, 1H), 3.36-3.44 (m, 2H), 3.48-3.59 (m, 2H), 3.68 (s, 3H), 4.27 (tt, $J = 8.6, 3.9$ Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 13.8, 22.4, 29.1, 29.6, 44.4, 45.4, 46.3, 51.8, 61.8, 158.4, 174.9; IR (neat) 1736 cm⁻¹; EI-LRMS m/z 230 [(M+H)⁺], 170, 100, 56; EI-HRMS calcd for C₁₁H₁₉NO₄ 229.13141, found 229.13117.

Compound **3m** (Scheme 15)



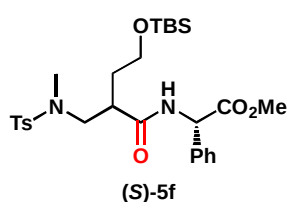
3m

Following the general procedure using **2m** (51.5 mg, 0.212 mmol), [Rh(nbd)₂]SbF₆ (5.6 mg, 10.7 μmol), and SL W008-1 (10.1 mg, 10.7 μmol) in chlorobenzene (3.0 mL) to give **3m** (37.5 mg, 72%) as a colorless oil. The enantiomeric excess was determined to be 5% by HPLC analysis with DAICEL CHIRALCEL OJ-H + OD-H [eluent: hexane/2-propanol = 98/2, flow rate: 0.3 mL/min, detector: UV (210 nm)]: $t_R(\text{major}) = 23.2$ min; $t_R(\text{minor}) = 22.3$ min. ¹H NMR (500 MHz, CDCl₃) δ 0.87 (s, 3H), 1.22-1.31 (m, 4H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.36-1.46 (br, 1H), 1.52-1.61 (m, 1H), 2.63-2.77 (br, 1H), 2.86 (d, $J = 10.9$, 3H), 3.28-3.51 (m, 2H), 3.66 (s, 3H), 4.10 (q, $J = 7.1$ Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 13.8, 14.6, 22.5, 29.2, 29.7, 35.4, 44.8, 50.9, 51.7, 61.3, 156.4, 175.3; IR (neat) 1738, 1706 cm⁻¹; EI-LRMS m/z 245 (M⁺), 116, 44; EI-HRMS calcd for C₁₂H₂₃NO₄ 245.16271, found 245.16244.

Determination of the absolute configuration

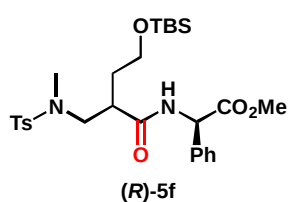
The absolute configuration of the C2 position of **3f** was determined using Kusumi's PGME method by analyzing the positive and negative distribution patterns of the chemical shift difference between (*S*)-**5f** and (*R*)-**5f**. The same method was used for determination of the absolute configuration of the C2 position of **3a**.

Preparation of (S)-5f (Scheme 17)



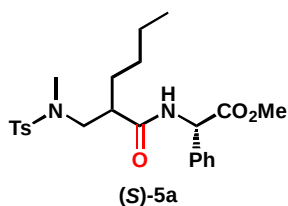
To a solution of **3f** (48.3 mg, 0.11mmol) in 1,2-dichloroethane (2.8 mL), was added trimethyltinhydroxide (304.9 mg, 1.69mmol). The mixture was stirred at 80 °C for 83 hours. After cooled to room temperature, the solvent was evaporated and the residue was taken up in AcOEt. The solution was washed with 0.01 M aqueous solution of KHSO₄, dried over Na₂SO₄, and concentrated to give **4f**, which was used for the next reaction without purification. To a solution of the crude **4f** in DMF (1.0 mL) were successively added (S)-PGME (25.6 mg, 0.13mmol), PyBOP (66.1 mg, 0.13mmol), HOBT (17.2 mg, 0.13mmol) and 4-methylmorpholine (40μL, 0.37mmol) at 0 °C, and the mixture was stirred at room temperature for 23 hours. After the mixture was diluted with AcOEt, the organic layer was washed with 10% aqueous solution of HCl, and saturated aqueous solution of NaHCO₃, dried over Na₂SO₄ and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 3/1) to give (S)-5f (40.4 mg, 64% in 2 steps) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 0.06 (s, 6H), 0.88 (s, 9H), 1.75 (dd, *J* = 12.0, 6.3 Hz, 2H), 2.41 (s, 3H), 2.53 (s, 3H), 2.87-2.94 (m, 2H), 3.27 (dd, *J* = 17.2, 9.7 Hz, 1H), 3.72 (s, 3H), 3.70-3.81 (m, 2H), 5.50 (d, *J* = 6.9 Hz, 1H), 6.92 (d, *J* = 6.9 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.32-7.41 (m, 5H), 7.63 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ -5.4, 18.2, 21.4, 25.9, 33.1, 37.0, 43.1, 52.6, 52.7, 56.8, 60.3, 127.4, 127.5, 128.5, 128.9, 129.6, 134.0, 136.1, 143.4, 170.9, 173.2; IR (neat) 1748 cm⁻¹; EI-LRMS *m/z* 547 [(M-CH₃)⁺], 505, 407, 198, 155, 91; EI-HRMS calcd for C₂₇H₃₉N₂O₆SSi 547.2298, found 547.2294.

Preparation of (R)-5f. Similar to the synthesis of (S)-5f from **3f**, (R)-5f (7.5 mg, 24% in 2 steps)



was obtained from **3f** (23.5 mg, 0.05 mmol) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 0.00 (s, 6H), 0.85 (s, 9H), 1.66 (dq, *J* = 18.7, 4.7 Hz, 1H), 1.77 (dq, *J* = 18.7, 4.8 Hz, 1H), 2.43 (s, 3H), 2.76 (s, 3H), 2.89 (m, 1H), 3.01 (dd, *J* = 13.8, 8.3 Hz, 1H), 3.27 (dd, *J* = 13.8, 6.3 Hz, 1H), 3.44 (td, *J* = 9.9, 4.2 Hz, 1H), 3.59 (m, 1H), 3.73 (s, 3H), 5.54 (d, *J* = 6.9 Hz, 1H), 6.88 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.33-7.38 (m, 5H), 7.68 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ -5.4, 18.2, 21.5, 25.9, 33.2, 36.7, 42.5, 52.4, 52.7, 56.7, 60.1, 127.3, 127.5, 128.6, 129.0, 129.7, 134.1, 136.4, 143.4, 170.9, 172.9; IR (neat) 1747 cm⁻¹; EI-LRMS *m/z* 547 [(M-CH₃)⁺], 505, 407, 198, 155, 91; EI-HRMS calcd for C₂₇H₃₉N₂O₆SSi 547.2298, found 547.2294.

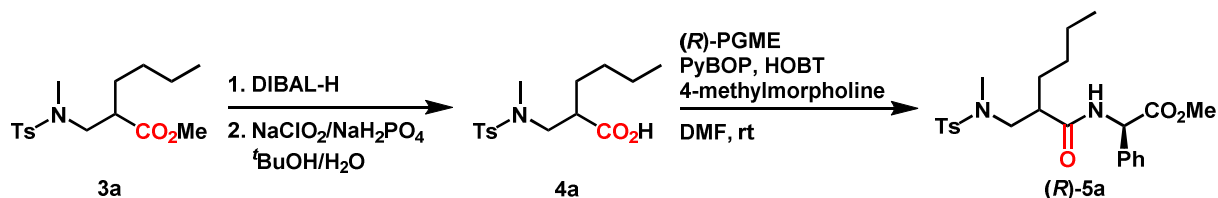
Preparation of (S)-5a



To a solution of **3a** (33.0 mg, 0.10 mmol) in 1,2-dichloroethane (2.3 mL), was added trimethyltinhydroxide (273.5 mg, 1.50 mmol), and the mixture was stirred at 80 °C for 89 hours. After the mixture was cooled to room temperature, volatiles were evaporated and the residue was taken up in AcOEt. The solution was washed with 0.01 M KHSO₄ aqueous solution

three times, dried over Na₂SO₄, and concentrated. Similar to the synthesis of **18** from **17**, (**S**)-**5a** (31.3 mg, 67% in 2 steps) was obtained from the crude carboxylic acid **4a** (34.6 mg) as a colorless solid. IR (film, CHCl₃) 1746 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.90 (t, *J* = 6.9 Hz, 3H), 1.34-1.24 (m, 4H), 1.43-1.36 (m, 1H), 1.60-1.51 (m, 1H), 2.41 (s, 3H), 2.45 (s, 3H), 2.68-2.64 (m, 1H), 2.80 (dd, *J* = 25.5, 11.2 Hz, 1H), 3.19 (dd, *J* = 14.3, 5.2 Hz, 1H), 3.74 (s, 3H), 5.59 (d, *J* = 6.9 Hz, 1H), 6.81 (d, *J* = 6.9 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 6.9 Hz, 1H), 7.37 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.42 (d, *J* = 6.9 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 13.8, 21.4, 22.6, 29.1, 30.0, 37.3, 48.0, 52.8, 53.2, 56.5, 127.3, 127.4, 128.4, 128.9, 129.7, 133.9, 136.3, 143.4, 171.0, 173.4; EI-LRMS *m/z* 401[(M-CO₂CH₃)⁺], 198, 155, 140, 91, 77; EI-HRMS calcd for C₂₂H₂₉N₂O₃S 401.1899, found 401.1889.

Preparation of (R)-5a



To a solution of **3a** (33.0 mg, 0.10 mmol) in CH₂Cl₂ (0.5 mL) was added a solution of DIBAL-H in hexane (1.02 M, 0.11 mmol, 0.11 mL) at -78 °C, and the mixture was stirred at the same temperature for 1 hour. To the mixture was added saturated NH₄Cl aqueous solution, and the aqueous layer was extracted with AcOEt. The organic layer was dried over Na₂SO₄, and concentrated. The crude product was dissolved in *tert*-butanol (1.9 mL), and 2-methyl-2-butene (0.5 mL) was added to the solution. To the mixture was added a mixed solution of NaClO₂ (77.9 mg, 0.86 mmol) and NaH₂PO₄ (77.5 mg, 0.65 mmol) in H₂O (0.9 mL), and the mixture was stirred at room temperature for 9 hours. After acidification with 10% HCl aqueous solution, the aqueous layer was extracted with AcOEt. The organic layer was dried over Na₂SO₄ and concentrated. The crude product was dissolved in DMF (0.5 mL), (*R*)-phenylglycine methyl ester (21.5 mg, 0.11 mmol), PyBOP (55.4 mg, 0.11 mmol) and HOBT (14.4 mg, 0.11 mmol) were added to the DMF solution. To the mixture was added

4-methylmorpholine (34 μ L, 0.31mmol) at 0 °C, and the mixture was stirred at room temperature for 16 hours. After the mixture was diluted with AcOEt, the resulting organic layer was washed by 10% HCl aqueous solution and saturated NaHCO₃ aqueous solution, dried over Na₂SO₄, and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to afford the **(R)-5a** (13.4 mg, 29% in 3 steps) as an amorphous solid. IR (film, CHCl₃) 1742 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 0.81 (t, *J* = 7.2 Hz, 3H), 1.18-1.12 (m, 2H), 1.24-1.20 (m, 2H), 1.46-1.39 (m, 1H), 1.57-1.49 (m, 1H), 2.43 (s, 3H), 2.77 (s, 3H), 2.65-2.59 (m, 1H), 2.99 (dd, *J* = 14.3, 9.2 Hz, 1H), 3.15 (dd, *J* = 13.7, 5.7 Hz, 1H), 3.74 (s, 3H), 5.55 (d, *J* = 6.9 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.41-7.34 (m, 5H), 7.68 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 13.8, 21.5, 22.6, 29.2, 30.2, 37.4, 47.5, 52.8, 52.9, 56.7, 127.3, 127.5, 128.6, 129.0, 129.7, 134.0, 136.3, 143.5, 171.0, 173.3; EI-LRMS *m/z* 401 [(M-CO₂CH₃)⁺], 198, 155, 140, 91, 77; EI-HRMS calcd for C₂₂H₂₉N₂O₃S 401.1899, found 401.1892.

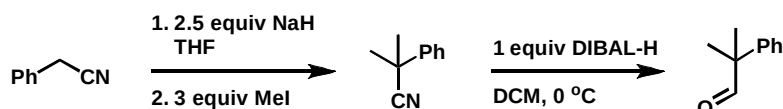
Chapter 2

Preparation of Ynamides

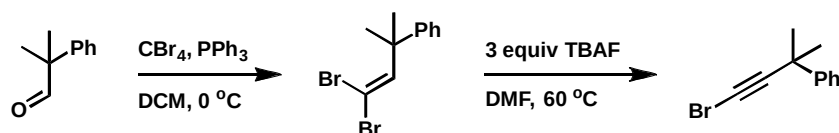
Ynamides except for new ones **1q**, **1t** and **1w** were prepared by previously reported methods³⁵⁻³⁸.

Ynamide **1q**³⁵

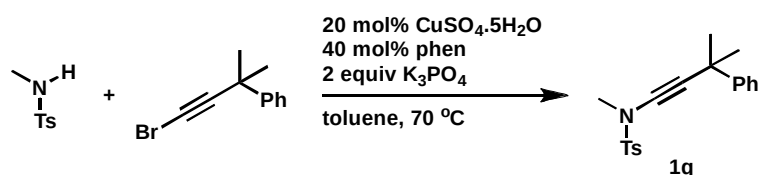
Step 1:



Step 2:



Step 3:



[Step 1] 2-methyl-2-phenyl-propanenitrile was prepared according to the method reported by Miura *et al.*³⁷ To a mixture of sodium hydride (55 wt%, 1.60 g, 36.7 mmol) and THF (26 mL) was added benzyl cyanide (1.73mL, 15.0 mmol) at 0 °C. The resulting solution was stirred for 1.5 h at room temperature. Iodomethane (2.8 mL, 45.0 mmol) was then added at 0 °C and the resulting solution was then stirred for an additional 16 h. The mixture was quenched with water, extracted with dichloromethane (DCM), dried over Na₂SO₄ and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give 2-methyl-2-phenylpropanenitrile in a quantitative yield.

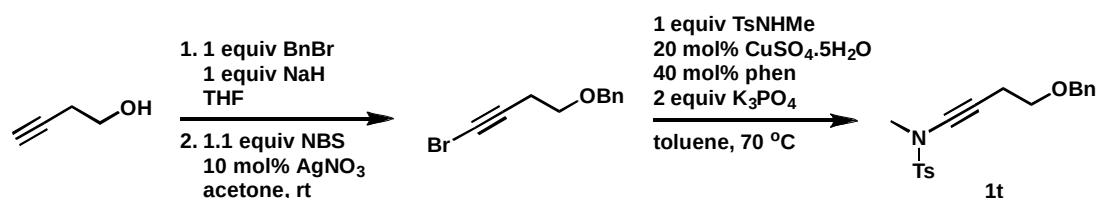
To a solution of 2-methyl-2-phenylpropanenitrile (15.0mmol) in DCM (60 mL) at 0°C was added DIBAL-H (1.03 M in hexane, 15.5 mL, 16.0 mmol). After stirring for 5 min, 1 M HCl was added. The phases were separated and the aqueous media was extracted with DCM. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated. The crude aldehyde was used in the next step without further purification.

[Step 2] To a solution of Ph_3P (15.74 g, 60.01 mmol) in DCM (75 mL) at 0 °C was added CBr_4 (9.95 g, 30.00 mmol) and the solution was stirred for 30 min. A solution of 2-methyl-2-phenylpropanal from previous step in DCM (3 mL) was added and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was then quenched by addition of saturated NaHCO_3 . The layers were separated and the aqueous phase was extracted with DCM. The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated. Hexane was then added to the residue and the precipitated was filtered off *via* filtration through a plug of silica gel (washed with hexane/ Et_2O mixtures). The dibromoolefin (1.43 g, 31% yield) was used in the next step without further purification.⁴⁰

To a solution of dibromoolefin in DMF (24 mL) was added TBAF hydrate (3.68 g, 14.07 mmol). The temperature was raised to 60 °C and the mixture was stirred for 2 h. After diluted with Et_2O , the mixture was washed with water several times, dried over anhydrous Na_2SO_4 , and concentrated. The crude product was used in the next step without further purification.⁴¹

[Step 3] To a solution of (4-bromo-2-methylbut-3-yn-2-yl)benzene in toluene (24 mL) was added $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.23 g, 0.92 mmol), 1,10-phenanthroline (0.34 g, 1.89 mmol), K_3PO_4 (1.99 g, 9.38 mmol) and N-methyl-tosylamide (0.87 g, 4.70 mmol). The mixture was stirred for 11 h at 70 °C. After cooled to room temperature, the mixture was filtered through a pad of Celite, washed with Et_2O , and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/ AcOEt = 8/1) to give ynamide **1q** as a white to pale yellow solid (544.8 mg, 36% yield). ^1H NMR (500 MHz, CDCl_3): δ 1.57 (s, 6H), 2.47 (s, 3H), 3.08 (s, 3H), 7.24 (tt, J = 7.2 Hz, 1.6 Hz, 1H), 7.30-7.50 (m, 6H), 7.79 (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 21.6, 31.7, 35.8, 39.4, 75.0, 76.9, 125.5, 126.3, 127.9, 128.2, 129.6, 133.0, 144.5, 146.9.

Ynamide **1t**³⁵



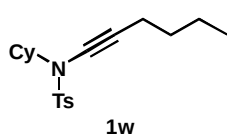
To a mixture of NaH (55 wt%, 219.6 mg, 5.0 mmol) and THF (10 mL) was added but-3-yn-1-ol dropwise at 0 °C and stirred for 20 minutes. Benzyl bromide solution in THF was added at the same temperature, and the resulting solution was stirred at room temperature for 13 h. The mixture was diluted with AcOEt , poured into water, extracted with AcOEt , dried over anhydrous Na_2SO_4 , and concentrated. The crude product was then purified by flash column

chromatography on silica gel (hexane/AcOEt = 10/1) to give benzyl-protected product (748.0 mg, 93% yield).

To a solution of benzyl-protected product (736.2 mg, 4.595 mmol) in acetone (9 mL) was added NBS (0.90 g, 5.06 mmol) and AgNO₃ (78.0 mg, 0.46 mmol). The mixture was stirred at room temperature for 1.5 h, and then concentrated in vacuo. The mixture was then diluted with Et₂O, filtered by a pad of Celite, and concentrated. The crude product was then purified by flash column chromatography on silica gel using hexane to give bromoalkyne product (775.6 mg, 71%).

To a solution of bromoalkyne product (761.6mg, 3.19 mmol) in toluene (16 mL) were added 1,10-phenanthroline (229.6 mg, 1.27 mmol), CuSO₄·5H₂O (159.0 mg, 0.64 mmol), K₃PO₄ (1.35 g, 6.36 mmol) and N-methyltosylamide (590.0mg, 3.19 mmol) at room temperature. The mixture was stirred and the temperature was raised to 70 °C. After 70 h, the mixture was cooled to room temperature, filtered through a pad of Celite and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give **1t** (901.2 mg, 82%) as colorless oil. ¹H NMR(400 MHz, CDCl₃): δ 2.42 (s, 3H), 2.57 (t, *J* = 6.8 Hz, 2H), 3.01 (s, 3H), 3.57 (t, *J* = 7.0 Hz, 2H), 4.54 (s, 2H), 7.27-7.38 (m, 7H), 7.77 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 19.7, 21.5, 39.1, 65.4, 68.6, 72.8, 75.6, 127.5, 127.6, 127.7, 128.3, 129.6, 133.0, 138.0, 144.4; IR (film, CHCl₃): 2257, 2058, 1363, 1172 cm⁻¹; EI-HRMS calcd for C₁₂H₁₄NO 188.10754, found 188.10737.

Ynamide **1w**³⁵



1w

To a solution of 1-bromohex-1-yne (0.703 g, 4.365 mmol) in toluene (22 mL) were added 1,10-phenanthroline (314.6 mg, 1.746 mmol), CuSO₄·5H₂O (217.9 mg, 0.87mmol), K₃PO₄ (1.85 g, 8.72mmol) and N-cyclohexyl-4-methylbenzenesulfonamide (1.11 g, 4.37 mmol) at room temperature. The mixture was stirred and the temperature was raised to 110 °C. After 23 h, the mixture was cooled to room temperature, filtered with a pad of Celite and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give **1w** (400.9 mg, 28%) as colorless oil. ¹H NMR(500 MHz, CDCl₃): δ 0.89 (t, *J* = 7.2 Hz, 3H), 0.96-1.75 (m, 14H), 2.28 (t, *J* = 7.2, 2H), 2.43 (s, 3H), 3.72 (tt, *J* = 11.7, 4.1 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 13.5, 18.2, 21.6, 21.8, 24.9, 25.4, 30.9, 31.1, 58.9, 70.4, 71.6, 127.3, 129.5, 136.4, 143.9; IR (neat): 2246, 2044, 1363, 1169 cm⁻¹; EI-HRMS calcd for C₁₉H₂₇NO₂S 333.17625, found 333.17609.

Nickel-Catalyzed Hydrocarboxylation of Ynamides

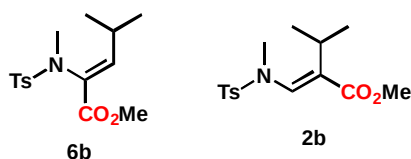
General procedure: Ni(cod)₂ (11.0 mg, 0.040mmol), 2,2'-bipyridine (6.3 mg, 0.040 mmol), Zn (78.5 mg, 1.20mmol), and MgBr₂ (221.0 mg, 1.20 mmol) were weighed into a flame-dried round bottom flask in a glove box (argon or nitrogen atmosphere). Then, the flask was taken out of the glove box, and DMF (2.8 mL) was added at 0 °C to the flask. To the resulting suspension was added a solution of ynamide **1a** (106.2 mg, 0.40 mmol) and water (3.6 μL, 0.20mmol) in DMF (2.9 mL) at the same temperature via cannulation. After removal of argon/nitrogen gas in the flask by performing a freeze-pump-thaw procedure (3 times), the flask was backfilled with CO₂ gas using a balloon. The reaction mixture was stirred at 0 °C for 12 hours. To the mixture was added 10% aqueous solution of HCl at 0 °C. The resulting solution was extracted with diethyl ether several times. The combined organic layer was washed with water, dried over Na₂SO₄, and concentrated. The residue was treated with diazomethane, which was generated by treatment of 1-methyl-3-nitro-1-nitrosoguanidine with 40% aqueous KOH, in Et₂O at 0 °C. After the mixture had been concentrated, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 10/1) to give a mixture of carboxylated product, **6a** and **2a** (105.0 mg, 78% yield (83/17)). The regioisomer mixture was then separated by second flash column chromatography on silica gel (toluene/hexane/ether = 10/1/1) to give **6a** as colorless oil.

Compound 6a. ¹H NMR(500 MHz, CDCl₃): δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.34 (td, *J* = 14.7, 7.3 Hz, 2H), 1.42-1.48 (m, 2H), 2.38 (q, *J* = 8.2 Hz, 2H), 2.42 (s, 3H), 3.00 (s, 3H), 3.52 (s, 3H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 13.8, 21.5, 22.6, 28.6, 30.2, 37.0, 51.8, 127.7, 129.2, 130.3, 136.3, 143.2, 149.7, 164.4; IR (film, neat): 1725 cm⁻¹; EI-HRMS calcd for C₁₆H₂₃NO₄S 325.13478, found 325.13404.

Compound 6p and 2p. Following the general procedure using **1p** (123.8 mg, 0.395 mmol), Ni(cod)₂ (21.7 mg, 0.079 mmol), bpy (12.4 mg, 0.079mmol), Zn (77.5 mg, 1.19mmol), MgBr₂ (218.2 mg, 1.19mmol), and water (3.6μL, 0.2mmol) in DMF (5.6 mL) to afford a regioisomeric mixture of **6p** and **2p** (106.7 mg, 72% yield (79/21)) as colorless oil. Second flash column chromatography on silica gel (toluene/hexane/ether = 5/1/1) was performed to give **6p** as colorless oil. Characterization of **6p**: ¹H NMR (500 MHz, CDCl₃): δ 2.41 (s, 3H), 2.73 (t, *J* = 6.8 Hz, 2H), 2.77-2.85 (m, 5H), 3.49 (s, 3H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.16-7.32 (m, 7H), 7.68 (d, *J* =

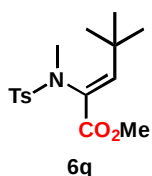
8.6 Hz, 2H) ; ^{13}C NMR (125 MHz, CDCl_3): δ 21.5, 30.6, 34.0, 36.8, 51.80, 51.79, 126.2, 127.7, 128.4, 129.2, 130.7, 136.1, 140.7, 143.2, 148.2, 164.2; IR (film, CHCl_3): 1724 cm^{-1} ; ESI-HRMS calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_4\text{NaS}$ 396.12400, found 396.12363. Characterization of **2p**: ^1H NMR(500 MHz, CDCl_3): δ 2.44 (s, 3H), 2.68 (s, 4H), 2.96 (s, 3H), 3.77 (s, 3H), 7.11-7.25 (m, 5H), 7.34 (d, $J = 8.0\text{ Hz}$, 2H), 7.60 (s, 1H), 7.68 (d, $J = 8.6\text{ Hz}$, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 21.6, 28.4, 35.6, 35.8, 52.0, 118.6, 126.1, 127.3, 128.37, 128.41, 130.0, 134.3, 137.8, 141.2, 144.5, 168.4; IR (neat): 1708 cm^{-1} ; EI-HRMS calcd for $\text{C}_{20}\text{H}_{23}\text{NO}_4\text{S}$ 373.13478, found 373.13403.

Compound 6b and 2b. Following the general procedure using **1b** (99.6 mg, 0.40mmol), $\text{Ni}(\text{cod})_2$ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.20 mmol), MgBr_2 (221.0 mg, 1.20 mmol) and water (3.6 μL , 0.2mmol) in DMF (5.7 mL) to afford regioisomeric mixture of

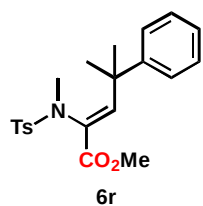


6b and **2b** (92.3 mg, 75% yield (95/5)). Second flash column chromatography on silica gel (toluene/hexane/ether = 10/2/1) was performed to give **6b** and **2b** as colorless oil. Characterization of **6b**: ^1H NMR(500 MHz, CDCl_3): δ 1.05 (d, $J = 5.7\text{ Hz}$, 6H), 2.40 (s, 3H), 2.93 - 2.98 (m, 1H), 2.99 (s, 3H), 3.48 (s, 3H), 6.84 (d, $J = 10.9\text{ Hz}$, 1H), 7.27 (d, $J = 8.0\text{ Hz}$, 2H), 7.68 (d, $J = 8.0\text{ Hz}$, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 21.4, 28.1, 37.3, 51.7, 125.3, 127.7, 128.2, 129.1, 136.2, 143.2, 155.3, 164.5; IR (film, CHCl_3): 1725 cm^{-1} ; EI-HRMS calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_4\text{S}$ 311.11913, found 311.11869. Characterization of **2b**: ^1H NMR(500 MHz, CDCl_3): δ 1.17 (d, $J = 6.9\text{ Hz}$, 6H), 2.43 (s, 3H), 2.96 (s, 3H), 3.03-3.09 (m, 1H), 3.72 (s, 3H), 6.97 (s, 1H), 7.34 (d, $J = 8.0\text{ Hz}$, 2H), 7.69 (d, $J = 8.0\text{ Hz}$, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 20.6, 21.5, 27.1, 37.7, 51.4, 127.5, 129.9, 132.9, 133.8, 136.5, 144.2, 167.1; IR (neat): 1714 cm^{-1} ; EI-HRMS calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_4\text{S}$ 311.11913, found 311.11880.

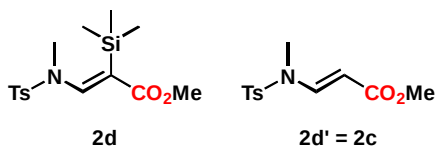
Compound 6q. Following the general procedure using **1q** (105.9 mg, 0.3991 mmol), $\text{Ni}(\text{cod})_2$ (11.0 mg, 0.0400 mmol), bpy (6.3 mg, 0.0403 mmol), Zn (78.5 mg, 1.2007 mmol), MgBr_2 (221.0 mg, 1.2004 mmol) and water (3.6 μL , 0.1998 mmol) in DMF (5.7 mL) to afford **6q** as white solid (109.4 mg, 84% yield). ^1H NMR (500 MHz, CDCl_3): δ 1.27 (s, 9H), 2.40 (s, 3H), 3.00 (s, 3H), 3.33 (s, 3H), 6.94 (s, 1H), 7.27 (d, $J = 8.0\text{ Hz}$, 2H), 7.62 (d, $J = 8.0\text{ Hz}$, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 21.4, 29.1, 34.7, 38.2, 51.6, 127.2, 127.8, 129.0, 135.8, 143.0, 156.5, 165.2; IR (film, CHCl_3): 1724 cm^{-1} ; EI-HRMS calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_4\text{S}$ 325.13478, found 325.13420.



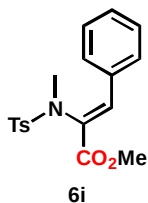
Compound 6r. Following the general procedure using **1r** (130.2 mg, 0.398 mmol), Ni(cod)₂ (11.0 mg, 0.040 mmol), bpy (6.3 mg, 0.040 mmol), Zn (78.5 mg, 1.201 mmol), MgBr₂ (221.0 mg, 1.200 mmol) and water (3.6 μL, 0.200 mmol) in DMF (5.7 mL) to afford **6r** as colorless oil (97.4 mg, 63% yield). ¹H NMR(500 MHz, CDCl₃): δ 1.71 (d, *J* = 14.9, 6H), 2.42 (s, 3H), 2.80 (s, 3H), 3.38 (s, 3H), 7.18 (s, 1H), 7.22-7.25 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.32-7.41 (m, 4H), 7.64 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 21.5, 37.5, 41.6, 51.7, 77.2, 126.1, 126.4, 128.0, 128.2, 128.4, 129.0, 135.7, 143.1, 147.5, 155.0, 165.1; IR (film, CHCl₃): 1723 cm⁻¹; EI-HRMS calcd for C₁₄H₁₈NO₂ 232.13375, found 232.13365.



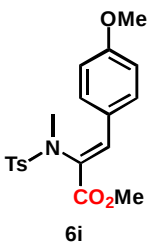
Compound 2d and 2d'. Following the general procedure using **1d** (112.0 mg, 0.398 mmol), Ni(cod)₂ (11.0 mg, 0.040 mmol), bpy (6.3 mg, 0.040 mmol), Zn (78.5 mg, 1.201 mmol), MgBr₂ (221.0 mg, 1.200 mmol) and water (3.6 μL, 0.200 mmol) in DMF (5.7 mL) to afford **2d** and **2d'** in 21% ¹H NMR yield (48/52).



Compound 6i. Following the general procedure using **1i** (114.3 mg, 0.401 mmol), Ni(cod)₂ (11.0 mg, 0.040 mmol), bpy (6.3 mg, 0.040 mmol), Zn (78.5 mg, 1.201 mmol), MgBr₂ (221.0 mg, 1.200 mmol) and water (3.6 μL, 0.200 mmol) in DMF (5.7 mL) to afford regioisomeric mixture of **6i** and **2i** (44.3 mg, 32% yield (94/6)). Second flash column chromatography on silica gel (toluene/hexane/ether = 10/2/1) was performed to give **6i** as white solid. Characterization of **6i**: ¹H NMR(500 MHz, CDCl₃): δ 2.42 (s, 3H), 3.09 (s, 3H), 3.59 (s, 3H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.35-7.41 (m, 3H), 7.67-7.71 (m, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 21.5, 36.4, 52.1, 127.9, 128.1, 128.8, 129.2, 130.7, 130.8, 132.4, 136.2, 141.6, 143.4, 165.5; IR (film, CHCl₃): 1719 cm⁻¹; EI-HRMS calcd for C₁₈H₁₉NO₄S 345.10348, found 345.10369.

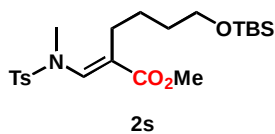
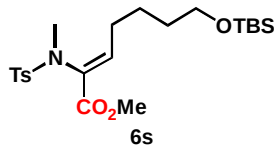


Compound 2h. Following the general procedure using **1h** (126.9 mg, 0.402 mmol), Ni(cod)₂ (11.0 mg, 0.040 mmol), bpy (6.3 mg, 0.040 mmol), Zn (78.5 mg, 1.201 mmol), MgBr₂ (221.0 mg, 1.200 mmol), and water (3.6 μL, 0.200 mmol) in DMF (5.7 mL) to afford regioisomeric mixture of **2h** and **3h** (43% yield (95/5)). Characterization of **2h**: ¹H NMR(400 MHz, CDCl₃): δ 2.43 (s, 3H), 3.10 (s, 3H), 3.53 (s, 3H), 3.85 (s, 3H), 6.91 (d, *J* = 9.1 Hz, 2H), 7.28 (d, *J* = 7.7 Hz, 2H), 7.67 (s, 1H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.79 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 21.5, 36.4, 51.9, 55.4, 114.3, 125.1, 125.5,



127.9, 129.2, 133.0, 136.3, 141.6, 143.3, 161.7, 165.7; IR (film, CHCl₃): 1716, 1259, 1175 cm⁻¹; EI-HRMS calcd for C₁₉H₂₁NO₅S 375.11404, found 375.11405.

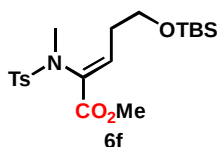
Compound 6s and 2s. Following the general procedure using **1s** (155.0 mg, 0.392mmol), Ni(cod)₂



(22.0 mg, 0.080mmol), bpy (12.6 mg, 0.081mmol), Zn (78.5 mg, 1.201mmol), MgBr₂ (221.0 mg, 1.200 mmol), and water (3.6μL, 0.200mmol) in DMF (5.7

mL) to afford regioisomeric mixture of **6s** and **2s** (143.5 mg, 80% yield (84/16)). Second flash column chromatography on silica gel (toluene/hexane/ether = 10/2/1) was performed to give **6s** and **2s** as colorless oil. Characterization of **6s**: ¹H NMR (500 MHz, CDCl₃): δ 0.04 (s, 6H), 0.88 (s, 9H), 1.47-1.57 (m, 4H), 2.36-2.43 (m, 5H), 2.99 (s, 3H), 3.50 (s, 3H), 3.60 (t, *J* = 5.7 Hz, 2H), 7.06 (t, *J* = 7.4 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ -5.4, 18.3, 21.5, 24.4, 25.9, 28.6, 32.5, 37.0, 51.8, 62.6, 127.7, 129.2, 130.3, 136.2, 143.2, 149.4, 164.3; IR (film, neat): 1726 cm⁻¹; EI-HRMS calcd for C₂₁H₃₄NO₅SSi 440.19269, found 440.19156. Characterization of **2s**: ¹H NMR(500 MHz, CDCl₃): δ 0.01 (s, 6H), 0.86 (s, 9H), 1.35-1.43 (m, 2H), 1.44-1.51 (m, 2H), 2.37 (t, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 3.11 (s, 3H), 3.55 (t, *J* = 6.3 Hz, 2H), 3.74 (s, 3H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.60 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ -5.3, 18.3, 21.6, 25.8, 25.9, 26.3, 32.7, 35.7, 51.9, 62.6, 119.2, 127.3, 130.0, 134.3, 137.3, 144.4, 168.6; IR (film, CHCl₃): 1709, 1629 cm⁻¹; EI-HRMS calcd for C₂₁H₃₄NO₅SSi 440.19269, found 440.19224.

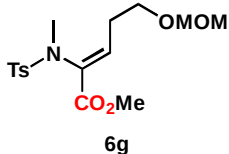
Compound 6f. Following the general procedure using **1f** (151.1 mg, 0.41 mmol), Ni(cod)₂ (22.6



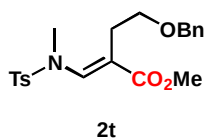
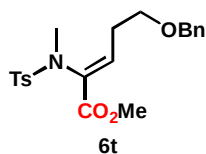
mg, 0.082mmol), bpy (12.8 mg, 0.082mmol), Zn (80.6 mg, 1.23 mmol), MgBr₂ (227.1 mg, 1.23 mmol), and water (3.7μL, 0.20 mmol) in DMF (5.7 mL) to afford a crude product which was then purified by flash column chromatography

on silica gel (hexane/AcOEt = 15/1) to afford regioisomeric mixture of **6f** and **2f** (128.8 mg, 73% yield (81/19)). Second flash column chromatography on silica gel (toluene/hexane/ether = 5/1/1) was performed to give **6f** as colorless oil. Characterization of **6f**: ¹H NMR (500 MHz, CDCl₃): δ 0.04 (s, 6H), 0.87 (s, 9H), 2.40 (s, 3H), 2.59 (q, *J* = 6.3 Hz, 2H), 2.99 (s, 3H), 3.49 (s, 3H), 3.74 (t, *J* = 6.0 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ -5.4, 18.2, 21.5, 25.8, 32.5, 37.0, 51.8, 61.1, 127.7, 129.2, 131.3, 136.1, 143.2, 146.7, 164.1; IR (film, CHCl₃): 1727 cm⁻¹; EI-HRMS calcd for C₁₉H₃₀NO₅SSi 412.16139, found 412.16076.

Compound 6g. Following the general procedure using **1g** (112.0 mg, 0.38mmol), Ni(cod)₂ (20.7 mg, 0.075 mmol), bpy (11.8 mg, 0.076 mmol), Zn (73.9 mg, 1.13 mmol), MgBr₂ (208.0 mg, 1.13mmol), and water (3.4μL, 0.19mmol) in DMF (5.4 mL) to afford a regioisomeric mixture of **6g** and **2g** (95.4 mg, 71% yield). Second flash column chromatography on silica gel (toluene/hexane/AcOEt = 10/2/1) was performed to give **6g** as colorless oil. Characterization of **6g**: ¹H NMR(500 MHz, CDCl₃): δ 2.40 (s, 3H), 2.68 (q, *J* = 6.3 Hz, 2H), 3.00 (s, 3H), 3.34 (s, 3H), 3.49 (s, 3H), 3.65 (t, *J* = 6.3 Hz, 2H), 4.60 (s, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 21.5, 29.5, 36.9, 51.8, 55.2, 65.4, 96.3, 127.7, 129.2, 131.5, 136.0, 143.3, 146.2, 164.0; IR (film, CHCl₃): 1725 cm⁻¹; EI-HRMS calcd for C₁₅H₂₀NO₅S 326.10622, found 326.10587.

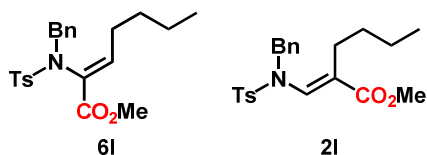


Compound 6t and 2t. Following the general procedure using **1t** (138.9 mg, 0.404 mmol), Ni(cod)₂ (11.0 mg, 0.040mmol), bpy (6.3 mg, 0.040 mmol), Zn (78.5 mg, 1.201 mmol), MgBr₂ (221.0 mg, 1.200 mmol), and water (3.6 μL, 0.200 mmol) in DMF (5.7 mL) to afford a regioisomeric mixture of **6t** and **2t** (79.0 mg, 48% yield (75/25)). Characterization of **6t**: ¹H NMR (500 MHz, CDCl₃): δ 2.42 (s, 3H), 2.72 (q, *J* = 6.1 Hz, 2H), 3.00 (s, 3H), 3.52 (s, 3H), 3.62 (t, *J* = 6.3 Hz, 2H), 4.52 (s, 2H), 7.19 (t, *J* = 7.2 Hz, 1H), 7.27-7.36 (m, 7H), 7.69 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 21.5, 29.6, 37.0, 51.9, 68.0, 72.9, 127.3, 127.6, 127.7, 128.4, 129.3, 131.5, 136.1, 138.1, 143.3, 146.4, 164.1; IR (film, CHCl₃): 1725, 1347, 1163; EI-HRMS calcd for C₁₄H₁₈NO₃ 248.12867, found 248.12920. Characterization of **2t**: ¹H NMR(500 MHz, CDCl₃): δ 2.43 (s, 3H), 2.72 (t, *J* = 6.6 Hz, 2H), 3.21 (s, 3H), 3.49 (t, *J* = 6.6 Hz, 2H), 3.73 (s, 3H), 4.42 (s, 2H), 7.21-7.33 (m, 7H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.88 (s, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 21.6, 26.6, 35.5, 51.9, 68.9, 72.9, 112.5, 127.3, 127.4, 127.5, 128.3, 130.0, 134.4, 138.3, 138.8, 144.4, 168.6; IR (film, CHCl₃): 1707, 1357, 1164 cm⁻¹; EI-HRMS calcd for C₁₄H₁₈NO₃ 248.12867, found 248.12914.



Compound 6l and 2l. Following the general procedure using **1l** (135.4 mg, 0.40 mmol), Ni(cod)₂ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.20 mmol), MgBr₂ (221.0 mg, 1.20 mmol) and water (3.6μL, 0.20 mmol) in DMF (5.7 mL) to afford a regioisomeric mixture of **6l** and **2l** as white solid(121.0 mg, 76% yield (91/9)). Second flash column chromatography on silica gel

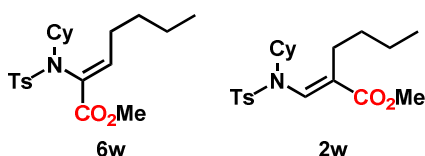
(toluene/hexane = 5/1) was performed to separate **6l** and **2l**. Characterization of **6l**: ^1H NMR(500 MHz, CDCl_3): δ 0.60-1.15 (m, 7H), 1.89-2.22 (br, 2H), 2.44 (s, 3H), 3.48 (s, 3H), 4.03-4.20 (br,



1H), 4.84-4.99 (br, 1H), 7.01 (t, J = 7.4 Hz, 1H), 7.25-7.27 (m, 5H), 7.31 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.7, 21.5, 22.5, 29.2, 29.9, 51.7, 52.8,

126.3, 127.7, 127.9, 128.3, 129.3, 129.7, 135.6, 137.0, 143.2, 152.7, 164.2; IR (film, CHCl_3): 1722 cm^{-1} ; ESI-HRMS calcd for $\text{C}_{22}\text{H}_{27}\text{O}_4\text{NNaS}$ 424.15530, found 424.15518; X-ray data: M = 402.53, colorless, block, triclinic, P-1 (#2), a = 9.3258(3) Å, b = 9.3714(3) Å, c = 12.7379(3) Å, α = 104.226(7)°, β = 99.435(7)°, γ = 96.838(7)°, V = 1049.62(7) Å³, Z = 2, D_{calc} = 1.274 g/cm^3 , T = -140 °C, $R_1(wR_2)$ = 0.0448 (0.1117). Characterization of **2l**: ^1H NMR (500 MHz, CDCl_3): δ 0.74 (t, J = 7.4 Hz, 3H), 0.93-1.01 (m, 2H), 1.04-1.13 (m, 2H), 2.19 (t, J = 8.0 Hz, 2H), 2.44 (s, 3H), 3.71 (s, 3H), 4.47 (s, 2H), 7.07 (s, 1H), 7.19-7.30 (m, 5H), 7.33 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.8, 21.6, 22.7, 26.5, 31.2, 51.9, 53.2, 127.4, 127.7, 127.8, 128.6, 128.8, 129.9, 135.1, 135.2, 135.6, 144.2, 168.0; IR (film, CHCl_3): 1713 cm^{-1} ; ESI-HRMS calcd for $\text{C}_{22}\text{H}_{27}\text{O}_4\text{NNaS}$ 424.15530, found 424.15564.

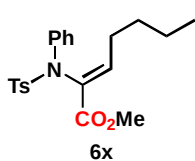
Compound 6w and 2w. Following the general procedure using **1w** (132.9 mg, 0.40mmol),



$\text{Ni}(\text{cod})_2$ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.20 mmol), MgBr_2 (221.0 mg, 1.20 mmol) and water (3.6 μL , 0.2mmol) in DMF (5.7 mL) to afford regioisomeric mixture of **6w** and **2w** (132.7 mg, 85% yield). Second flash

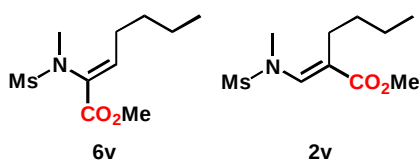
column chromatography on silica gel (toluene/hexane = 5/1) was performed to give **6w** as colorless oil. Characterization of **6w**: ^1H NMR(500 MHz, CDCl_3): δ 0.88-1.65 (m, 15H), 1.72 (d, J = 12.6 Hz, 1H), 1.98 (d, J = 12.0 Hz, 1H), 2.29-2.47 (m, 5H), 3.61-3.68 (m, 4H), 7.22-7.29 (m, 3H), 7.84 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.8, 21.5, 22.6, 25.0, 25.8, 26.1, 29.6, 30.2, 30.7, 32.3, 51.9, 60.1, 125.8, 128.0, 129.0, 138.2, 142.9, 152.2, 166.5; IR (film, CHCl_3): 1727 cm^{-1} ; ESI-HRMS calcd for $\text{C}_{21}\text{H}_{31}\text{NO}_4\text{NaS}$ 416.18660, found 416.18587. Characterization of **2w**: ^1H NMR(500 MHz, CDCl_3): δ 0.86-1.73 (m, 17H), 2.41-2.47 (m, 5H), 3.75-3.82 (m, 4H), 6.62 (s, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.9, 21.5, 23.2, 25.1, 25.8, 27.5, 30.2, 30.8, 51.9, 60.2, 127.2, 129.7, 131.3, 137.4, 141.1, 143.5, 167.6; IR (film, CHCl_3): 1720 cm^{-1} ; ESI-HRMS calcd for $\text{C}_{21}\text{H}_{31}\text{NO}_4\text{NaS}$ 416.18660, found 416.18601.

Compound 6x. Following the general procedure using **1x** (130.0 mg, 0.40 mmol), Ni(cod)₂ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.20 mmol), MgBr₂ (221.0 mg, 1.20 mmol) and water (3.6 μL, 0.20 mmol) in DMF (5.7 mL) to afford a regioisomeric mixture of **6x** and **2x** (55.5 mg, 44% yield (89/11)). Flash column chromatography on silica (hexane/AcOEt = 5/1) provides **6x** as a yellow oil.



Characterization of **6x**: ¹H NMR (500 MHz, CDCl₃): δ 0.85 (t, *J* = 7.2 Hz, 3H), 1.24-1.37 (m, 4H), 2.36-2.43 (m, 5H), 3.76 (s, 3H), 7.09 (t, *J* = 7.7 Hz, 1H), 7.14-7.25 (m, 5H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 13.8, 21.5, 22.5, 28.5, 29.9, 52.3, 126.2, 126.7, 128.4, 128.9, 129.0, 131.1, 136.6, 140.6, 143.5, 148.8, 165.5; IR (neat): 1726, 1356, 1164 cm⁻¹; EI-HRMS calcd for C₂₁H₂₅NO₄S 387.15043, found 387.15032.

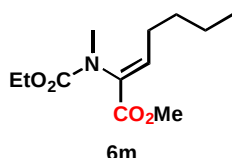
Compound 6v and 2v



Following the general procedure using **1v** (78.7 mg, 0.42 mmol), Ni(cod)₂ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.20 mmol), MgBr₂ (221.0 mg, 1.20 mmol) and water (3.6 μL, 0.20 mmol) in DMF (5.7 mL) to afford **6v** as colorless oil (36.2 mg, 35% yield) and **2v** as white solid (30.0mg, 29% yield).

Characterization of **6v**: ¹H NMR (500 MHz, CDCl₃): δ 0.91 (t, *J* = 7.2 Hz, 3H), 1.32-1.39 (m, 2H), 1.42-1.48 (m, 2H), 2.41 (q, *J* = 7.4 Hz, 2H), 3.01 (s, 3H), 3.05 (s, 3H), 3.77 (s, 3H), 7.06 (t, *J* = 7.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 13.8, 22.5, 28.5, 30.1, 36.6, 38.1, 52.2, 130.2, 150.2, 164.5; IR (film, neat): 1721 cm⁻¹; EI-HRMS calcd for C₁₀H₁₉NO₄S 249.10348, found 249.10323. Characterization of **2v**: ¹H NMR (500 MHz, CDCl₃): δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.32-1.38 (m, 2H), 1.39-1.45 (m, 2H), 2.42 (t, *J* = 7.7 Hz, 2H), 2.96 (s, 3H), 3.29 (s, 3H), 3.74 (s, 3H), 7.56 (s, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 13.8, 22.8, 25.9, 32.2, 35.8, 37.8, 51.9, 119.1, 136.6, 168.5; IR (film, CHCl₃): 1706 cm⁻¹; EI-HRMS calcd for C₁₀H₁₉NO₄S 249.10348, found 249.10327.

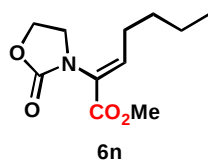
Compound 6m. Following the general procedure using **1m** (72.0 mg, 0.39 mmol), Ni(cod)₂ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (79.0 mg, 1.21mmol), MgBr₂ (221.0 mg, 1.20 mmol) and water (3.6 μL, 0.20 mmol) in DMF (5.7 mL) to afford a regioisomeric mixture of **6m** and **2m** as colorless oil (70.7 mg, 74% yield (85/15)).



Characterization of **6m**: ¹H NMR (500 MHz, CDCl₃): δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.09-1.44 (m, 7H), 2.10-2.17 (m, 2H), 2.97 (s, 3H), 3.71 (s, 3H), 4.02-4.17 (m, 2H), 6.68-6.79 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 13.7, 14.5, 22.3, 27.3, 30.0, 36.1, 52.0, 61.5, 132.3, 142.0,

155.9, 164.9; IR (neat): 1728, 1656 cm^{-1} ; EI-HRMS calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_4$ 243.14706, found 243.14709.

Compound 6n. Following the general procedure using **1n** (66.9 mg, 0.40 mmol), $\text{Ni}(\text{cod})_2$ (11.0 mg,



0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.20 mmol), MgBr_2 (221.0 mg, 1.20 mmol) and H_2O (3.6 μL , 0.2 mmol) in DMF (5.7 mL) to afford regioisomeric mixture of **6n** and **2n** (28.0 mg, 31% yield (13/87)).

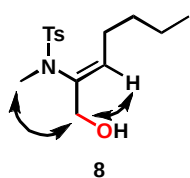
Characterization of **6n**: ^1H NMR (500 MHz, CDCl_3): δ 0.91 (t, J = 7.2 Hz, 3H), 1.30-1.51 (m, 4H), 2.25 (q, J = 7.4 Hz, 2H), 3.75-3.80 (m, 5H), 4.47 (t, J = 7.9 Hz, 2H), 7.02 (t, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.9, 22.5, 28.0, 30.1, 46.3, 52.3, 62.6, 126.7, 146.7, 157.0, 163.7; IR (neat): 1759, 1722 cm^{-1} ; EI-HRMS calcd for $\text{C}_{11}\text{H}_{17}\text{NO}_4$ 227.11576, found 227.11636.

Other Experiments

Structure Elucidation of 6a

<Scheme 22>

To a solution of **6a** (86.0 mg, 0.26 mmol) in toluene (0.5 mL) was added a solution of DIBAL-H in hexane (1.02 M, 0.78 mL, 0.79 mmol) at -78°C , and the mixture was stirred at the same temperature for 3 hours. To the mixture was added a saturated aqueous solution of potassium sodium tartrate, and the mixture was stirred at room temperature for 2 h. After the aqueous layer



was extracted with AcOEt, the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. A crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 3/1) to give **8** (70.5 mg, 90% yield) as a colorless oil. The result of NOE experiment is shown with

double-headed arrows on the chemical structure of **8** above. ^1H NMR (500 MHz, CDCl_3): δ 0.79 (t, J = 6.9 Hz, 3H), 1.09-1.19 (m, 4H), 1.68 (q, J = 7.3 Hz, 2H), 2.23 (brs, 1H), 2.41 (s, 3H), 3.01 (s, 3H), 4.13 (s, 2H), 5.62 (t, J = 7.4 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 13.7, 21.4, 22.4, 27.3, 30.8, 37.6, 64.8, 127.4, 129.6, 133.3, 136.6, 138.3, 143.4; IR (film, CHCl_3): 3470, 2953, 2927, 1154 cm^{-1} ; ESI-HRMS calcd for $\text{C}_{15}\text{H}_{23}\text{O}_3\text{NNaS}$ 320.12909, found 320.12918.

Isotop labeling experiments

<Scheme 23, first row>

Following the general procedure for Ni-catalyzed hydrocarboxylation of ynamides using **1a** (107.0 mg, 0.403 mmol), Ni(cod)₂ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.201 mmol), MgBr₂ (221.0 mg, 1.200 mmol) and D₂O (3.6 μ L, 0.200 mmol) in DMF (5.7 mL) to afford a regioisomeric mixture of **6a-D** and **2a-D** in 52% ¹H NMR yield (71/29).

<Scheme 23, second row>

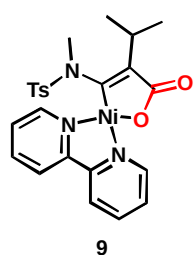
Following the general procedure for Ni-catalyzed hydrocarboxylation of ynamides using **1a** (106.9 mg, 0.403 mmol), Ni(cod)₂ (11.0 mg, 0.04 mmol), bpy (6.3 mg, 0.04 mmol), Zn (78.5 mg, 1.201 mmol), MgBr₂ (220.9 mg, 1.200 mmol) and D₂O (22 μ L, 1.219 mmol) in DMF (5.8 mL) to afford a regioisomeric mixture of **6a-D** and **2a-D** as colorless oil (56.8 mg, 43% yield (35/65)).

Synthesis of Nickelalactone **9**

<Scheme 27>

A Schlenk flask was charged with Ni(cod)₂ (137.5 mg, 0.50 mmol), 2,2'-bipyridine (78.1 mg, 0.50 mmol), ynamide **1b** (138.23 mg, 0.55 mmol) under nitrogen atmosphere. To the solids were added 3 mL of THF. The suspension was quickly degassed and then back filled with CO₂ by using a balloon. The reaction mixture was stirred for 1 day at 0 °C. The precipitate was filtered off, washed with cold ether (distilled from Na/benzophenone) and dried out to yield orange powder (155.1 mg, 61%).

Red needle crystals for X-ray diffraction study was obtained by diffusion of pentane into the solution of **9** in THF/toluene/CH₂Cl₂ mixture. ¹H NMR (500 MHz, CD₂Cl₂): δ 0.63 (d, *J* = 7 Hz,

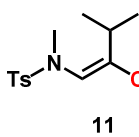


3H), 0.94 (d, *J* = 6.5 Hz, 3H), 1.77 (m, 1H), 2.36 (s, 3H), 3.20 (s, 3H), 7.26 (d, *J* = 8 Hz, 2H), 7.46 (t, *J* = 6.5 Hz, 1H), 7.55 (t, *J* = 6.5 Hz, 1H), 7.78 (d, *J* = 8 Hz, 2H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.92-8.05 (m, 3H), 8.56 (d, *J* = 6 Hz, 1H), 8.78 (d, *J* = 5.5 Hz, 1H); ¹³C NMR (125 MHz, CD₂Cl₂): δ 20.0, 20.4, 21.5, 29.1, 39.1, 120.6, 121.2, 126.3, 126.4, 127.6, 129.9, 137.2, 138.9, 139.8, 143.6, 149.7, 152.0, 153.0,

155.6 (three signals were missing due to very low intensity); Elemental analysis did not give good results probably due to instability of the complex to the moisture; X-ray data: *M* = 510.24, red, needle, monoclinic, P2₁/n (#14), *a* = 18.6357(6) Å, *b* = 6.4232(2) Å, *c* = 19.8474(7) Å, β = 110.723(8)°, *V* = 2222.05(17) Å³, *Z* = 4, *D*_{calc} = 1.525 g/cm³, *T* = -140 °C, *R*₁(*wR*₂) = 0.0498 (0.1190).

Treatment of Nickelalactone **9** with H₂O/MgBr₂/Zn system to give compound **11**

<Scheme 28>



Nickelalactone **9** (25.0 mg, 0.049 mmol), Zn (10.0 mg, 0.153 mmol), and MgBr₂ (27.3 mg, 0.148 mmol) were weighed into a flame-dried round bottom flask in a glove box (nitrogen atmosphere). Then, the flask was taken out of the glove box, and a solution of water (0.5 μ L, 0.028 mmol) in DMF (0.7 mL) was added at 0 °C to the flask. After removal of nitrogen gas in the flask by performing a freeze-pump-thaw procedure (3 times), the flask was backfilled with CO₂ gas using a balloon. The reaction mixture was stirred at 0 °C for 21 hours. To the mixture was added 10% aqueous solution of HCl at 0 °C. The resulting solution was extracted with diethyl ether several times. The combined organic layers was washed with water, dried over Na₂SO₄, and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 2/1) to give **11** (10.3 mg, 71% yield) as a white solid. ¹H NMR (500 MHz, CDCl₃): δ 1.21 (d, *J* = 6.9 Hz, 6H), 2.45 (s, 3H), 3.01-3.07 (m, 4H), 7.34-7.38 (m, 3H), 7.72 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 20.7, 21.6, 26.8, 37.4, 127.5, 128.2, 130.0, 133.8, 138.9, 144.5, 172.4; IR (neat): 2963, 1681 cm⁻¹; EI-HRMS calcd for C₁₄H₁₉NO₄S 297.10348, found 297.10375.

Hydrocarboxylation of **1a** in the presence of nickelalactone **9** as catalyst

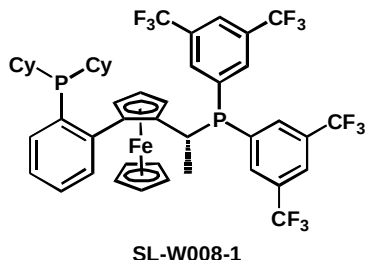
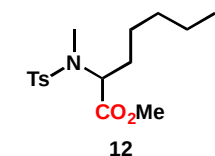
<Scheme 29>

Nickelalactone **9** (20.4 mg, 0.040 mmol), Zn (39.2 mg, 0.600 mmol), and MgBr₂ (110.5 mg, 0.600 mmol) were weighed into a flame-dried round bottom flask in a glove box. Then, the flask was taken out of the glove box, and DMF (1.4 mL) was added at 0 °C to the flask. To the resulting suspension was added a solution of ynamide **1a** (51.6 mg, 0.194 mmol) and water (2.0 μ L, 0.111 mmol) in DMF (1.5 mL) at the same temperature via cannulation method. After removal of nitrogen gas in the flask by performing a freeze-pump-thaw procedure (3 times), the flask was backfilled with CO₂ gas using a balloon. The reaction mixture was stirred at 0 °C for 12 hours. To the mixture was added 10% aqueous solution of HCl at 0 °C. The resulting solution was extracted with diethyl ether several times. The combined organic layer was washed with water, dried over Na₂SO₄, and concentrated. The residue was treated with diazomethane in Et₂O at 0 °C. After the mixture had been concentrated, the crude product was analyzed by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard to give a mixture of carboxylated product, **6a** and **2a** (51% yield (67/33) based on the initial amount of **1a**) and **2b** (53% yield based on the initial amount of nickelalactone **9**).

Trial of Asymmetric Hydrogenation

<Scheme 31>

[Rh(nbd)₂]SbF₆ (3.9 mg, 7.5 μmol, nbd = norbornadiene) and SL W008-1 (7.0 mg, 7.4 μmol) were added to a flame-dried 10 mL test tube. The test tube was purged with H₂. Chlorobenzene (0.5 mL) was added to the test tube, and the resulting mixture was stirred for 10 min under an atmosphere of H₂ (1 atm). To the mixture was added a solution of **6a** (48.5 mg, 0.15 mmol) in chlorobenzene (1.6 mL). The test tube was placed in an autoclave and pressurized under an H₂ atmosphere (5 atm). The reaction mixture was stirred at 60 °C for 20 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to afford **12** (12.2 mg, 25% yield) as a colorless oil. The enantiomeric excess was determined to be 25% by HPLC analysis with a DAICEL CHIRALPAK AS-H [eluent: hexane/2-propanol = 98/2, flow rate: 0.5 mL/min, detector: UV (254 nm)]: *t*_R(major) = 28.0 min; *t*_R(minor) = 32.0 min. ¹H NMR (500 MHz, CDCl₃): δ 0.87 (t, *J* = 6.9 Hz, 3H), 1.24-1.33 (m, 6H), 1.56-1.61 (m, 1H), 1.78-1.83 (m, 1H), 2.41 (s, 3H), 2.82 (s, 3H), 3.47 (s, 3H), 4.57 (dd, *J* = 10.0, 5.4 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 13.9, 21.5, 22.4, 25.5, 29.2, 29.7, 31.1, 51.7, 58.7, 127.3, 129.4, 136.2, 143.2, 171.4; IR (neat): 1742 cm⁻¹; ESI-HRMS calcd for C₉H₁₈NO₂ 172.13375, found 172.13441.

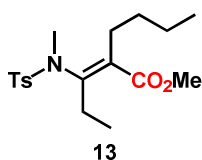


Ni-catalyzed regioselective β-carboxylation

<Scheme 32>

Ni(cod)₂ (11.8 mg, 0.043 mmol), 2,2'-bipyridine (6.7 mg, 0.043 mmol), and MgBr₂ (237.3 mg, 1.289 mmol) were weighed into a flame-dried round bottom flask in a glove box (argon atmosphere). Then, the flask was taken out of the glove box, and DMF (3.0 mL) was added at 0 °C to the flask. To the resulting suspension was added a solution of ynamide **1a** (114.0 mg, 0.430 mmol) in toluene (2.93.0 mL) at the same temperature via cannulation. After removal of argon gas in the flask by performing a freeze-pump-thaw procedure (3 times), the flask was backfilled with CO₂ gas using a balloon. Diethylzinc solution in toluene (1.29 mL, 1 M) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 0 °C for 41 hours. To the mixture was added

10% aqueous solution of HCl at 0 °C. The resulting solution was extracted with diethyl ether several times. The combined organic layer was washed with water, dried over Na₂SO₄, and concentrated. The residue was treated with diazomethane, and concentrated. After the mixture had been concentrated, the crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 5/1) to give a mixture of carboxylated product, **2a** and **13** (115.4 mg, 78% yield (33/67)). Characterization of **13**: ¹H NMR (500 MHz, CDCl₃) δ 0.80 (t, *J* = 7.0 Hz, 3H), 0.97 (t, *J* =



7.3 Hz, 3H), 1.10-1.24 (m, 4H), 2.03-2.04 (m, 2H), 2.29-2.35 (m, 1H), 2.42 (s, 3H), 2.42-2.49 (m, 1H), 2.99 (s, 3H), 3.74 (s, 3H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H); ¹³C NMR (500 MHz, CDCl₃) δ 12.9, 13.7, 21.4, 22.7, 27.5, 29.8, 29.8, 38.2, 51.7, 127.3 (2C), 129.6 (2C), 135.1, 136.6, 143.4, 145.4, 169.4; IR (CH₃Cl) 2957, 1724 cm⁻¹; EI-HRMS calcd for C₁₈H₂₇NO₄S (M⁺) 353.16608, found 353.16623.

<Scheme 33>

Ynamide **1a** (60.4 mg, 0.228 mmol), Ni(cod)₂ (6.3 mg, 0.023 mmol), and MgBr₂ (125.7 mg, 0.683 mmol) were weighed into a flame-dried round bottom flask in a glove box (nitrogen atmosphere). Then, the flask was taken out of the glove box, and DMF (1.1 mL) was added at 0 °C to the flask. After removal of argon gas in the flask by performing a freeze-pump-thaw procedure (3 times), the flask was backfilled with CO₂ gas using a balloon. Then, diethylzinc solution in toluene (0.7 ml, 1 M) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at 50 °C for 13 hours. To the mixture was added 10% aqueous solution of HCl at 0 °C. The resulting solution was extracted with diethyl ether several times. The combined organic layer was washed with water, dried over Na₂SO₄, and concentrated. The residue was treated with diazomethane, and then concentrated to afford **2a** in 47% and **13** in 3% ¹HNMR yields.

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