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Doctoral Dissertation

Development of Nickel- and Cobalt-Catalyzed Transformations of Conjugated Alkenes and Alkynes via Metallacycle Intermediate

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Preface and Acknowledgment

The studies in this thesis have been carried out under the direction of Professor Sensuke Ogoshi at the Department of Applied Chemistry, Faculty of Engineering, Osaka University from April 2008 to March 2014. The thesis is concerned with the transformations of conjugated alkenes and alkynes catalyzed by nickel and cobalt complexes via metallacycle intermediate.

I could complete this thesis with help, advice and support from a lot of people and I owe all of them a great debt of gratitude. However, I regret to say that I cannot all of them here.

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Contents

Abbreviations

The following abbreviations are used in the thesis.

anal.	Elemental anaylsys
Ac	acetyl
atm	atmospheric pressure
aq.	aqueous
Ar	aryl
br	broad
Bu	butyl
cat.	catalyst
COSY	correlated spectroscopy
cod	1,5-cyclooctadiene
Cy	cyclohexyl
Cyp	cyclopentyl
ºC	degrees Celcius
calcd	calculated
d	doublet
δ	chemical shift of NMR signal in ppm
DCE	1,2-dichloroethane
DFT	density functional theory
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomer excess
El	electrophile
eq.	equation
eq.	equivalent
ESI	electrospray ionization
Et	ethyl
Et_2O	diethylether
GC	gas chromatography
h (hr)	hour(s)

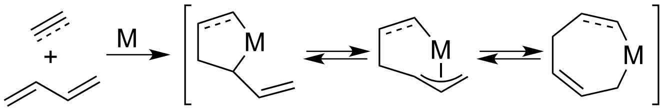
Hex	hexyl
HMBC	hetero-nuclear multiple-bond connectivity
HMQC	hetero-nuclear multiple quantum coherence
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass specra
Hz	hertz
i	iso
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
J	coupling constant in NMR
L	ligand
M	metal
m	meta
Me	methyl
min	minute(s)
mL	milliliter
μL	microliter
MS	mass spectral
n	normal
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	NOE correlated spectroscopy
o	ortho
ORTEP	Oak Ridge thermal ellipsoid plot
p	para
Ph	phenyl
PhthN	phthalimido
pin	pinacolate
PMP	*p*-methoxyphenyl
Pr	propyl
PR_3	trialkyl- or triaryl-phosphine
q	quartet
quant	quantitative

rt	room temperature
s	singlet
sec	second
sept	septet
sext	sextet
t	triplet
t (*tert*)	tertiary
Mes	mesityl
TBS	*tert*-butyldimethylsilyl
temp.	temperature
THF	tetrahydrofuran
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMS	trimethylsilyl

General Introduction

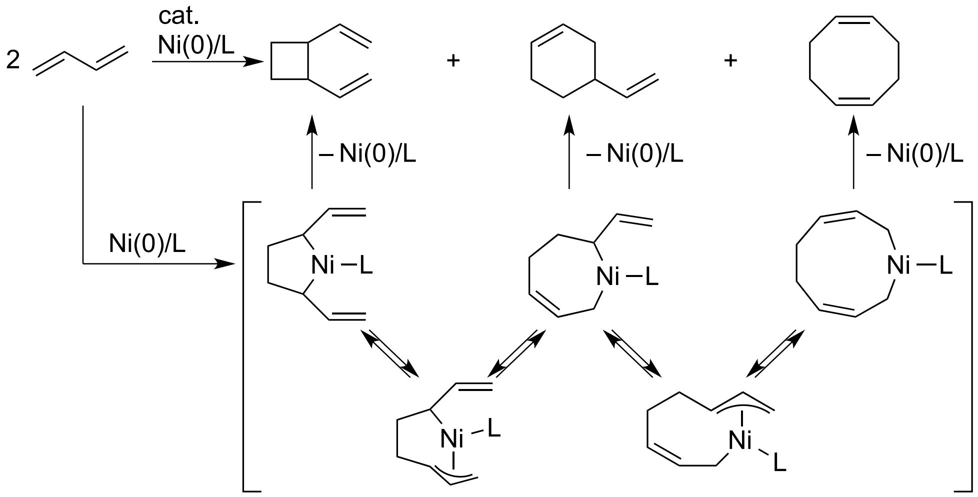
1. Effect of π-conjugation

Oxidative cyclization of two π-components coordinated to a transition metal center to form a metallacycle is the fundamental reaction in organometallic chemistry. This process is known as the key step for a variety of synthetic methods such as cycloaddition, linear oligomerization, reductive coupling, multicomponent reaction and other reactions.[1–3] Late-transition-metal complexes are often utilized for the achievement of the catalytic version of such transformations. Conjugated unsaturated compounds display unique reactivity in the reactions involving oxidative cyclization step. For example, three forms of metallacycle could be generated from 1,3-diene with another unsaturated bond: a five-membered metallacycle, a seven-membered metallacycle, and an intermediary η^3-allyl metallacycle, and they would be in equilibrium via the η^1-η^3 isomerization under reaction conditions (Scheme 1).



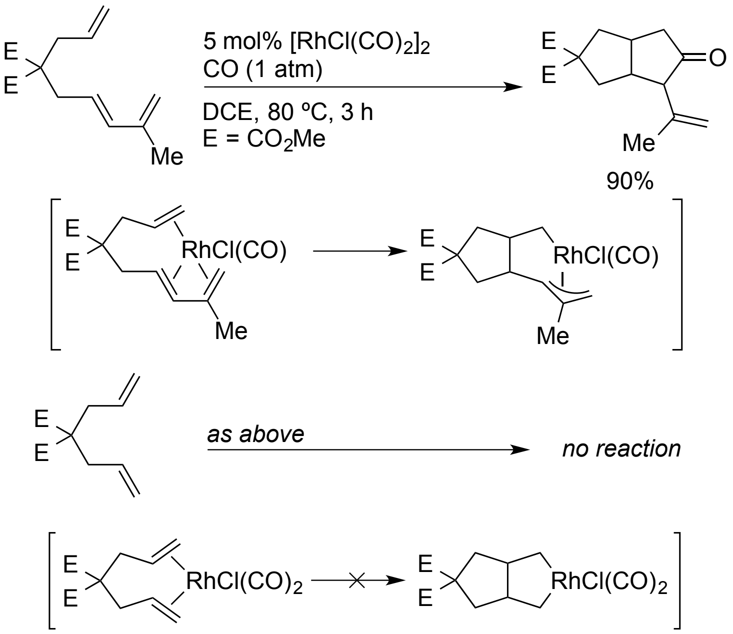
Scheme 1. Oxidative cyclization of 1,3-diene

The nickel-catalyzed dimerization of 1,3-butadiene serves as a prime example of the reaction involving such η^1-η^3 isomerization, which was precisely investigated both in catalytic and stoichiometric reactions by Wilke and Heimbach (Scheme 2).[4] Under the catalytic conditions, four- six- and eight-membered carbocyclic compounds are obtained. These cyclic products could be generated by reductive elimination from either five-, seven- or nine-membered nickelacycle, all of which would be in equilibrium through the intermediary η^3-allyl intermediates. Some of such η^3-allyl nickelacycles are unambiguously characterized by means of X-ray crystallography and/or NMR experiments.



Scheme 2. Nickel-catalyzed dimerization of 1,3-butadiene

It is also known that the π-conjugation in unsaturated substrates promotes the oxidative cyclization step. Trost reported that a Pauson–Khand reaction of ene-diene took place in the presence of rhodium catalyst, while 1,6-diene was intact to give no product under the same reaction conditions (Scheme 3).[5] A DFT calculation performed by Baik suggested that energetic barrier of oxidative cyclization of the (η^2:η^4-ene-diene)rhodium complex is significantly lower than that of the (η^2:η^2-ene-diene)rhodium analogue.[6] Moreover, the resultant η^3-allyl metallacycle is more stable than the corresponding five-membered metallacycle. Thus, oxidative cyclization of an ene-diene to form an η^3-allyl metallacycle is kinetically and thermodynamically favorable process.

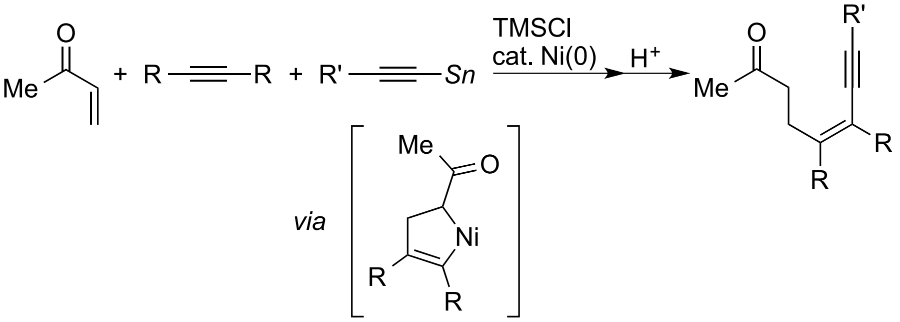


Scheme 3. Rhodium catalyzed pauson–Khand reaction of ene-diene

Therefore, reactions of unsaturated π-compounds via metallacycle intermediates are very attractive methods for the synthesis of various carbon skeletons. However, it is difficult to control the chemo-, regio- and stereoselectivities in intermolecular reactions. Thus, the development of catalyst systems that overcome such problems is desired.

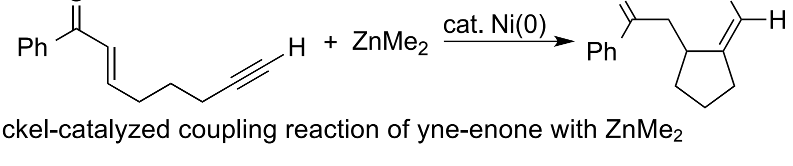
2. Nickel-catalyzed reaction of α,β-unsaturated carbonyl compounds

Nickel(0) complexes are known to bound more tightly with electron-deficient unsaturated compounds than with the electron-rich compounds through η^2-coordination because of the predominant contribution of the back-donation from the metal center.[7] This feature makes nickel as an effective catalyst for the reaction of α,β-unsaturated carbonyl compounds with other unsaturated hydrocarbons. Ikeda and Sato first reported the nickel-catalyzed multi-component coupling of enones, alkynes, alkynyltins and silylchloride, in which oxidative cyclization of an enone with an alkyne at the nickel(0) is proposed as a key step (Scheme 4).[8]

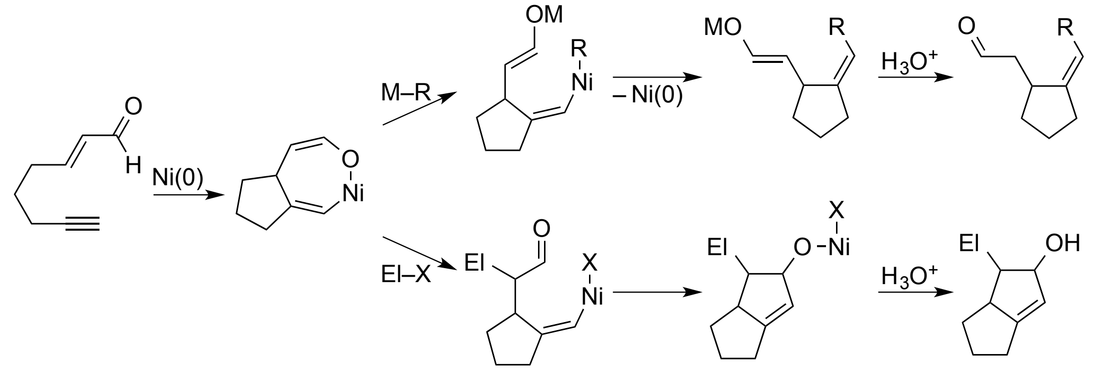


Scheme 4. Nickel-catalyzed multi-component coupling of enone/alkyne/alkynyltin

Later, Montgomery reported the nickel-catalyzed coupling reaction of yne-enone with organozinc reagents which is proposed to proceed via nickelacycle intermediate based on stoichiometric reactions as well as DFT calculations (Scheme 5).[9,10] In relation to this reaction, a seven-membered η^1-*O*-enolate nickelacycle prepared from yne-enal with Ni(cod)$_2$ and TMEDA was isolated and its reactivity was investigated.[10] This η^1-*O*-enolate complex showed two aspects of reactivity: one is transmetallation of Ni–O bond with an organometallic reagent, and the other is nucleophilic attack of enolate to an electrophile (Shceme 6).



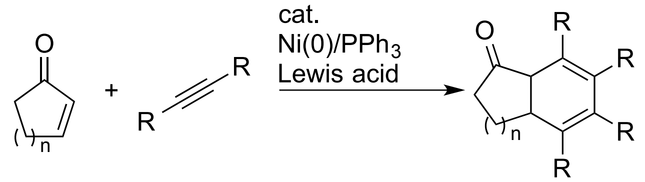
Scheme 5. Nickel-catalyzed coupling reaction of yne-enone with ZnMe$_2$



Scheme 6. Reactivities of η^1-*O*-enolate nickelacycle

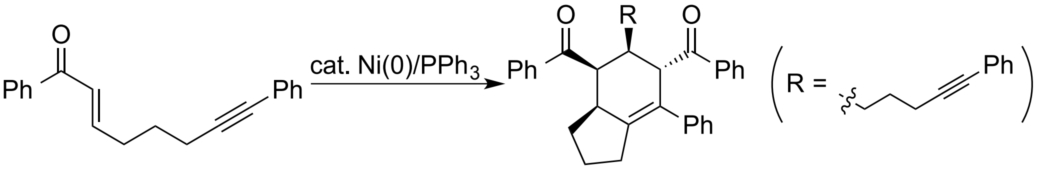
After these pioneering discoveries, a variety of nickel-catalyzed transformations utilizing enones or enals with alkynes, allenes or alkenes via multi-component coupling reactions, reductive coupling reactions and reductive cyclizations have been developed.[3a,b]

In the absence of organometallic reagent or reducing agent, nickel-catalyzed cycloaddition or linear oligomerization of α,β-unsaturated carbonyls with alkynes takes place. Ikeda and Cheng demonstrated the [2 + 2 + 2] cycloaddition of a cyclic enone with two alkynes to afford a cyclohexadiene derivative in the presence of nickel(0), PPh_3, and a Lewis acid. (Scheme 7).[11]



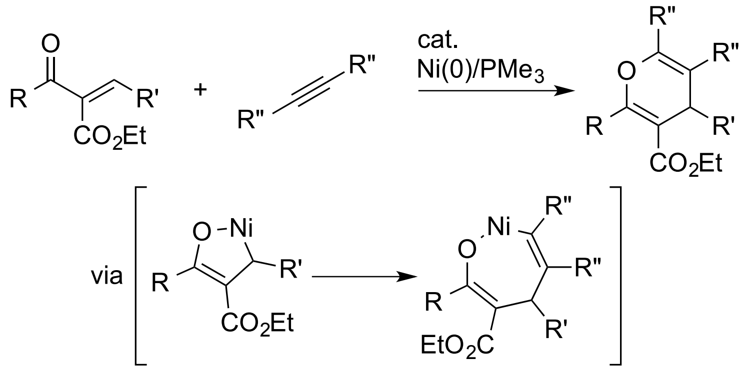
Scheme 7. Nickel-catalyzed [2 + 2 + 2] cycloaddition of an enone with two alkynes

Montgomery reported that yne-enones underwent [2 + 2 + 2] cyclodimerization in which two enone units with one alkyne unit to construct a cyclohexene skeleton. This reaction stereoselectively provided bicyclic cyclohexenes as a single diastereomer (Scheme 8).[12]



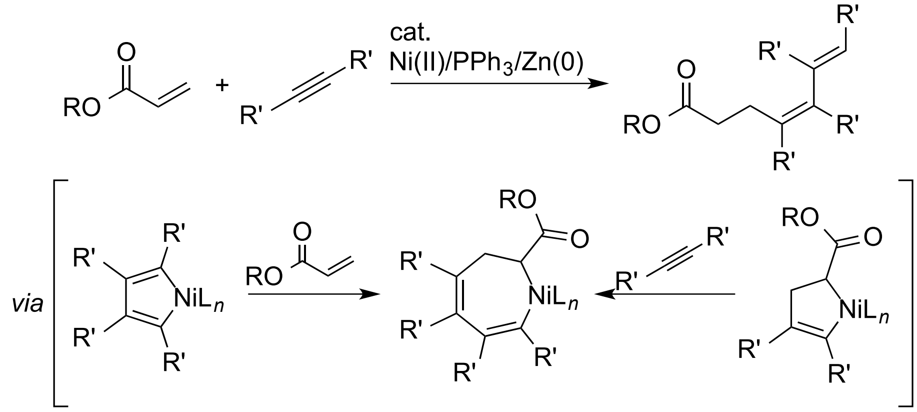
Scheme 8. Nickel-catalyzed [2 + 2 + 2] cyclodimerization of yne-enone.

Kurahashi and Matsubara reported that enones possessing an ester group at the α-position reacted with alkynes in a [4 + 2] cycloaddtion manner (Scheme 9).[13] They proposed that this reaction might proceed via a five-membered nickelacycle formed by oxidative cyclization of an enone with nickel(0) species followed by insertion of alkyne and reductive elimination. The corresponding five-membered nickelacycle was isolated and characterized by X-ray crystallography, and the generation of [4 + 2] cycloadduct from the five-membered nickelacycle was also observed.



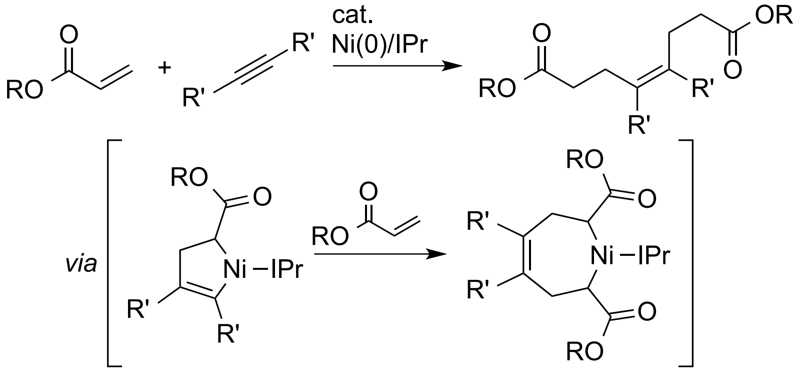
Scheme 9. Nickel-catalyzed [4 + 2] cycloaddition of enones with alkynes

On the other hand, the nickel-catalyzed reactions of α,β-unsaturated esters with alkynes provide linear products. Cheng reported that, in the presence of a Ni(0)/PPh_3 catalyst, acrylates undergo linear trimerization with two alkynes to afford 1,3,5-trienes (Scheme 10).[14] Formation of niclelacyclopentadiene or nickelacyclopentene followed by insertion of the corresponding π-substrate is proposed as key step in this reaction.



Scheme 10. Nickel-catalyzed linear trimerization of acrylates with two alkynes

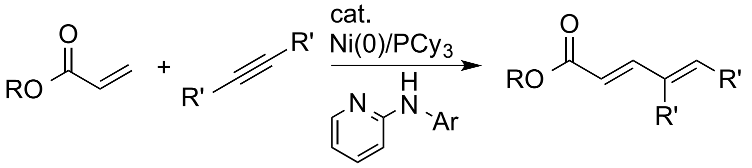
Kurahashi and Matsubara expanded this reaction to the linear trimerization of two molecules of acrylates with alkynes by the use of NHC ligand (Scheme 11).[15] The NHC ligand might enable a selective insertion of an acrylate into the nickelacyclopentene



Scheme 11. Nickel-catalyzed linear trimerization of two molecules of acrylates with alkynes

intermediate.

In addition, nickel-catalyzed cross-dimerization of acrylates with alkynes has been achieved in the presence of 2-aminopyridine additives which might circumvent the insertion of the third π-component before β-H elimination from the five-membered nickelacycle (Scheme 12).[16]

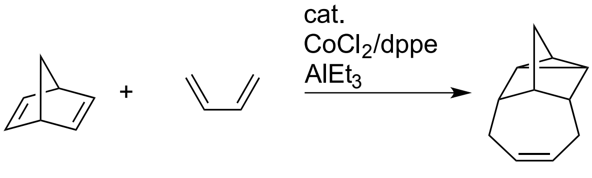


Scheme 12. Nickel-catalyzed linear dimerization of acrylates with alkynes

As reviewed above, the nickel-catalyzed reactions of α,β-unsaturated compounds are efficient methods for construction of highly functionalized carbon frameworks. The appropriate design of catalyst system would provide more diverse molecular complexity.

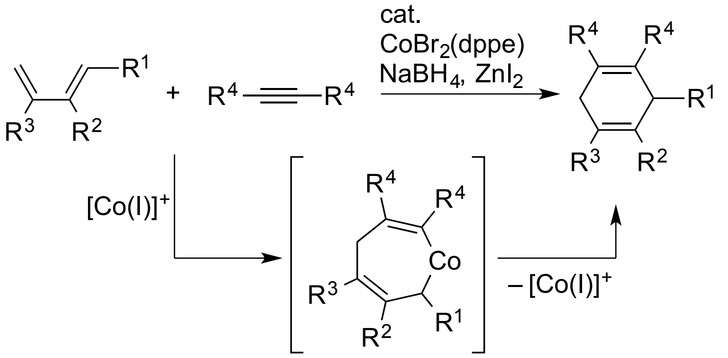
2. Cobalt-catalyzed reaction

In contrast to the nickel complexes, low-valent cobalt complexes efficiently catalyze the dimerization of electronically unbiased unsaturated hydrocarbons via oxidative cyclization. The primitive examples of such transformations are the cyclodimerization of norbornadiene with 1,3-butadiene reported in 1970's (Scheme 13).[17]



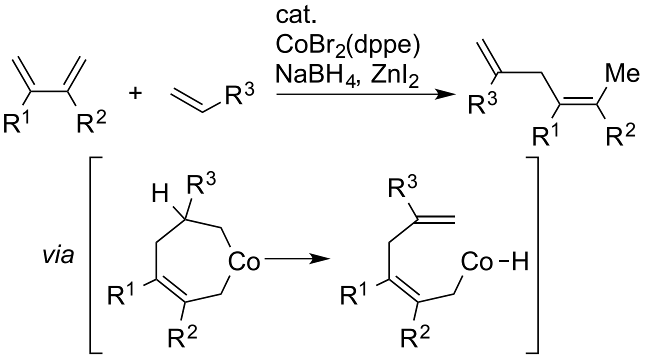
Scheme 13. Cobalt-catalyzed cyclodimerization of norbornadiene with 1,3-enyne

The catalyst system is usually composed of a cobalt(II) or (III) salt and a reducing agent, which generate a catalytically active cobalt(I) species, and the oxidative cyclization of unsaturated π-substrates occurs at the cobalt(I) center. Cyclic products are obtained by [2 + 2], [2 + 2 + 2], [4 + 2], [4 + 2 + 2] or [6 + 2] cycloaddition via reductive elimination from cobaltacycle intermediates.[18] For a typical example, 1,3-dienes react with alkynes to afford 1,4-cyclohexadiene via [4 + 2] cycloaddition in the presence of $CoBr_2(dppe)$, $NaBH_4$ and ZnI_2 (Scheme 12)[18c] A DFT study as well as ESI-MS experiments suggested the formation of the cobaltacycle via oxidative cyclization at the cataionic cobalt(I) center.[19]



Scheme 14. Cobalt-catalyzed [4 + 2] cycloaddition of 1,3-dienes with alkyne

Acyclic products are generated by 1,2-hydrovinylation, 1,4-hydrovinylation or Alder–ene reaction.[20] The cobalt-catalyzed 1,3-diene with alkenes gives 1,4-dienes via 1,4-hydrovinylation (Scheme 15).[20a] This reaction would proceed via the β-H elimination from the seven-membered cobaltacycle. The regioselectivity of both 1,3-dienes and alkenes could be controlled by proper choice of the ligand.



Scheme 15. Cobalt-catalyzed1,4-hydrovinylation of 1,3-dienes with alkene

As overviewed, cobalt complexes are utilized as the catalyst for assembly of electronically unbiased unsaturated compounds. In contrast to the nickel(0), relatively electron-deficient cobalt(I) complexes might be readily coordinated by more electron-rich unsaturated compounds.

The purpose of this thesis is the development of novel transformations of alkenes and alkynes into molecules that are hardly accessible in conventional methods. I envisage that the reactivity of the metallacycle intermediate could be controlled by the use of conjugated unsaturated substrate. This thesis consists of the following four chapters.

In chapter 1, the nickel-catalyzed intermolecular [2 + 2 + 2] cycloaddition of two enones with an alkyne is described.

Chapter 2 discusses the nickel-catalyzed co-trimerization of enones with ethylene in which ethylene can be incorporated as a C4 building block.

Chapter 3 deals with the nickel-catalyzed [2 + 2] cycloaddition of electron-deficient alkenes with 1,3-enynes.

In chapter 4, the cobalt-catalyzed [2 + 2] cycloaddition of simple aklenes with 1,3-enynes is reported. The methodology of nickel catalysis in chapter 3 is successfully expanded to the cobalt-catalyzed reaction. In addition, hydroallylation of 1,3-enyne with alkyl alkenes is also described.

Finally, this thesis is summarized in conclusion.

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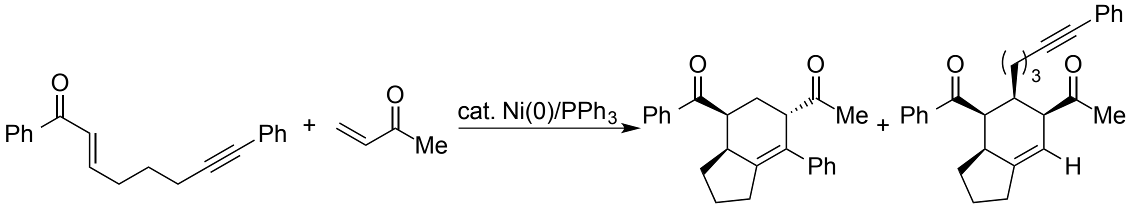
Chapter 1

Nickel-Catalyzed [2 + 2 + 2] Cycloaddition of Two Enones with One Alkyne

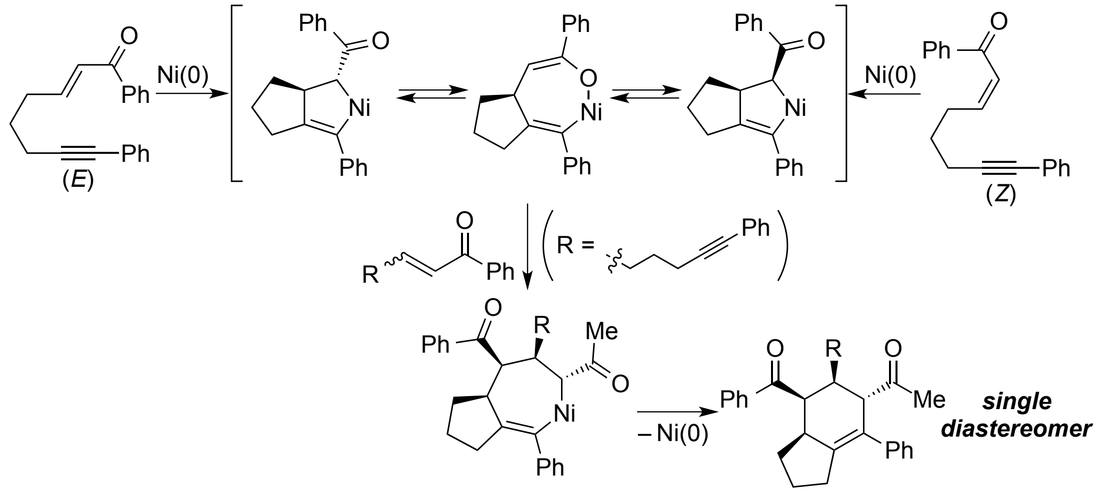
1.1 Introduction

Since Reppe's discovery of the cyclotrimerization of acetylene to benzene in the presence of a nickel complex,[1] the transition-metal-catalyzed [2 + 2 + 2] cycloaddition have become one of the most powerful tools for construction of a six-membered cyclic compounds. To date, various transition metal complexes have been utilized as the catalyst and a variety of coupling patterns has been reported.[2] The [2 + 2 + 2] cycloaddition of two alkene units with one alkyne unit provides cyclohexene derivatives possessing up to four stereogenic centers in a single step.[3] However, alkenes are usually less reactive than alkynes in the transition-metal-catalyzed reactions, thus, [2 + 2 + 2] cycloaddition of two alkenes with an alkyne is limited to the intramolecular reaction of diene-ynes[3a–f] and the intermolecular reaction of 1,*n*-enynes with an alkenes.[3g,h] Montgomery described the Ni(0)/PPh_3-catalyzed [2 + 2 + 2] cyclodimeriation of an yne-enone to afford a bicyclic cyclohexene derivative in a diastereoselective manner.[3g] The intermolecular reaction of an yne-enone with another enone is also applicable while the diastereomer or the homo-dimer of the yne-enone was obtained in some cases (Scheme 1.1).



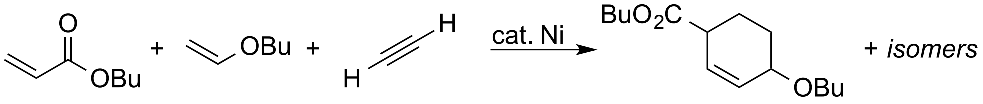
Scheme 1.1. Nickel-catalyzed [2 + 2 + 2] cycloaddition of a yne-enone with an enone

This reaction is not stereospecific but stereoselective since both (*E*)- and (*Z*)-yne-enones provided the same diastereoisomer, which indicates the involvement of equilibrium between five- and seven-membered nickelacycle (Scheme 1.2). A diastereoselective incorporation of the second enone to the nickelacycle followed by reductive elimination is a possible reaction pathway.



Scheme 1.2. A mechanism for [2 + 2 + 2] cycloaddition of (*E*)- or (*Z*)-yne-enone

Only one example of the fully intermolecular [2 + 2 + 2] cycloaddition of two alkenes with an alkyne appeared in literature. Reppe reported the [2 + 2 + 2] cycloaddition of acetylene with an acrylate and a vinyl ether (Scheme 1.3).[4] However, the resulting cyclohexene derivatives has not been identified spectroscopically.



Scheme 1.3. Nickel-catalyzed [2 + 2 + 2] cycloaddition of an acrylate, a vinyl ether and acetylene

Herein, a nickel-catalyzed fully intermolecular [2 + 2 + 2] cycloaddition of two enones with one alkyne and its asymmetric variant are described. Mechanistic studies including stoichiometric reaction and isolation of η^3-oxaallyl-nickel complexes are also discussed.

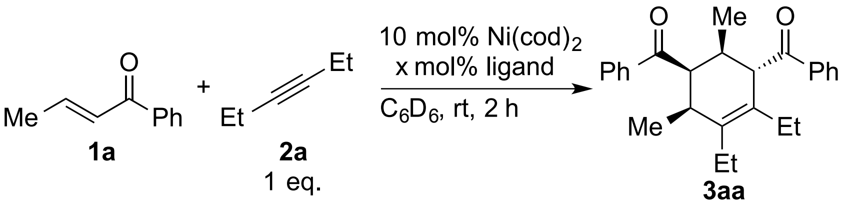
1.2 Results and Discussion

1.2.1 Nickel-catalyzed intermolecular [2 + 2 + 2] cycloaddition of enones and alkynes

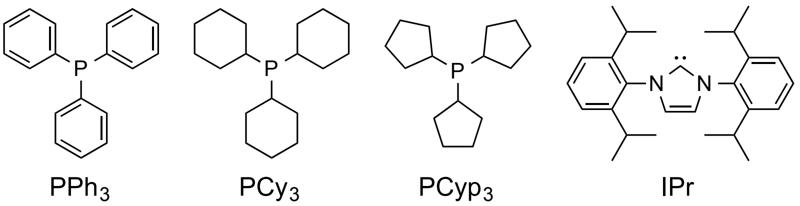
Initially, an intermolecular reaction of (*E*)-1-phenyl-2-buten-1-one (**1a**) with 3-hexyne (**2a**) in the presence of Ni(cod)$_2$ and PPh$_3$ was conducted (Table 1.1, run 1). Although the Ni(0)/PPh$_3$ system efficiently catalyzed the [2 + 2 + 2] cycloaddition of yne-enones,[3g] only a generation of an unreactive complex (η^2-**2a**)Ni(PPh$_3$)$_2$ was observed.[5] This result indicated that the coordination of **1a** is less favorable than that of

2a under Ni(0)/PPh_3 system. Therefore, more electron-donating and bulkier ligands were investigated. Utilizing PCy_3, $PCyp_3$ or IPr, the desired cyclohexene derivative **3aa** was obtained in high yield (runs 2–4). Although **3aa** has four stereogenic centers in the six-membered ring, only a single isomer was obtained out of the eight possible diasteromers. Among these ligands, the most effective $PCyp_3$ was used for further investigation.

Table 1.1. Screening of ligands

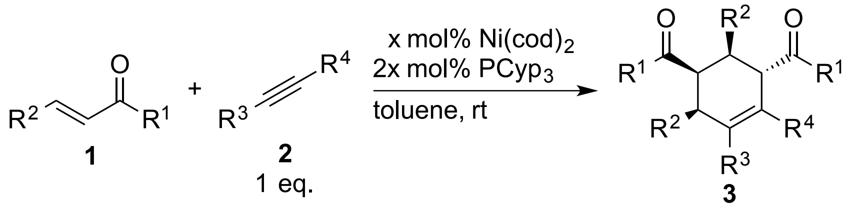


run	ligand	x/mol%	yield/%
1	PPh_3	40	0
2	PCy_3	40	87
3	$PCyp_3$	40	90
4	IPr	10	81



In the presence of 1mol% of $Ni(cod)_2/PCyp_3$ (1:2), the reaction of **1a** with **2a** took place to give **3aa** in 94% yield (Table 1.2). Enone **1a** also reacted with internal alkynes **2b**–**2e** to give the corresponding [2 + 2 + 2] cycloadduct **3ab**–**3ae** in excellent yields. The molecular structure of **3ab** was unambiguously confirmed by X-ray crystallography (Figure 1.1). With 10 mol% catalyst loading, the reactions of terminal alkynes **2f** and **2g** took place to afford **3af** and **3ag** in high yields. Among the unsymmetrical alkynes, phenyl-substituted **2d** and **2f** showed much better regioselectivities than **2e** and **2g**, probably due to the contribution of an η^3-benzyl intermediate. Although the reactions of other enones were slower than **1a**, (*E*)-3-penten-2-one (**1b**) and (*E*)-4-hexen-3-one (**1c**) reacted with **2a** and **2c** to afford **3bc**, **3ca** and **3cc** in high yields using 10mol% of nickel catalyst. Chalcone (**1d**) also reacted with **2a** to give the expected cyclohexene **3da** (49%) with a concomitant formation of a cyclohexadiene derivative (7%), a [2 + 2 + 2] cycloadduct of an enone with two alkynes. Notably, all of these cyclohexene

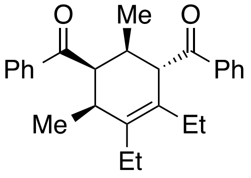
Table 1.2. Ni-catalyzed [2 + 2 + 2] cycloaddition of enones with alkynes



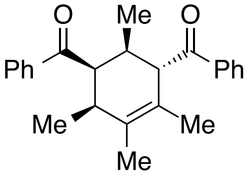
1a: R^1 = Ph, R^2 = Me
1b: R^1,R^2 = Me
1c: R^1 = Et, R^2 = Me
1d: R^1,R^2 = Ph

2a: R^3,R^4 = Et
2b: R^3,R^4 = Me
2c: R^3,R^4 = Ph
2d: R^3 = Me, R^4 = Ph

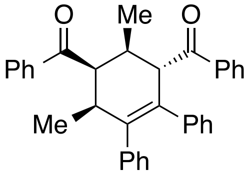
2e: R^3 = Pr, R^4 = Me
2f : R^3 = H, R^4 = Ph
2g: R^3 = Bu, R^4 = H



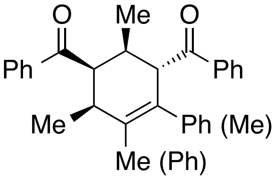
3aa: 94%
(1 mol%, 5 h)



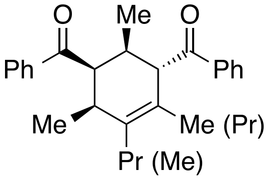
3ab: 96%
(1 mol%, 5 h)



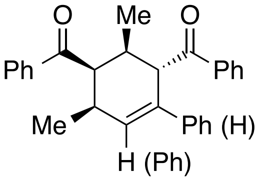
3ac: 96%
(1 mol%, 5 h)



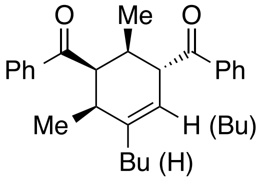
3ad: 97% (90:10)
(1 mol%, 5 h)



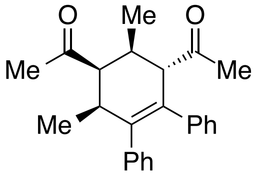
3ae: 93% (68:32)
(1 mol%, 5 h)



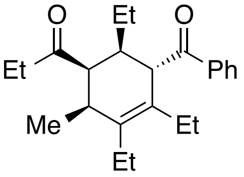
3af: 89% (92:8)
(10 mol%, 20 h)



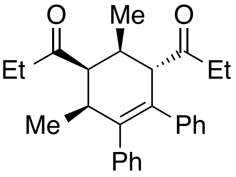
3ag: 74% (65:35)
(10 mol%, 20 h)



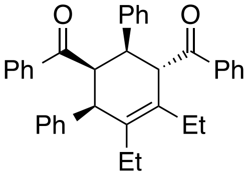
3bc: 98%
(10 mol%, 20 h)



3ca: 82%
(10 mol%, 20 h)



3cc: 81%
(10 mol%, 20 h)



3da: 49%
(10 mol%, 20 h)

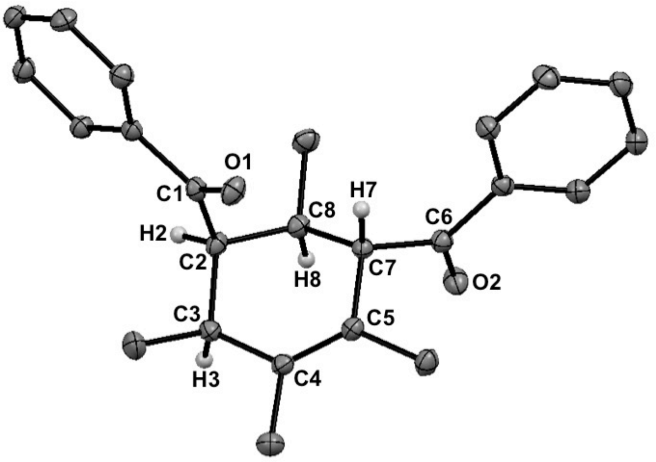
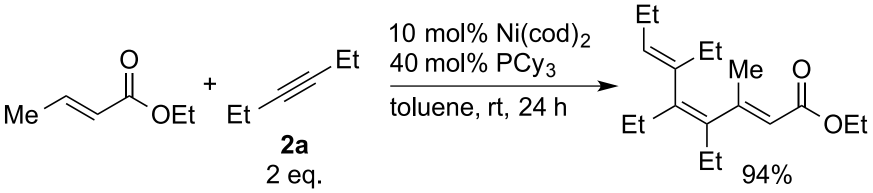


Figure 1.1. Molecular structure of **3ab** with thermal ellipsoids at the 30% probability level. H atoms except for **H2**, **H3**, **H7** and **H8** are omitted for clarity.

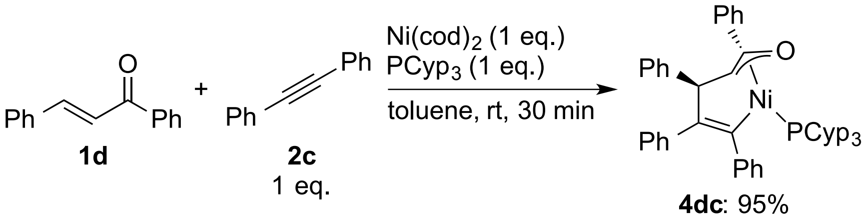
products were obtained as a single diastereoisomer.

In contrast to enones, the reaction of (*E*)-ethyl crotonate with **2a** gave an acyclic hexatriene in 94% yield (eq. 1.1).[6] Niclkelacycles prepared from α,β-unsaturated esters are known to form *C*-enolate structure, which might be the reason why crotonate did not give the corresponding cyclohexene derivative (*vide infra*).[7]



(1.1)

To elucidate the reaction mechanism, a stoichiometric reaction was conducted. Treatment of **1d** with **2c**, $Ni(cod)_2$ and $PCyp_3$ gave a nickelacycle **4dc** in 95% isolated yield (eq. 1.2). The molecular structure of **4dc** was confirmed by X-ray diffraction analysis that revealed the formation of an η^3-oxaallyl structure (Figure 1.2). The ^{1}H and



(1.2)

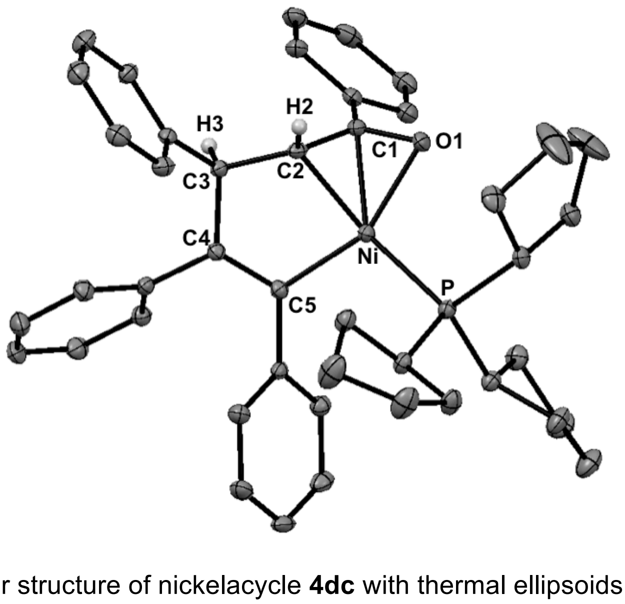
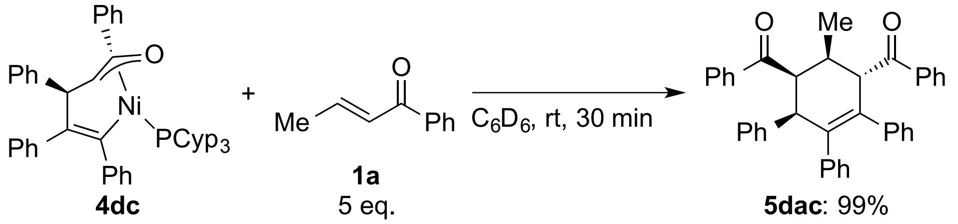


Figure 1.2. Molecular structure of nickelacycle **4dc** with thermal ellipsoids at the 30% probability level. H atoms except for **H2** and **H3** are omitted for clarity.

^{13}C NMR spectra of **4dc** were also consistent with the η^3-oxaallyl coordination. In addition, the configuration between **H2** and **H3** was *trans* to each other.

In order to clarify the possible reaction pathway, the reaction of **4dc** with another enone was examined. As a result, nickelacycle **4dc** reacted with **1a** at room temperature to give **5dac**, a [2 + 2 + 2] cycloadduct of **1d**, **1a** and **2c**, quantitatively (eq. 1.3). During this reaction, the inversion of the stereochemistry of the chalcone moiety was observed. On the other hand, when treating nickelacycle **4dc** with less-reactive enone **1c**, a mixture of three-component [2 + 2 + 2] cycloadduct **5dcc** and two-component [2 + 2 + 2] cycloadduct **3cc** was obtained (eq. 1.4). The formation of **3cc** indicated that oxidative cyclization is a reversible process in this reaction.

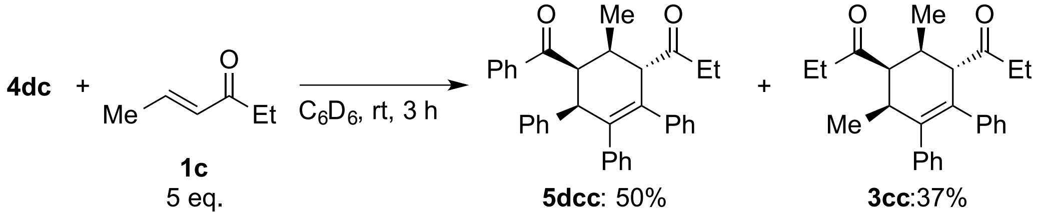


4dc

1a
5 eq.

5dac: 99%

(1.3)



4dc

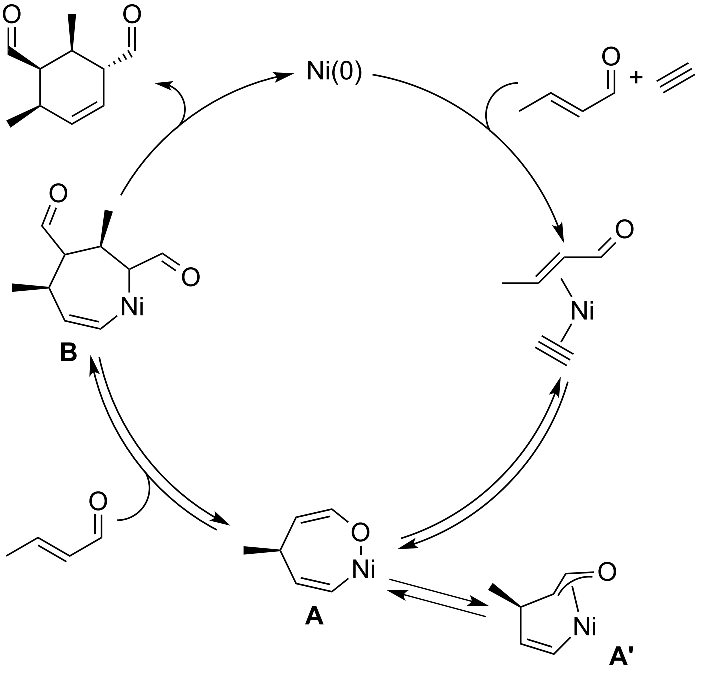
1c
5 eq.

5dcc: 50%

3cc:37%

(1.4)

Based on these observations, a plausible mechanism is shown in Scheme 1.4. The oxidative cyclization of an enone and an alkyne at the nickel(0) center occurs to give a nickelacycle intermediate, which is in equilibrium between η^1-*O*-nickelenolate **A** and η^3-oxaallylnickel **A'**. The inversion of the stereochemistry of the chalcone moiety from **4da** to **5dac** indicated the involvement of η^1-*O*-nickelenolate **A**. In addition, Montgomery reported the isolation of a seven-membered η^1-*O*-nickelenolate complex by the oxidative cyclization of an yne-enal with an nickel(0) complex.[8] Then, a seven-membered nickelacycle intermediate **B** is generated by 1,4-addition of η^1-*O*-nickelenolate **A** to the second enone. The reaction of the six-membered η^1-*O*-nickelenolate with an enone to give the corresponding nickelacycle has been reported.[9] Reductive elimination from intermediate **B** affords the [2 + 2 + 2] cycloaddition product and nickel(0) species is regenerated.

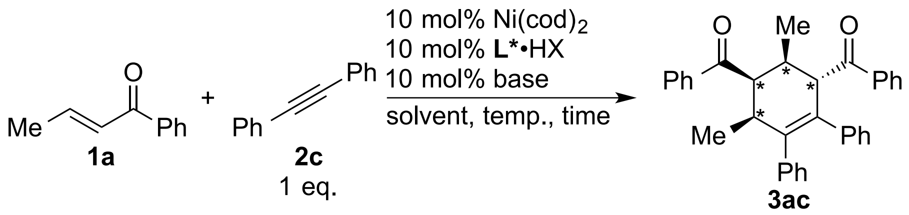


Scheme 1.4. A plausible mechanism

1.2.2 Nickel/chiral NHC-catalyzed asymmetric [2 + 2 + 2] cycloaddition of enones and alkynes

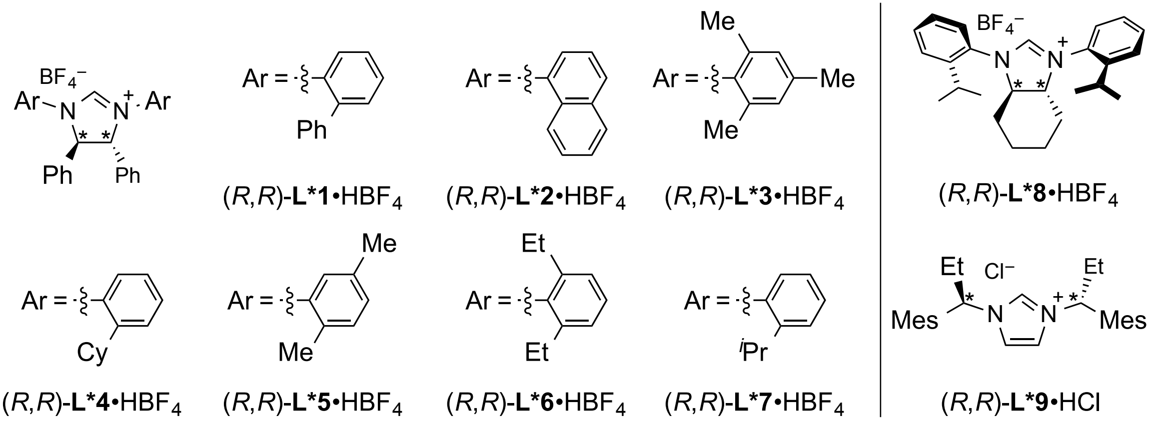
As mentioned above, the nickel-catalyzed [2 + 2 + 2] cycloaddition of enones and alkynes afforded cyclohexene derivatives with four stereogenic centers diastereoselectively. Thus, the asymmetric version of this reaction was next investigated. To achieve the reaction, bulky and highly electron donating monodentate ligands are suitable to promote oxidative cyclization effectively. Among such ligands, I focused on the chiral *N*-heterocyclic carbenes (NHCs), which can be prepared from readily available chiral amines.[10] Optimizations of reaction conditions was performed utilizing **1a** and **2c** (Table 1.3). First, a series of chiral NHCs was examined in the presence of Ni(cod)$_2$ and KO^{t}Bu (runs 1–9). As for chiral NHC, *N*-2-biphenyl substituted **L*1** and *N*-1-naphthyl substituted **L*2** showed high enantioselectivity of (+)-**3ac** (runs 1, 2). The reaction with *N*-2,4-xylyl substituted **L*5** and *N*-1-mesylpropyl substituted **L*9** gave oligomers of **1a** and no **3ac** was generated (runs 5, 9). When utilizing **L*6**, **L*7** and **L*8**, the opposite enantiomer (–)-**3ac** was obtained probably due to the different steric environment around the nickel center (runs 6–8). Next, the base was screened using **L*1** and **L*2**, and LiO^{t}Bu with **L*1** was found to be the most suitable to give (+)-**3ac** in 85%*ee* (run 11). On the other hand, the reaction with LiO^{t}Bu and **L*2** was very slow to

Table 1.3. Optimization for nickel/chiral NHC-catalyzed asymmetric [2 + 2 + 2] cycloaddition



run	L*•HX	base	solvent	temp (ºC)	time (h)	yield (%)	*ee* (%)
1	(*R*,*R*)-**L*1**•HBF$_4$	KO^{t}Bu	benzene	23	24	58	77
2	(*R*,*R*)-**L*2**•HBF$_4$	KO^{t}Bu	benzene	23	24	33	80
3	(*R*,*R*)-**L*3**•HBF$_4$	KO^{t}Bu	benzene	23	1	77	36
4	(*R*,*R*)-**L*4**•HBF$_4$	KO^{t}Bu	benzene	23	24	54	10
5	(*R*,*R*)-**L*5**•HBF$_4$	KO^{t}Bu	benzene	23	0.25	0	
6	(*R*,*R*)-**L*6**•HBF$_4$	KO^{t}Bu	benzene	23	1	21	–39
7	(*R*,*R*)-**L*7**•HBF$_4$	KO^{t}Bu	benzene	23	48	68	−35
8	(*R*,*R*)-**L*8**•HBF$_4$	KO^{t}Bu	benzene	23	5	59	−6
9	(*R*,*R*)-**L*9**•HCl	KO^{t}Bu	benzene	23	24	0	
10	(*R*,*R*)-**L*1**•HBF$_4$	NaO^{t}Bu	benzene	23	24	47	61
11	(*R*,*R*)-**L*1**•HBF$_4$	LiO^{t}Bu	benzene	23	48	56	85
12	(*R*,*R*)-**L*2**•HBF$_4$	LiO^{t}Bu	benzene	23	170	51	68
13	(*R*,*R*)-**L*1**•HBF$_4$	LiO^{t}Bu	tolunene	23	48	46	70
14	(*R*,*R*)-**L*1**•HBF$_4$	LiO^{t}Bu	THF	23	48	54	85
15	(*R*,*R*)-**L*1**•HBF$_4$	LiO^{t}Bu	MeCN	23	48	29	70
16	(*R*,*R*)-**L*1**•HBF$_4$	LiO^{t}Bu	benzene	30	48	52	92
17	(*R*,*R*)-**L*1**•HBF$_4$	LiO^{t}Bu	benzene	40	24	72	74
18	(*R*,*R*)-**L*1**•HBF$_4$	LiO^{t}Bu	benzene	10	48	11	80
19[a]	(*R*,*R*)-**L*1**•HBF$_4$	LiO^{t}Bu	benzene	30	24	84	92

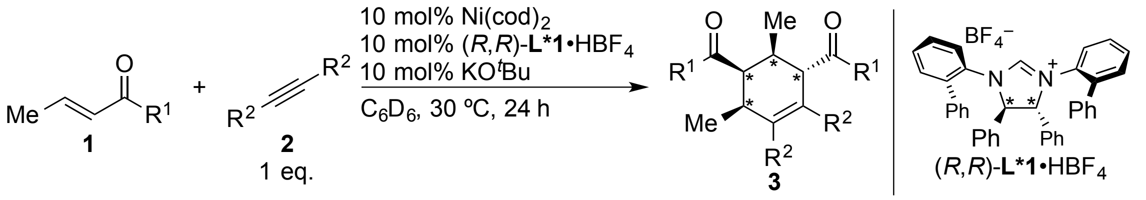
[a] The reaction performed upon stirring.



give (+)-**3ac** in inferior yield and *ee* (run 12). As for solvent, THF was comparable to benzene (runs 11, 14), while toluene and acetonitrile were less effective in both yield and *ee* (runs 13, 15). The temperature was critical to this reaction. By elevating the reaction temperature to 30 ºC, the enantioselectivity was improved to 92%*ee* (run 16). Although the reaction proceeded faster at 40 ºC, enantioselectivity was diminished (run 17). At 10 ºC, (+)-**3ac** was obtained in 11% and 80%*ee* (run 18). Remarkably, stirring the reaction mixture improved the yield without loss of enantioselectivity, which might due to the low solubility of the chiral NHC salt and the base to benzene (84%, 92%*ee*, run 19). Thus, the optimized reaction conditions were determined as follows: 10 mol% of Ni(cod)$_2$, (*R*,*R*)-**L*1**·HBF$_4$ and LiO^{t}Bu in benzene at 30 ºC upon stirring.

The scope and limitations of this asymmetric [2 + 2 + 2] cycloaddition is summarized in Table 1.4. The reaction of **1a** with bis(*p*-tolyl)acetylene (**2h**) and bis(*m*-tolyl)acetylene (**2i**) gave (+)-**3ah** (95%, 76%*ee*) and (+)-**3ai** (58%, 74%*ee*). On the other hand, bis(*o*-tolyl)acetylene (**2j**) gave no desired product which might be due to the bulkiness of *o*-tolyl group. In the reaction of electron-withdrawing group substituted acetylene, bis(*p*-trifluoromethylphenyl)acetylene (**2l**) and bis(*p*-fluorophenyl)acetylene (**2m**) gave (+)-**3al** and (+)-**3am** in moderate yields and enantioselectivities. On the other hand, the use of the methoxy groups substituted diphenylacetylene **2k** resulted in no reaction probably because of low coordination ability of an electron-rich substrate. The reaction of bis(2-thienyl)acetylene **2n** gave (+)-**3an** in good yield and *ee* (81%, 79%ee). Among the reactions of alkyl acetylenes, the use of 3-hexyne (**2a**) gave (−)-**3aa** in 69%*ee* and the other alkynes resulted in lower *ee*. Thus, both the bulkiness and the electronic nature of alkynes might affect to yields and enantioselectivities. Next, the substituents on enones were examined. The reaction of enone bearing *p*-fluorophenyl group (**1g**) gave (+)-**3gc** in 74%, 93%*ee*. On the other hand, enones with the electron-donatng substituents resulted in low yield and moderate *ee* of (+)-**3ec** and (+)-**3fc**. Although yield was low, 2-hexen-3-one (**1c**) reacted with **2c** to give (+)-**3cc** in 91%*ee*. Since the absolute configuration of the obtained [2 + 2 + 2] cycloadducts has not yet been determined, the possible enantioinduction pathway is still ambiguous. However, the crystal structure of **L1***•HBF$_4$ reported by Hoveyda indicated that **L*1** has a *pseudo*-axial chirality between two biphenyl groups arising from the chirality of the backbone.[11] This *pseudo*-axial chirality might construct a rigid chiral environment around nickel center during the reaction.

Table 1.4. Nickel/chiral NHC-catalyzed asymmetric [2 + 2 + 2] cycloaddition

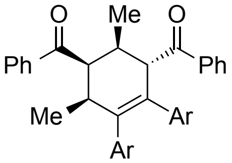


1a: R^1 = Ph
1c: R^1 = Et
1e: R^1 = *p*-MeC_6H_4
1f : R^1 = *p*-$MeOC_6H_4$
1g: R^1 = *p*-FC_6H_4

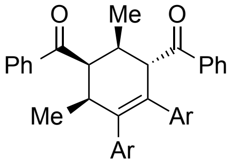
2a: R^2 = Et
2b: R^2 = Me
2c: R^2 = Ph
2h: R^2 = *p*-MeC_6H_4

2i : R^2 = *m*-MeC_6H_4
2j : R^2 = *o*-MeC_6H_4
2k : R^2 = *p*-$MeOC_6H_4$
2l : R^2 = *p*-FC_6H_4

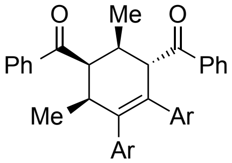
2m: R^2 = *p*-$F_3CC_6H_4$
2n : R^2 = 2-thienyl
2o : R^2 = Pr
2p : R^2 = Bu



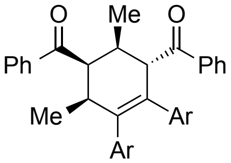
(+)-**3ac**
Ar = Ph
84%, 92%*ee*



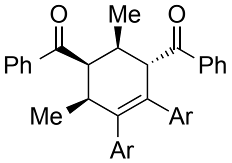
(+)-**3ah**
Ar = *p*-MeC_6H_4
95%, 76%*ee*



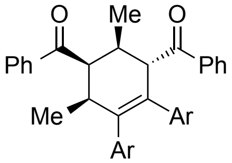
(+)-**3ai**
Ar = *m*-MeC_6H_4
58%, 74%*ee*



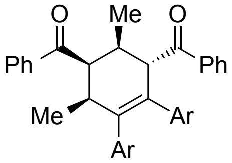
3aj
Ar = *o*-MeC_6H_4
0%



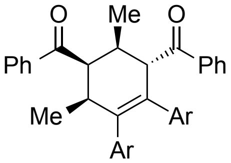
3ak
Ar = *p*-$MeOC_6H_4$
0%



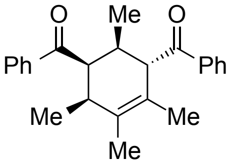
(+)-**3al**
Ar = *p*-FC_6H_4
76%, 69%*ee*



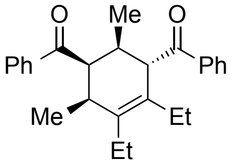
(+)-**3am**
Ar = *p*-$CF_3C_6H_4$
54%, 52%*ee*



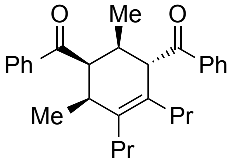
(+)-**3an**
Ar = 2-thienyl
81%, 79%*ee*



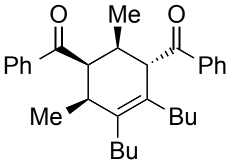
(–)-**3ab**
60%, 60%*ee*



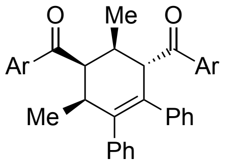
(–)-**3aa**
60%, 69%*ee*



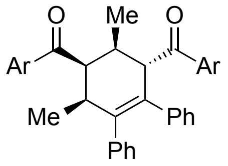
(–)-**3ao**
73%, 50%*ee*



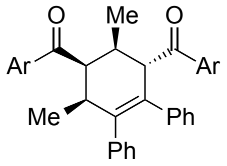
(–)-**3ap**
65%, 30%*ee*



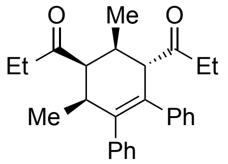
(+)-**3ec**
R = *p*-MeC_6H_4
31%, 64%*ee*



(+)-**3fc**
R = *p*-$MeOC_6H_4$
19%, 70%*ee*



(+)-**3gc**
R = *p*-FC_6H_4
74%, 93%*ee*



(+)-**3cc**[b]
22%, 91%*ee*

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[a] For 72 h.

1.3 Conclusion

In chapter 1, a nickel-catalyzed fully intermolecular [2 + 2 + 2] cycloaddition of two enones with one alkyne was developed. Isolation of key reaction intermediate and its reaction with enone revealed that this reaction proceeded via the nucleophilic attack of η^1-*O*-enolate complex to another enone, which is the determining step of relative stereochemistry. The asymmetric [2 + 2 + 2] cycloaddition was also successfully established by utilizing chiral NHC ligand. This reaction provided highly enantio-enriched cyclohexene derivatives with four chiral centers in one step from simple substrates.

1.4 Experimental section

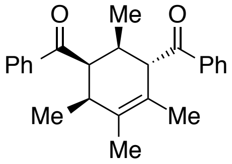
General: All manipulations were conducted under a nitrogen atmosphere using standard Schlenk or dry box techniques. ^{1}H, ^{31}P, and ^{13}C nuclear magnetic resonance spectra were recorded on JEOLGSX–270S, Brucker DPX 400, Brucker AVANCE 400, Brucker Avance III spectrometers. The chemical shifts in ^{1}H nuclear magnetic resonance spectra were recorded relative to Me_4Si or residual protiated solvent ($CHCl_3$ (δ 7.27) or C_6D_5H (δ 7.16)). The chemical shifts in the ^{13}C spectra were recorded relative to Me_4Si. The chemical shifts in the ^{31}P spectra were recorded using 85% H_3PO_4 as external standard. Assignment of the resonances in ^{1}H and ^{13}C NMR spectra was based on ^{1}H-^{1}H COSY, HMQC, and HMBC experiments. Elemental analyses were performed at Instrumental Analysis Center, Faculty of Engineering, Osaka University. X-ray crystal data were collected by a Rigaku RAXIS-RAPID Imaging Plate diffractometer. High performance liquid chromatography (HPLC) was performed on HITACHI D-7400 (UV-Detector). HPLC with detection at 254 nm using a Chiralpak IA and OJ column using a flow rate of 0.5 mL per minute. Optical rotations were measured with JASCO DIP-181 at Instrumental Analysis Center, Graduate School of Engineering, Osaka University.

Materials: The degassed and distilled toluene used in this work was commercially available. C_6D_6 was distilled from sodium benzophenone ketyl. All commercially available reagents were distilled and degassed prior to use. (*E*)-1-phenylbut-2-en-1-one (**1a**) was prepared by the methods in the literature.

General procedure A for the 1 mol% Ni-catalyzed [2+2+2] cycloaddition: To a solution of Ni(cod)$_2$ (0.01 mmol) and PCyp$_3$ (0.02 mmol) in toluene (2 mL) was added a solution of enone (1.0 mmol) and alkyne (1.0 mmol) in toluene (2 mL) at room temperature. The reaction mixture was stirred for 5 h. The reaction mixture was directly filtered through a short silica column and washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was purified via column chromatography (SiO$_2$, hexane/Et$_2$O = 95:5).

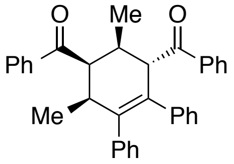
General procedure B for the 10 mol% Ni-catalyzed [2+2+2] cycloaddition: To a solution of Ni(cod)$_2$ (0.05 mmol) and PCyp$_3$ (0.10 mmol) in toluene (1 mL) was added a solution of enone (0.50 mmol) and alkyne (0.50 mmol) in toluene (1 mL) at room temperature. The reaction mixture was stirred for 20 h. The reaction mixture was directly filtered through a short silica column and washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was purified via column chromatography (SiO$_2$, hexane/Et$_2$O = 95:5).

(2,4,5,6-tetramethylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ab)



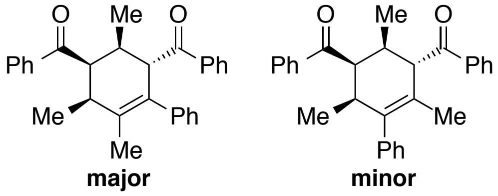
Following the general procedure **A**, Ni(cod)$_2$ (2.6 mg, 0.009 mmol), PCyp$_3$ (4.8 mg, 0.020 mmol), **1a** (147.2 mg, 1.00 mmol) and 2-butyne (78 µL, 1.00 mmol) were stirred at room temperature for 5 h. Purification by column chromatography gave 167.8 mg of **3ab** (96%) as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$, rt, δ/ppm): 0.95 (d, J_{HH} = 7.2 Hz, 3H), 1.26 (d, J_{HH} = 6.8 Hz, 3H), 1.63 (s, 3H), 1.75 (s, 3H), 2.54 (m, 1H), 2.76 (m, 1H), 3.89 (dd, J_{HH} = 6.0, 3.2 Hz, 1H), 4.09 (s, 1H), 7.40-7.60 (m, 6H), 7.88 (d, J_{HH} = 7.2 Hz, 2H), 8.02 (d, J_{HH} = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 15.7, 17.1, 18.7, 19.2, 33.1, 37.2, 46.4, 56.2, 122.8, 128.0, 128.4, 128.6, 128.7, 131.7, 132.5, 133.1, 137.2, 138.7, 203.2, 204.0; HRMS: calcd for $C_{24}H_{26}O_2$ 346.1933, found m/z 346.1922. X-ray data for **3ab**: M = 346.45, colorless, monoclinic, $P2_1/a$ (No.14), a = 10.2808(3) Å, b = 15.2707(5) Å, c = 12.1054(4) Å, β = 95.070(2) °, V = 1892.91(10) Å^3, Z = 4, D_{calcd} = 1.216 g/cm^3, T = -150.0 °C, R_1 (wR_2) = 0.0509 (0.1421).

(2,6-dimethyl-4,5-diphenylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ac)



Following the general procedure **A**, Ni(cod)$_2$ (2.7 mg, 0.010 mmol), PCyp$_3$ (5.1 mg, 0.021 mmol) **1a** (152.5 mg, 1.04 mmol) and tolan (187.6 mg, 1.05 mmol) in toluene (2 mL) were stirred at room temperature for 5 h. Purification by column chromatography gave 235.3mg of **3ac** (96%) as a white solid. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.74 (d, J_{HH} = 7.2 Hz, 3H), 1.49 (d, J = 6.8 Hz, 3H), 2.81 (m, 1H), 3.43 (m, 1H), 4.21 (dd, J = 6.4, 3.2 Hz, 1H), 4.76 (dd, J = 6.0, 2.4 Hz, 1H), 6.8-7.1 (m, 10H), 7.30-7.60 (m, 6H), 7.83 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 16.1, 18.8, 32.9, 36.6, 46.2, 56.4, 125.8, 126.0, 127.4, 127.5, 128.1, 128.2, 128.5, 128.7, 129.6, 129.8, 132.3, 132.7, 132.9, 137.1, 138.7, 140.9, 141.3, 141.8, 201.8, 203.6; HRMS: calcd for $C_{34}H_{30}O_2$ 470.2246, found m/z 470.2242.

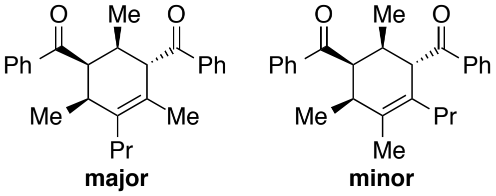
(2,5,6-trimethyl-4-phenylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ad major) and (2,4,6-trimethyl-5-phenylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ad minor)



Following the general procedure **A**, Ni(cod)$_2$ (2.7 mg, 0.010 mmol), PCyp$_3$ (4.9 mg, 0.021 mmol), **1a** (150.7 mg, 1.03 mmol) and 1-phenyl-1-propyne (120.8 mg, 1.04 mmol) were stirred at room temperature for 5 h. Purification by column chromatography gave 204.0 mg of **5** (97%, 90:10) as a white solid. **Spectral data for 3ad major:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.03 (d, J_{HH} = 7.6 Hz, 3H), 1.38 (d, J_{HH} = 7.2 Hz, 3H), 1.61 (s, 3H), 2.68 (m, 1H), 2.95 (dq, J_{HH} = 7.6, 7.2 Hz, 1H), 4.06 (dd, J_{HH} = 6.0, 3.2 Hz, 1H), 4.40 (dd, J_{HH} = 2.0, 1.6 Hz, 1H), 7.05-7.63 (m, 11H), 7.80 (d, J_{HH} = 7.6 Hz, 2H,), 7.95 (d, J_{HH} = 7.6 Hz, 2H,); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 18.1, 20.5, 20.9, 34.6, 38.2, 47.4, 57.5, 124.0, 125.9, 125.9, 126.0, 126.2, 126.4, 126.8, 127.6, 130.3, 130.4, 132.4, 134.7, 136.0, 140.2, 197.3, 198.7; HRMS: calcd for $C_{29}H_{28}O_2$

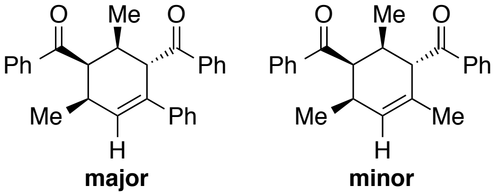
408.2089, found m/z 408.2083. Most of ^{1}H resonances of **3ae minor** were obscured by those of **3ae major**, and thus, characteristic ^{1}H resonances are listed as follows: δ/ppm 3.14 (m, 1H), 4.28, (d, J_{HH} = 3.6 Hz, 1H), 8.07, (d, J_{HH} = 11.6 Hz, 2H).

(2,5,6-trimethyl-4-propylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ae major) and (-2,4,6-trimethyl-5-propylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ae minor)



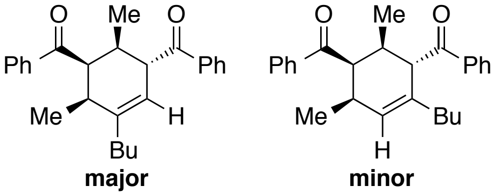
Following the general procedure **A**, Ni(cod)$_2$ (2.6 mg, 0.009 mmol), PCyp$_3$ (6.2 mg, 0.026 mmol), **1a** (143.3 mg, 0.98 mmol) and 2-hexyne (85.4 mg, 1.04 mmol) were stirred at room temperature for 5 h. Purification by column chromatography gave 170.7 mg of **3ae** (93%, 68:32) as a colorless oil. **Spectral data for 3ae major:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.95 (d, J_{HH} = 7.2 Hz, 3H), 0.97 (t, J_{HH} = 7.2 Hz, 3H), 1.28 (d, J_{HH} = 7.2 Hz, 3H), 1.3-1.6 (m, 2H), 1.64 (d, J_{HH} = 1.2 Hz, 3H) 2.13 (m, 2H), 2.53 (m, 1H), 2.83 (m, 1H), 3.86 (dd, J_{HH} = 6.0, 3.2 Hz, 1H), 4.03 (d, J_{HH} = 3.6 Hz, 1H), 7.40-7.60 (m, 6H), 7.87 (d, J_{HH} = 8.4 Hz, 2H), 8.02 (d, J_{HH} = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 14.2, 15.9, 18.8, 19.2, 22.0, 32.7, 32.7, 35.3, 46.4, 56.7, 123.4, 128.0, 128.4, 128.6, 128.7, 132.5, 133.1, 136.3, 137.1, 138.6, 202.8, 204.0; HRMS: calcd for $C_{26}H_{30}O_2$ 374.2246, found m/z 374.2239. **Spectral data for 3ae minor:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.89 (t, J_{HH} = 7.2 Hz, 3H), 0.94 (d, J_{HH} = 7.2 Hz, 3H), 1.36 (d, J_{HH} = 7.2 Hz, 3H), 1.30-1.50 (m, 2H), 1.55-1.65 (m, 1H), 1.78 (s, 3H), 2.26-2.37 (m, 1H), 2.74 (m, 1H), 3.32 (m, 1H), 3.86 (dd, J_{HH} = 3.2, 6.4 Hz, 1H), 4.09 (s, 1H), 7.40-7.61 (m, 10H), 7.86 (d, J_{HH} = 7.2 Hz, 3H), 8.01 (dd, J_{HH} = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 14.1, 15.8, 17.3, 18.7, 21.6, 32.2, 35.3, 37.1, 45.6, 54.6, 127.0, 128.1, 128.4, 128.6, 128.8, 132.5, 132.9, 133.1, 137.0, 138.3, 202.7, 204.0.

(2,6-dimethyl-4-phenylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3af major) and (2,6-dimethyl-5-phenylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3af minor)



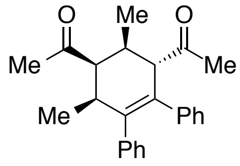
Following the general procedure **B**, Ni(cod)$_2$ (13.6 mg, 0.049 mmol), PCyp$_3$ (24.1 mg, 0.101 mmol), **1a** (74.5 mg, 0.51 mmol) and phenylacetylene (49.7 mg, 0.49 mmol) were stirred at room temperature for 20 h. Purification by column chromatography gave 89.0 mg of **3af** (89%, 92:8) as a pale yellow oil. **Spectral data for 3af major:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.05 (d, J_{HH} = 7.6 Hz, 3H), 1.24 (d, J_{HH} = 6.8 Hz, 3H), 2.71 (m, 1H), 3.15 (m, 1H), 4.08 (dd, J_{HH} = 6.4, 3.6 Hz, 1H), 4.91 (d, J_{HH} = 7.2 Hz, 1H), 5.99 (dd, J_{HH} = 2.8, 1.6 Hz, 1H), 7.08-7.22 (m, 3H), 7.30-7.61 (m, 8H), 7.95-8.01 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 21.0, 21.6, 35.9, 37.3, 48.1, 53.5, 124.1, 124.6, 125.7, 125.9, 126.2, 126.3, 126.4, 128.9, 130.3, 130.5, 133.4, 134.8, 136.6, 138.5, 197.2, 197.7; HRMS: calcd for $C_{28}H_{26}O_2$ 394.1933, found m/z 394.1925. Most of ^{1}H resonances of **3af minor** were obscured by those of **3af major**, and thus, characteristic ^{1}H resonances are listed as follows: δ/ppm 0.75 (d, J_{HH} = 7.2 Hz, 3H), 1.02 (d, J_{HH} = 7.2 Hz, 3H), 5.65 (dd, J_{HH} = 2.8, 2.4 Hz, 1H), 7.93 (d, J_{HH} = 7.6 Hz, 2H), 7.98 (d, J_{HH} = 7.6 Hz, 2H).

(4-butyl-2,6-dimethylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ag major) and (5-butyl-2,6-dimethylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ag minor)



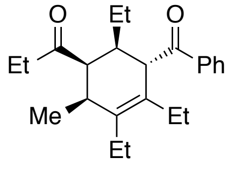
Following the general procedure **B**, Ni(cod)$_2$ (13.9 mg, 0.050 mmol), PCyp$_3$ (24.4 mg, 0.102 mmol), **1a** (71.3 mg, 0.49 mmol) and 1-hexyne (43.4 mg, 0.53 mmol) were stirred at room temperature for 20 h. Purification by column chromatography gave 67.7 mg of **3ag** (74%, 65:35) as a colorless oil. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.89 (t, J_{HH} = 7.2 Hz, 3H$_{min}$), 0.92 (t, J_{HH} = 7.2 Hz, 3H$_{maj}$), 0.98 (d, J_{HH} = 7.6 Hz, 3H$_{min}$), 1.02 (d, J_{HH} = 6.4 Hz, 3H$_{maj}$), 1.04 (d, J_{HH} = 7.2 Hz, 3H$_{maj}$), 1.08 (d, J_{HH} = 7.2 Hz, 3H$_{min}$), 1.17-1.58 (m, 4H$_{maj}$ + 4H$_{min}$), 1.90-2.08(m, 1H$_{maj}$ + 2H$_{min}$), 2.15 (m, 1H$_{maj}$), 2.63 (m, 1H$_{min}$), 2.75-2.90 (m, 2H$_{maj}$), 3.01 (m, 1H$_{min}$), 4.04 (dd, J_{HH} = 6.4, 3.6 Hz, 1H$_{min}$), 4.21 (t, J_{HH} = 6.4, 4.0 Hz, 1H$_{maj}$), 4.40 (m, 1H$_{maj}$ + 1H$_{min}$), 5.48 (s, 1H$_{maj}$ + 1H$_{min}$), 7.42-7.62(m, 6H$_{maj}$ + 6H$_{min}$), 7.94 (d, J_{HH} = 8.0 Hz, 2H$_{min}$), 8.00 (d, J_{HH} = 8.0 Hz, 2H$_{maj}$), 8.04-8.10(m, 2H$_{maj}$ + 2H$_{min}$); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 16.7 (min), 16.8 (maj), 18.5 (maj), 21.0 (min), 21.1 (maj), 21.2 (min), 24.8 (min), 25.0 (maj), 32.1 (min), 32.3 (maj), 34.6 (maj), 35.5 (min), 36.4 (maj), 37.1 (maj), 37.4 (min), 37.5 (min), 48.5 (maj), 49.9 (min), 50.6 (min), 53.5 (maj), 116.8 (maj), 124.6 (min), 125.8, 125.8, 126.2, 126.3, 126.4, 126.5, 130.2 (min), 130.2 (maj), 130.6 (maj), 130.6 (min), 133.0 (min), 134.0, 135.3, 136.8, 137.2, 138.1, (maj), 195.7 (maj), 197.6 (min), 198.5 (maj), 198.6 (min), two signals were probably obscured by other signals; HRMS: calcd for $C_{28}H_{26}O_2$ 374.2246, found m/z 374.2242.

1,1'-(-2,6-dimethyl-4,5-diphenylcyclohex-4-ene-1,3-diyl)diethanone (3bc)



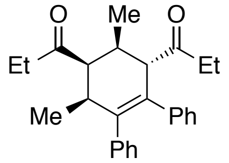
Following the general procedure **B**, Ni(cod)$_2$ (13.2 mg, 0.048 mmol), PCyp$_3$ (24.6 mg, 0.103 mmol), **1b** (75 µL, 0.50 mmol) and tolan (89.5 mg, 0.50 mmol) were stirred at room temperature for 20 h. Purification by column chromatography gave 85.3 mg of **3bc** (98%) as a white solid. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.83 (d, J_{HH} = 7.2 Hz, 3H), 1.29 (d, J_{HH} = 6.8 Hz, 3H), 1.88 (s, 3H), 2.26 (s, 3H), 2.61 (m, 1H), 3.24 (m, 1H), 3.32 (m, 1H), 3.75 (d, J_{HH} = 4.0 Hz, 1H), 6.80-7.20 (m, 10H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 16.6, 18.6, 30.7, 31.0, 31.3, 35.4, 53.1, 61.6, 126.0, 126.0, 127.5, 127.6, 129.4, 129.6, 131.6, 140.6, 140.7, 141.5, 209.9, 210.3; HRMS: calcd for $C_{24}H_{26}O_2$ 346.1933, found m/z 346.1926.

1,1'-(-4,5-diethyl-2,6-dimethylcyclohex-4-ene-1,3-diyl)dipropan-1-one (3ca)



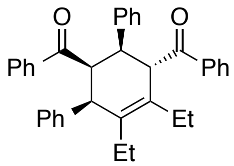
Following the general procedure **B**, Ni(cod)$_2$ (14.2 mg, 0.051 mmol), PCyp$_3$ (24.5 mg, 0.102 mmol), **1c** (48.9 mg, 0.50 mmol) and 3-hexyne (41.6 mg, 0.51 mmol) were stirred at room temperature for 20 h. Purification by column chromatography gave 56.8 mg of **3ca** (82%) as a colorless oil. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.90-1.10 (m, 18H), 1.49 (dq, J_{HH} = 7.6, 7.2 Hz, 1H), 2.04 (dq, J_{HH} = 7.6, 7.2 Hz, 1H), 2.13-2.62 (m, 7H), 2.70-2.85 (m, 2H), 3.09 (d, J_{HH} = 3.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 7.5, 8.0, 13.1, 13.7, 16.6, 18.8, 22.7, 25.3, 30.7, 32.3, 35.4, 35.6, 51.9, 58.7, 128.1, 137.3, 213.2, 213.5; HRMS: calcd for $C_{18}H_{30}O_2$ 278.2246, found m/z 278.2243.

1,1'-(2,6-dimethyl-4,5-diphenylcyclohex-4-ene-1,3-diyl)dipropan-1-one (3cc)



Following the general procedure **B**, Ni(cod)$_2$ (13.8 mg, 0.050 mmol), PCyp$_3$ (24.8 mg, 0.104 mmol) **1c** (49.0 mg, 0.50 mmol) and tolan (90.2 mg, 0.51 mmol) were stirred at room temperature for 20 h. Purification by column chromatography gave 76.1 mg of **3cc** (81%) as a colorless oil. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.71 (t, J_{HH} = 7.2 Hz, 3H), 0.77 (d, J_{HH} = 7.2 Hz, 3H), 1.08 (t, J_{HH} = 7.2 Hz, 3H), 1.20 (d, J_{HH} = 6.8 Hz, 3H), 1.96 (m, 1H), 2.26 (m, 1H), 2.46-2.65 (m, 3H), 3.23-3.33 (m, 2H), 3.78 (dd, J_{HH} = 6.0, 1.0 Hz, 1H), 6.87-7.12 (m, 10H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 7.4, 7.4, 16.8, 18.7, 32.0, 35.9, 37.4, 38.1, 53.0, 60.5, 125.8, 125.9, 127.4, 127.5, 129.4, 129.6, 132.2, 139.8, 140.7, 141.3, 213.1, 213.4; HRMS: calcd for $C_{26}H_{30}O_2$ 374.2246, found m/z 374.2244.

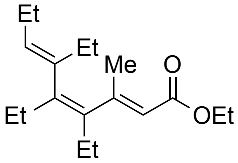
(4,5-diethyl-2,6-diphenylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3da)



Following the general procedure **B**, Ni(cod)$_2$ (13.4 mg, 0.048 mmol), PCyp$_3$ (24.2 mg, 0.101 mmol), **1d** (104.1 mg, 0.50 mmol) and 3-hexyne (41.2 mg, 0.50 mmol) were stirred at room temperature for 20 h. Purification by column chromatography gave 61.5

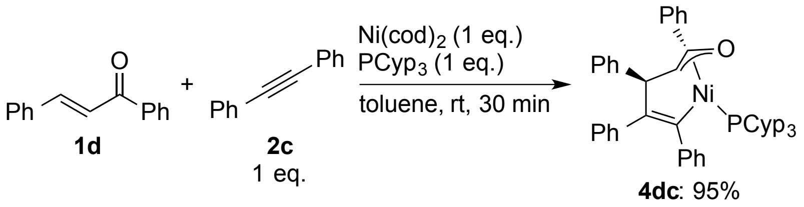
mg of **3da** (49%) as a white solid. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.97 (t, J_{HH} = 7.6 Hz, 3H), 1.22 (t, J_{HH} = 7.6 Hz, 3H), 1.92 (m, 2H), 2.47 (m, 2H), 3.89 (dd, J_{HH} = 11.2, 3.6 Hz, 1H), 4.37 (d, J_{HH} = 6.8 Hz, 1H,), 4.41 (dd, J_{HH} = 7.6, 3.6 Hz, 1H), 5.66 (d, J_{HH} = 11.2 Hz, 1H,), 6.85-7.53 (m, 18H), 7.95 (d, J_{HH} = 8.4 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 13.5, 14.2, 22.5, 25.2, 48.4, 49.4, 49.4, 52.3, 126.2, 126.7, 127.1, 127.4, 127.9, 128.2, 128.2, 128.3, 128.3, 130.0, 131.4, 132.6, 132.8, 135.0, 138.6, 140.3, 140.3, 140.4, 204.5, 204.7; HRMS: calcd for $C_{36}H_{34}O_2$ 498.2559, found m/z 498.2560.

(2*E*,4*Z*,6*E*)-ethyl 4,5,6-triethyl-3-methylnona-2,4,6-trienoate

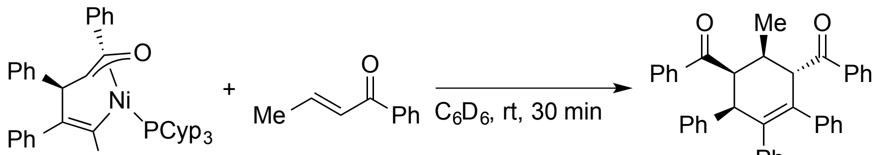


To a solution of Ni(cod)$_2$ (12.9 mg, 0.047 mmol) and PCy$_3$ (27.3 mg, 0.097 mmol) in toluene (2 mL) was added a solution of ethyl (*E*)-2-butenoate (55.0 mg, 0.48 mmol) and 3-hexyne (82.2 mg, 1.00 mmol) in toluene (2 mL) at room temperature. The reaction mixture was stirred for 20 h. The reaction mixture was directly filtered through a short silica column and washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was purified via column chromatography (SiO$_2$, hexane/ethyl acetate = 90:10) to afford 125.5 mg of the titled compound (94%, >95:5) as a colorless oil. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.80-1.05 (m, 12H), 1.26 (t, J_{HH} = 7.2 Hz, 3H), 1.90-2.25 (m, 11H), 4.13 (q, J_{HH} = 7.2 Hz, 2H), 5.06 (t, J_{HH} = 7.2 Hz, 1H), 5.54 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 13.1, 13.2, 13.5, 14.0, 14.3, 20.5, 21.1, 22.9, 23.5, 23.9, 59.2, 117.6, 130.8, 139.6, 139.9, 140.6, 160.6, 166.9; HRMS: calcd for $C_{18}H_{30}O_2$ 278.2246, found m/z 278.2242.

Isolation of [Ni{μ-η^1,η^3-C(Ph)=C(Ph)CH(Ph)CH=C(Ph)O}(PCyp$_3$)] (4dc)

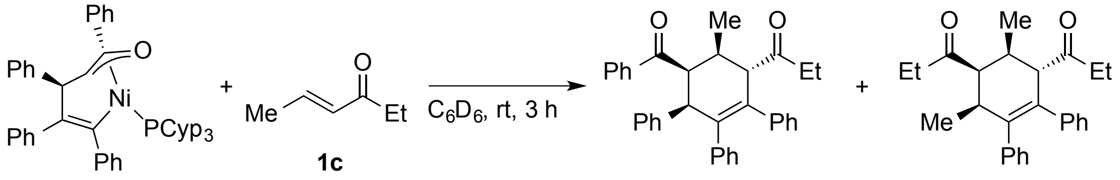


To a solution of Ni(cod)$_2$ (275.8 mg, 1.00 mmol) and PCyp$_3$ (239.2 mg, 1.00 mmol) in toluene (5 mL) was added a solution of **1d** (205.5 mg, 0.99 mmol) and tolan (179.5 mg, 1.01 mmol) in toluene (2 mL). The reaction mixture was stirred at room temperature for 30 minute. The solution was concentrated *in vacuo*. Hexane was added (5 mL) to the residue and the suspension was concentrated *in vacuo*. The residue was washed with cold pentane to give **4dc** (623.2 mg, an orange solid) in 92% yield. A single crystal for X-ray diffraction analysis was prepared by recrystallization from toluene/hexane at -20 °C. **Spectral data:** ^{1}H NMR (400 MHz, C$_6$D$_6$): δ 1.30-2.03 (m, 27H, Cyp), 5.07 (d, J_{HH} = 7.6Hz, 1H, -C***H***(Ph)CH=), 6.25 (d, J_{HH} = 7.6 Hz, 1H, -C***H***=C(Ph)ONi-), 6.18 (dd, J_{HH} = 7.2, J_{HP} = 2.0 Hz, 1H, -C***H***=C(Ph)ONi-), 6.8-7.7 (m, 18H, Ph), 8.43 (d, J_{HH} = 7.2 Hz, 2H, *o*-PhCO); ^{13}C{^{1}H} NMR (100 MHz, C$_6$D$_6$): δ 29.8 (d, J_{CP} = 9.2 Hz, Cyp), 33.7 (d, J_{CP} = 30.1 Hz, Cyp), 33.7 (d, J_{CP} = 30.8 Hz, Cyp), 37.4 (d, J_{CP} = 20.7 Hz, Cyp), 58.9 (s, -***C***H(Ph)CH-), 93.8 (d, J_{CP} = 13.0 Hz, -***C***H=C(Ph)ONi-), 123.6 (s, -NiC(Ph)=***C***(Ph)-), 125.1 (s, Ph), 126.4 (s, Ph), 127.0 (s, Ph), 127.9 (s, Ph), 128.4 (s, Ph), 128.7 (s, Ph), 128.8 (s, Ph), 129.1 (s, Ph), 129.6 (s, Ph), 130.4 (s, Ph), 131.8 (s, Ph), 138.9 (s, Ph), 141.9 (s, Ph), 143.5 (s, Ph), 148.0 (d, J_{CP} = 9.2 Hz, -Ni***C***(Ph)=C(Ph)-), 151.9 (d, J_{CP} = 3.8 Hz, Ph), 155.1 (s, Ph), 163.0 (d, J_{CP} = 4.6 Hz, -CH=***C***(Ph)ONi-); ^{31}P{^{1}H} NMR (109 MHz, C$_6$D$_6$): δ 20.0(s). Anal. Calcd for C$_{44}$H$_{49}$NiOP: C, 77.40; H, 7.22. Found: C, 77.32; H, 7.23. X-ray data for **15**: M = 683.54, red, monoclinic, $P2_1/c$ (No.14), a = 12.8408 (5) Å, b = 15.1873(6) Å, c = 18.4530(9) Å, β = 97.9023(15)°, V = 3564.5(3) Å^3, Z = 4, D_{calcd} = 1.274 g/cm^3, T = -150.0 °C, R_1 (wR_2) = 0.053 (0.132).



4dc **1a** 5 eq. **5dac**: 99%

Reaction of 4dc with 1a: **1a** (21.4 mg, 0.15 mmol) was added to a solution of **4dc** (19.7 mg, 0.029 mmol) in C$_6$D$_6$ (0.5 mL) at room temperature. The reaction was followed by ^{1}H and ^{31}P NMR spectra. After 24 h, the solution changed from brown to deep purple and **5adc** was generated in 99% yield.

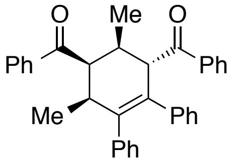


4dc **1c** 5 eq. **5dcc**: 50% **3cc**:37%

Reaction of 15 with 1c: **1c** (22.6 mg, 0.23 mmol) was added to a solution of **4bc** (33.4 mg, 0.049 mmol) in C_6D_6 (0.5 mL) at room temperature. The reaction was followed by 1^{1}H and ^{31}P NMR spectra. After 24 h, the solution changed from brown to deep purple. **5dcc** and **3dc** was generated 50% and 37%, respectively.

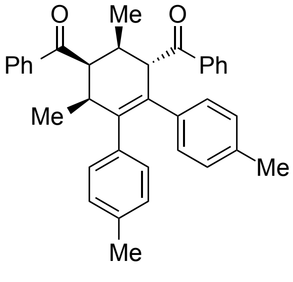
General procedure for the Ni-catalyzed enantioselective [2+2+2] cycloaddition: To a vial in a grovebox was added **L*1**•HBF_4 (0.05 mmol), LiO^{t}Bu (0.05 mmol), and C_6H_6 (0.8 mL). This suspension was allowed to stir at room temperature for 10 minutes. To this, $Ni(cod)_2$ (0.05 mmol) was added, and the suspension was further stirred at room temperature for 10 minutes. Finally, a solution of enone (0.5 mmol) and alkyne (0.5 mmol) in C_6H_6 (0.45 mL) was added. The reaction mixture was stirred for 24 h at 30 ºC. The reaction mixture was directly filtered through a short silica column, which was then washed with Et_2O. The filtrate was concentrated *in vacuo*, and the residue was purified via flash chromatography. Solvent systems varied from 0% to 10% ethyl acetate in hexanes.

(+)-(2,6-dimethyl-4,5-diphenylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ad)



Following the general procedure, chiral NHC salt (30.75 mg, 0.05 mmol), LiO^{t}Bu (3.96 mg, 0.05 mmol), $Ni(cod)_2$ (13.68 mg, 0.05 mmol), (*E*)-1-phenyl-2-buten-1-one (70 μL, 0.5 mmol) and diphenylacetylene (89.2 mg, 0.5 mmol) were used. Purification by flash column chromatography gave 99 mg of **3ad** (84%) as a white solid. $[\alpha]_D^{15} = +269$ (*c* = 0.336, $CHCl_3$).

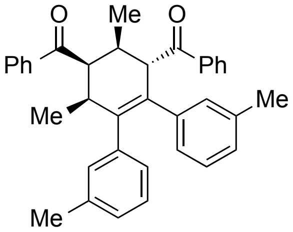
(+)-(2,6-dimethyl-4,5-(4,4-dimethyldiphenyl)cyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ah)



Following the general procedure, chiral NHC salt (30.73 mg, 0.05 mmol), LiO^{t}Bu (3.73 mg, 0.05 mmol), $Ni(cod)_2$ (13.72 mg, 0.05 mmol), (*E*)-1-phenyl-2-buten-1-one (70 μL, 0.5 mmol) and 1, 2-Di-*p*-tolyletyne (102.77 mg, 0.5 mmol) were used. Purification by flash column chromatography gave 118.4 mg of **3ah** (95%) as a white solid. **Spectral**

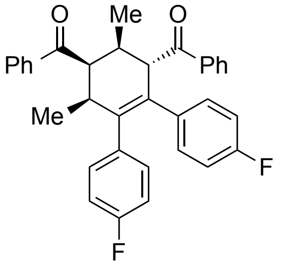
data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71 (d, *J* = 7.3 Hz , 3H), 1.51 (d, *J* = 7.0 Hz, 3H), 2.10 (s, 3H), 2.19 (s, 3H), 2.73-2.79 (m, 1H), 3.34-3.41 (m, 1H), 4.17 (dd, *J* = 6.3 Hz, 3.3 Hz, 1H), 4.69 (d, *J* = 2.3 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 2H), 6.78-6.91 (m, 6H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.44-7.57 (m, 4H), 7.83 (d, *J* = 7.3 Hz, 2H), 7.96 (d, *J* = 7.3 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.1, 18.9, 21.1, 21.2, 32.7, 36.7, 46.0, 56.9, 128.2, 128.3, 128.4, 128.6, 128.8, 129.6, 129.7, 131.7, 132.8, 132.9, 135.2, 135.4, 137.1, 138.1, 138.7, 139.2, 139.3, 141.2, 141.3, 141.3; HRMS: calcd for $C_{36}H_{34}O_2$, 498.26, found m/z 498.2555; HPLC(DAICEL CHIRALPAK IA, Hexane:*i*PrOH = 90:10, 0.5 mL/min); $[\alpha]_D^{15}$ = +71 (*c* = 0.992, $CHCl_3$).

(+)-(2,6-dimethyl-4,5-(3,3-dimethyldiphenylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ai)



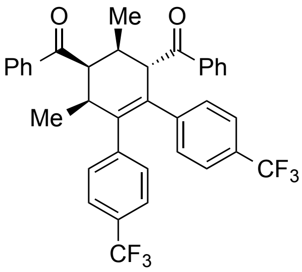
Following the general procedure, chiral NHC salt (30.71 mg, 0.05 mmol), LiO^{t}Bu (3.78 mg, 0.05 mmol), Ni(cod)$_2$ (13.56 mg, 0.05 mmol), (*E*)-1-phenyl-2-buten-1-one (70 μL, 0.5 mmol) and 1, 2-Di-*m*-tolyletyne (103.2 mg, 0.5 mmol) were used. Purification by flash column chromatography gave 72.5 mg of **3ai** (58%) as a white solid. **Spectral data:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.73 (d, *J* = 7.5 Hz, 3H), 1.48 (d, *J* = 7.0 Hz, 3H), 2.07 (s, 3H), 2.17 (s, 3H), 2.76-2.80 (m, 1H), 3.38 (m, 1H), 4.18 (dd, *J* = 6.3 Hz, 3.3 Hz, 1H), 4.73 (dd, *J* = 4.3 Hz, 1.5 Hz, 1H), 6.67-6.99 (m, 9H), 7.27-7.58 (m, 7H), 7.82 (d, *J* = 7.0 Hz, 2H), 7.98 (d, *J* = 7.0 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 16.3, 18.9, 21.3, 21.4, 33.0, 36.6, 46.2, 56.4, 126.6, 126.7, 126.9, 127.0, 127.3, 127.4, 128.2, 128.3, 128.5, 128.8, 130.3, 130.5, 132.1, 132.8, 132.9, 136.7, 136.9, 140.9, 141.2, 141.9, 202.0, 203.8; HRMS: calcd for $C_{36}H_{34}O_2$, 498.26, found m/z 498.2560; HPLC(DAICEL CHIRALPAK IA, Hexane:*i*PrOH = 90:10, 0.5 mL/min); $[\alpha]_D^{15}$ = +230.49 (*c* = 0.282, $CHCl_3$).

(+)-(2,6-dimethyl-4,5-(4,4-difluorodiphenyl)cyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3al)



Following the general procedure, chiral NHC salt (30.80 mg, 0.05 mmol), LiO^{t}Bu (3.95 mg, 0.05 mmol), Ni(cod)$_2$ (13.77 mg, 0.05 mmol), (*E*)-1-phenyl-2-buten-1-one (70 μL, 0.5 mmol) and 1, 2-Di-*p*- fluorophenyletyne (107.08 mg, 0.5 mmol) were used. Purification by flash column chromatography gave 95.8 mg of **3al** (76%) as a white solid. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.71 (d, *J* = 7.5 Hz, 3H), 1.37 (d, *J* = 7.0 Hz, 3H), 2.76-2.84 (m, 1H), 3.33-3.39 (m, 1H), 4.19 (dd, *J* = 6.0 Hz, 3.3 Hz, 1H), 4.73 (dd, *J* = 5.3 Hz, 1.8 Hz, 1H), 6.66 (t, *J* = 8.8 Hz, 2H), 6.79 (t, *J* = 9.0 Hz, 2H), 6.90-6.95 (m, 4H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.45-7.59 (m, 4H), 7.79 (d, *J* = 7.3 Hz, 2H), 7.98 (d, *J* = 7.3 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 16.4, 18.9, 33.6, 36.9, 46.7, 56.1, 114.6 (d, *J* = 21.3 Hz), 114.7 (d, *J* = 21.3 Hz), 128.1, 128.3, 128.4, 128.4, 128.5, 128.6, 128.9, 131.1 (d, *J* = 7.3 Hz), 131.4 (d, *J* = 7.3 Hz), 132.5, 133.0, 133.2, 137.3, 139.0, 140.6,161.1 (d, *J* = 230 Hz), 161.2 (d *J* = 260 Hz), 202.2, 203.7; HRMS: calcd for $C_{34}H_{28}O_2F_2$, 506.21, found m/z 506.2062; HPLC(DAICEL CHIRALPAK IA, Hexane:*i*PrOH = 90:10, 0.5 mL/min); $[\alpha]_D^{15}$ = +192.7 (*c* = 0.33, CHCl$_3$).

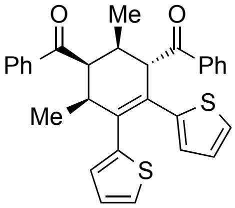
(+)-(2,6-dimethyl-4,5-(4,4-ditrifluoromethyldiphenyl)cyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3am)



Following the general procedure, chiral NHC salt (30.71 mg, 0.05 mmol), LiO^{t}Bu (3.99 mg, 0.05 mmol), Ni(cod)$_2$ (13.55 mg, 0.05 mmol), (*E*)-1-phenyl-2-buten-1-one (70 μL, 0.5 mmol) and 1, 2-Di-*p*- trifluoromethyphenyletyne (158.6 mg, 0.5 mmol) were used.

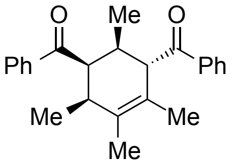
Purification by flash column chromatography gave 81.5 mg of **3am** (54%) as a white solid. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.72 (d, J = 7.3 Hz, 3H), 1.37 (d, J = 6.8 Hz, 3H), 2.87 (br, 1H), 3.41-3.45 (m, 1H), 4.22 (br, 1H), 4.81 (d, J = 5.5 Hz, 1H), 7.08-7.22 (m, 6H), 7.32-7.36 (m, 4H), 7.44-7.58 (m, 4H), 7.76 (d, J = 7.5 Hz, 2H), 8.00 (d, J = 7.5 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 16.3, 18.7, 33.7, 36.7, 46.7, 55.5, 123.9 (q, J = 272 Hz), 124.0 (q, J = 271 Hz), 124.6 (q, J = 3.7 Hz), 124.7 (q, J = 3.7 Hz), 128.0, 128.0 (q, J = 32.3 Hz), 128.1, 128.5, 128.5 (q, J = 33.0 Hz), 128.8, 129.7, 129.9, 133.0, 133.1, 133.2, 137.2, 138.9, 140.6, 144.1, 144.7, 201.8, 203.3; HRMS: calcd for $C_{36}H_{27}O_2F_6$, 605.19[M-H], found m/z 605.1923[M-H]; HPLC(DAICEL CHIRALPAK IA, Hexane:*i*PrOH = 99:1, 0.5 mL/min); $[\alpha]_D^{15}$ = +143.81 (c = 0.212, CHCl$_3$).

(+)-2,6-dimethyl-4,5-ditienylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3an)



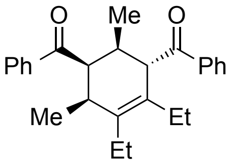
Following the general procedure, chiral NHC salt (30.98 mg, 0.05 mmol), LiO^{t}Bu (3.87 mg, 0.05 mmol), Ni(cod)$_2$ (13.79 mg, 0.05 mmol), (*E*)-1-phenyl-2-buten-1-one (70 μL, 0.5 mmol) and 1, 2-Di-(thiophen-2-yl)etyne (95.33 mg, 0.5 mmol) were used. Purification by flash column chromatography gave 96.6 mg of **3an** (81%) as a yellow solid. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.87 (d, J = 7.5 Hz, 3H), 1.57 (s, 1H), 2.73-2.76 (m, 1H), 3.34-3.39 (m, 1H), 4.11 (dd, J = 6.3 Hz, 3.0 Hz, 1H), 4.70 (br, 1H), 6.69-6.90 (m, 5H), 7.42-7.59 (m, 7H), 7.93 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 15.9, 18.9, 32.1, 38.1, 45.1, 57.7, 125.6, 125.8, 126.3, 126.7, 126.9, 127.3, 128.2, 128.3, 128.5, 128.8, 128.9, 132.9, 133.3, 136.3, 136.8, 138.0, 142.5, 143.9, 200.4, 203.1; HRMS: calcd for $C_{30}H_{26}O_2S_2$, 482.14, found m/z 482.1317; HPLC(DAICEL CHIRALPAK IA, Hexane:*i*PrOH = 90:10, 0.5 mL/min); $[\alpha]_D^{15}$ = +299.75(c = 0.406, CHCl$_3$).

(−)-(2,4,5,6-tetramethylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ab)



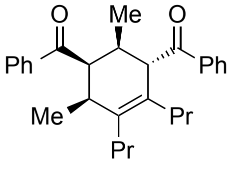
Following the general procedure, chiral NHC salt (30.74 mg, 0.05 mmol), LiO^{t}Bu (3.94 mg, 0.05 mmol), Ni(cod)$_2$ (13.71 mg, 0.05 mmol), (*E*)-1-phenyl-2-buten-1-one (70 μL, 0.5 mmol) and 2-butyne (39 μL, 0.5 mmol) were used. Purification by flash column chromatography gave 52 mg of **3ab** (60%) as a white solid. HPLC(DAICEL CHIRALPAK IA, Hexane:*i*PrOH = 90:10, 0.5 mL/min); $[\alpha]_D^{17}$ = -84.2 (*c* = 0.774, CHCl$_3$).

(−)-(4,5-diethyl-2,6-dimethylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3aa)



Following the general procedure, chiral NHC salt (30.79 mg, 0.05 mmol), LiO^{t}Bu (3.99 mg, 0.05 mmol), Ni(cod)$_2$ (13.70 mg, 0.05 mmol), (*E*)-1-phenyl-2-buten-1-one (70 μL, 0.5 mmol) and 3-hexyne (37.5 μL, 0.5 mmol) were used. Purification by flash column chromatography gave 56 mg of **3aa** (60%) as a colorless oil. HPLC(DAICEL CHIRALPAK OJ, Hexane:*i*PrOH = 200:1, 0.5 mL/min); $[\alpha]_D^{17}$ = -38.45 (*c* = 1.126, CHCl$_3$).

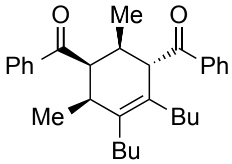
(−)-(4,5-dipropyl-2,6-dimethylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ao)



Following the general procedure, chiral NHC salt (30.88 mg, 0.05 mmol), LiO^{t}Bu (3.98 mg, 0.05 mmol), Ni(cod)$_2$ (13.51 mg, 0.05 mmol), (*E*)-1-phenyl-2-buten-1-one (70 μL, 0.5 mmol) and 4-octyne (73.5 μL, 0.5 mmol) were used. Purification by flash column chromatography gave 73.5 mg of **3ao** (73%) as a white solid. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.87 (t, J = 7.3 Hz, 3H), 0.93 (d, J = 7.5 Hz, 3H), 0.99 (t, J = 7.0

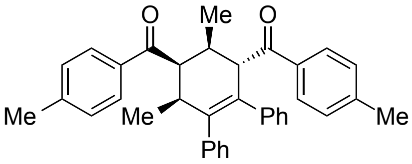
Hz, 3H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.42-148 (m, 4H), 2.0 (m, 1H), 2.19-2.34 (m, 2H), 2.50-2.52 (m, 1H), 2.81-2.84 (m, 1H), 3.83 (dd, *J* = 6.0 Hz, 3.0 Hz, 1H), 4.07 (s, 1H), 7.40-7.58 (m, 6H), 7.84 (d, *J* = 7.0 Hz, 2H), 8.00 (d, *J* = 7.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.2, 14.3, 16.1, 18.8, 22.1, 22.3, 32.0, 32.2, 34.3, 34.9, 45.7, 54.4, 127.5, 128.1, 128.4, 128.7, 128.8, 132.6, 133.1, 137.0, 137.2, 138.4, 202.4, 204.1; HRMS: calcd for $C_{28}H_{34}O_2$, 402.26, found m/z 402.2558; HPLC(DAICEL CHIRALPAK IA, Hexane:*i*PrOH = 99:1, 0.5 mL/min); $[\alpha]_D^{13}$ = -28.46 (*c* = 1.458, $CHCl_3$).

(−)-4,5-dibuthyl-2,6-dimethylcyclohex-4-ene-1,3-diyl)bis(phenylmethanone) (3ap)



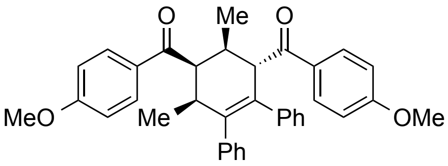
Following the general procedure, chiral NHC salt (30.77 mg, 0.05 mmol), LiO^{t}Bu (3.90 mg, 0.05 mmol), Ni(cod)$_2$ (13.74 mg, 0.05 mmol), (*E*)-1-phenyl-2-buten-1-one (70 μL, 0.5 mmol) and 5-decyne (89.7 μL, 0.5 mmol) were used. Purification by flash column chromatography gave 70.4 mg of **3ap** (65%) as a colorless oil. **Spectral data:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.0 Hz, 3H), 0.92-0.96 (m, 6H), 1.25-1.49 (md, *J* = 6.8 Hz, 11H), 1.50-1.59 (m, 1H), 2.03-2.05 (m, 1H), 2.21-2.36 (m, 2H), 2.51-2.54 (m, 1H), 2.82-2.86 (m, 1H), 3.83 (dd, *J* = 6.3 Hz, 3.3 Hz, 1H), 4.08 (s, 1H), 7.40-7.57 (m, 6H), 7.88 (d, *J* = 7.3 Hz, 2H), 8.00 (d, *J* = 7.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 13.9, 14.0, 15.9, 18.6, 22.8, 22.9, 29.7, 31.0, 31.2, 31.9, 32.5, 34.2, 45.6, 54.3, 127.3, 127.9, 128.3, 128.5, 128.6, 132.4, 132.9, 136.9, 137.0, 138.2, 202.3, 203.8; HRMS: calcd for $C_{30}H_{38}O_2$, 430.29, found m/z 430.2870; HPLC(DAICEL CHIRALPAK IA, Hexane:*i*PrOH = 99:1, 0.5 mL/min); $[\alpha]_D^{13}$ = -24.26 (*c* = 1.29, $CHCl_3$).

(+)-(2,6-dimethyl-4,5-diphenylcyclohex-4-ene-1,3-diyl)bis(4-methylphenylmethanone) (3ac)



Following the general procedure, chiral NHC salt (31.0 mg, 0.05 mmol), LiO^{t}Bu (4.06 mg, 0.05 mmol), Ni(cod)$_2$ (13.77 mg, 0.05 mmol), (*E*)-1-(*p*-tolyl)but-2-en-1-one (78.97 mg, 0.5 mmol) and diphenylacetylene (88.5 mg, 0.5 mmol) were used. Purification by flash column chromatography gave 38.2 mg of **3ac** (31%) as a white solid. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.66 (d, J = 7.5 Hz, 3H), 1.40 (d, J = 7.0 Hz, 3H), 2.28 (s, 3H), 2.37 (s, 3H), 2.71 (m, 1H), 3.35 (m, 1H), 4.12 (dd, J = 6.3 Hz, 3.3 Hz, 1H), 4.66 (d, J = 4.3 Hz, 1H), 6.81-7.24 (m, 14H), 7.68 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 16.2, 18.9, 21.6, 33.2, 36.8, 46.2, 56.3, 125.8, 126.0, 127.4, 127.5, 128.3, 128.5, 129.2, 129.5, 129.7, 129.9, 132.6, 134.7, 136.3, 141.1, 141.3, 142.0, 143.5, 143.7, 201.5, 203.3; HRMS: calcd for $C_{36}H_{34}O_2$, 498.26, found m/z 498.2556; HPLC(DAICEL CHIRALPAK IA, Hexane:*i*PrOH = 90:10, 0.5 mL/min); $[\alpha]_D^{15}$ = +238.6 (*c* = 0.083, CHCl$_3$).

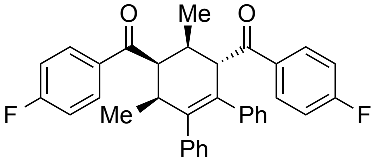
(+)-(2,6-dimethyl-4,5-diphenylcyclohex-4-ene-1,3-diyl)bis(4-methoxyphenylmethanone) (3fc)



Following the general procedure, chiral NHC salt (30.9 mg, 0.05 mmol), LiO^{t}Bu (4.02 mg, 0.05 mmol), Ni(cod)$_2$ (13.75 mg, 0.05 mmol), (*E*)-1-(4-methoxyphenyl)but-2-en-1-one (86.65 mg, 0.5 mmol) and diphenylacetylene (88.35 mg, 0.5 mmol) were used. Purification by flash column chromatography gave 24.5 mg of **3fc** (18%) as a white solid. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.73 (d, J = 7.3 Hz, 3H), 1.44 (d, J = 7.0 Hz, 3H), 2.73-2.80 (m, 1H), 3.37-3.44 (m, 1H), 3.79 (s, 3H), 3.86 (s, 3H), 4.18 (dd, J = 6.0 Hz, 3.3 Hz, 1H), 4.72 (d, J = 4.3 Hz, 1H), 6.80-7.08 (m, 15H), 7.83 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 9.0 Hz, 2H); ^{13}C{^{1}H} NMR

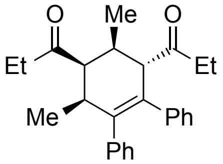
(100 MHz, $CDCl_3$): δ 16.3, 18.9, 33.6, 36.9, 46.0, 55.5, 55.9, 113.6, 113.9, 125.8, 125.9, 127.4, 127.5, 129.7, 129.8, 130.3, 130.4, 130.5, 130.7, 131.9, 132.7, 141.1, 142.0, 163.3, 163.4, 200.5, 202.1; HRMS: calcd for $C_{36}H_{34}O_2$, 530.25, found m/z 530.2455; HPLC(DAICEL CHIRALPAK IA, Hexane:*i*PrOH = 70:30, 0.5 mL/min); $[\alpha]_D^{15}$ = +177.1 (*c* = 0.504, $CHCl_3$).

(+)-(2,6-dimethyl-4,5-diphenylcyclohex-4-ene-1,3-diyl)bis(4-fluorophenylmethanone) (3gc)



Following the general procedure, chiral NHC salt (31.04 mg, 0.05 mmol), LiO^{t}Bu (4.0 mg, 0.05 mmol), Ni(cod)$_2$ (13.72 mg, 0.05 mmol), (*E*)-1-(4-fluorophenyl)but-2-en-1-one (81.15 mg, 0.5 mmol) and diphenylacetylene (88.0 mg, 0.5 mmol) were used. Purification by flash column chromatography gave 93 mg of **14** (75%) as a white solid. **Spectral data:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (d, *J* = 7.0 Hz, 3H), 1.43 (d, *J* = 7.0 Hz, 3H), 2.80 (br, 1H), 3.42 (m, 1H), 4.21 (dd, *J* = 5.8 Hz, 2.8 Hz, 1H), 4.75 (d, *J* = 4.5 Hz, 1H), 6.86-7.09 (m, 12H), 7.16 (t, *J* = 8.5 Hz, 3H), 7.84 (dd, *J* = 5.8 Hz, 2.5 Hz, 2H), 8.05 (dd, *J* = 5.5 Hz, 2.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.3, 18.9, 33.4, 36.8, 46.6, 56.1, 115.2 (d, *J* = 21.3 Hz), 115.9 (d, *J* = 22.0 Hz), 126.1, 126.1, 127.5, 127.6, 129.6, 129.8, 130.7 (d, *J* = 9.5 Hz), 130.9 (d, *J* = 9.5 Hz), 132.5, 133.8, 135.3, 140.7, 141.0, 141.6, 164.4, 166.9, 200.6, 202.0; HRMS: calcd for $C_{34}H_{28}F_2O_2$, 506.21, found m/z 506.2054; HPLC(DAICEL CHIRALPAK IA, Hexane:*i*PrOH = 70:30, 0.5 mL/min); $[\alpha]_D^{15}$ = +285 (*c* = 0.41, $CHCl_3$).

(+)-(2,6-dimethyl-4,5-diphenylcyclohex-4-ene-1,3-diyl)dipropan-1-one (3cc)



Following the general procedure, chiral NHC salt (30.81 mg, 0.05 mmol), LiO^{t}Bu (3.83 mg, 0.05 mmol), Ni(cod)$_2$ (13.3 mg, 0.05 mmol), 4-hexene-3-on (49.3 mg, 0.5 mmol) and diphenylacetylene (89.23 mg, 0.5 mmol) were used. Purification by flash column chromatography gave 20 mg of 1**6** (22%) as a colorless oil. HPLC(DAICEL CHIRALPAK IA, Hexane:*i*PrOH = 99:1, 0.5 mL/min); $[\alpha]_D^{17}$ = +80.59 (*c* = 0.268, $CHCl_3$).

1.5 Reference and Notes

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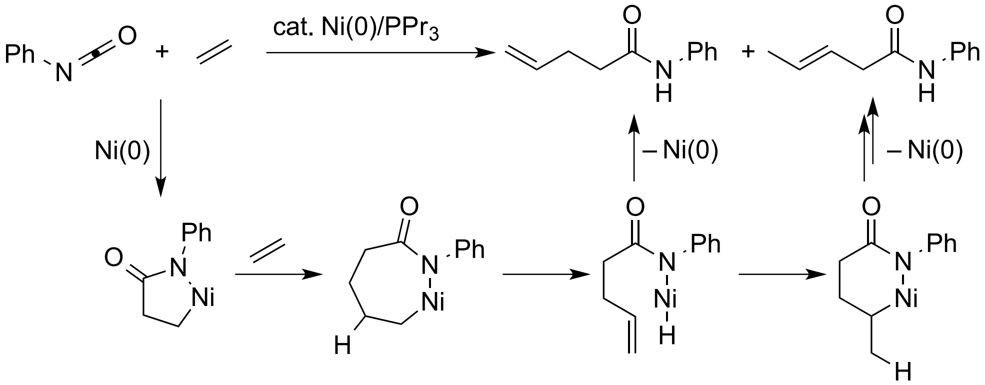
Chapter 2

Nickel-Catalyzed Trimerization of Enones with Ethylene

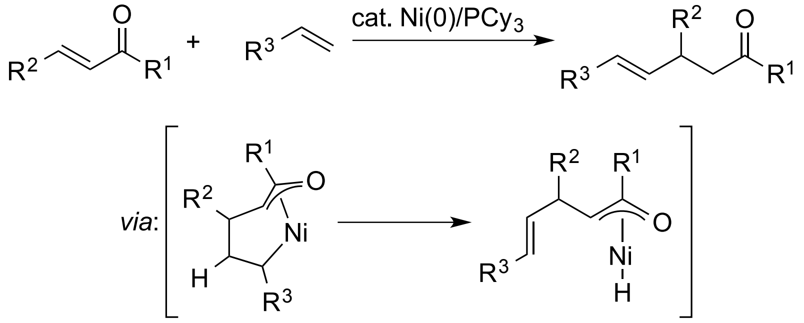
2.1 Introduction

Ethylene is an industrial feedstock and its production was more than 150 million tons in 2012.[1] Thus, developing the methods to transform such abundant chemicals into more valuable compounds is an important issue for organic chemists. In the transition-metal-catalyzed reactions, ethylene is incorporated into organic molecules as a C2-building block, such as vinyl or ethyl group.[2] However, introduction of two molecules of ethylene as a C4 building block is hardly achieved, because reductive elimination or β-H elimination takes place before the insertion of second ethylene. In contrast to the metal-alkyl species, β-H elimination from five-membered metallacycle is known to occur much slower due to its conformational matter.[3,4] Therefor, only one example has been known that achieved cross-trimerization of two ethylene with another unsaturated compound via metallacycle intermediate. Hoberg reported that phenyl isocyanate reacted with two molecules of ethylene in the presence of Ni(0)/PPr_3 catalyst to afford *N*-phenyl-4-pentenamide and its isomer (Scheme 2.1).[5] This reaction is proposed to proceed via a five-membered metallacycle formed from an isocyanate and ethylene with nickel(0) species, followed by insertion of another ethylene to generate a seven-membered metallacycle.



Scheme 2.1. Ni-catalyzed co-trimerization of phenyl isocyanate with ethylene

Ogoshi's group demonstrated the cross-dimerization of conjugated enones with terminal alkenes to afford 1,4-enone derivatives (Scheme 2.2).[6] This reaction is a formal conjugate addition of alkenes to enones. In the presence of bulky phosphine ligand, the oxidative cyclization of enone with alkene at the nickel(0) center occurs to form nickelacycle intermediate, which then undergoes β-H elimination and reductive elimination. The insertion of a second alkene might be prevented by the steric hindrance of alkene substituent. Based on this reaction, I assumed that the smallest alkene, ethylene, could accomplished the insertion to the nickelacycle before β-H elimination.

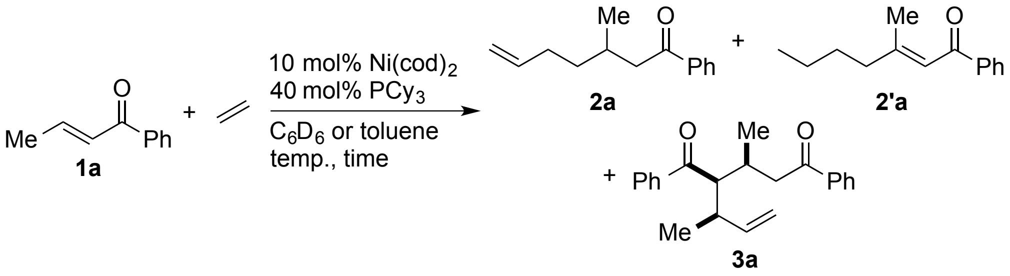


Scheme 2.2. Ni-catalyzed co-dimerization of enones with terminal alkenes

2.2 Results and Discussion

Initially, the reaction of (*E*)-phenyl propenyl ketone (**1a**) was investigated (Table 2.1). In the presence of Ni(cod)$_2$ (10 mol%) and PCy$_3$ (40 mol%), the reaction of **1a** (0.4 M) under ethylene pressure (5 atm) at room temperature afforded 7% of 1,6-enone **2a** and 41 % of 1,5-diketone **3a**. The product **2a** is a co-trimer of an enone with two ethylene while **3a** is a co-trimer of two enones with one ethylene. The relative stereochemistry of **3a** was presumed from the [2 + 2 + 2] cycloadduct of two enones and an alkyne (see Chapter 1). Elevating the reaction temperature to 80 ºC increased the yield of **2a**, accompanied by its isomer **2'a** (run 2). Based on this observation, the reaction was carried out under higher ethylene pressure (30 atm) at low concentration of **1a** (0.04 M) and at 100 ºC (run 3). As a result, **2a** and **2'a** were obtained in 61% combined yield and the production of **3a** was suppressed to 13% yield.

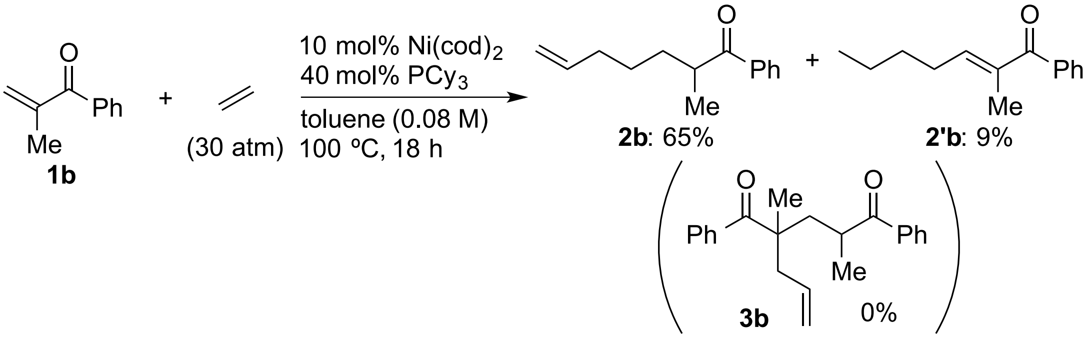
Table 2.1. Ni-catalyzed co-trimerization of enone **1a** with ethylene



run	ethylene (atm)	temp. (°C)	time (h)	yield (%) 2a	2'a	b
1[a]	5	rt	72	7	–	41
2[a]	5	80	18	20	3	19
3[b]	30	100	12	43	18	13

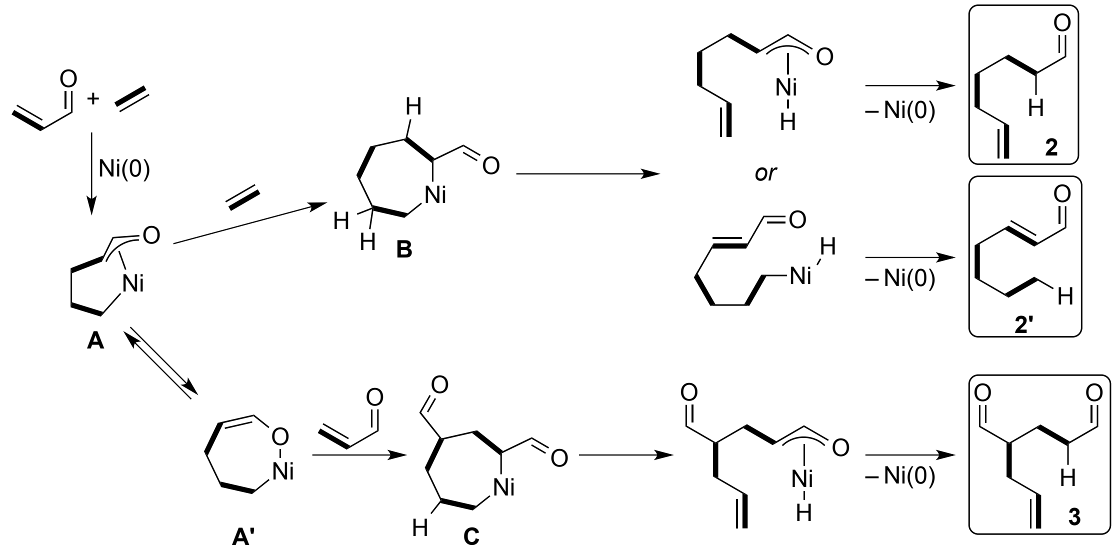
[a] C_6D_6 (0.4 M). [b] toluene (0.04 M).

Under similar conditions of run 3 in Table 2.1, the reaction of 2-methyl-1-phenyl-prop-2-en-1-one (**1b**) was also conducted. After heating at 100 ºC for 18 h, the reaction gave the desired co-trimerized product **2b** and **2'b** in 74% yield (Scheme 2.3). In contrast to the reaction of **1a**, no co-trimer of two enones with ethylene was detected, probably due to the steric repulsion of α-methyl group of enone at the insertion step (*vide infra*).



Scheme 2.3. Ni-catalyzed co-dimerization of enone **1b** with ethylene

A plausible mechanism is depicted in Scheme 2.4. At first, oxidative cyclization of an enone and ethylene occur to give η^3-oxaallyl nickelacycle **A**. Insertion of second ethylene molecule to intermediate **A** gives seven-membered nickelacycle **B**, followed by β-H elimination and reductive elimination to provide **2** and **2'**. As described in Chapter 1, nickelacycle **A** is in equilibrium with η^1-*O*-enolate nickelacycle **A'**, which undergo nuecleophilic attack to the second enone to form intermediate **C**. Then, β-H elimination from **C** followed by reductive elimination affords 1,5-diketone **3**. At higher temperature, the insertion of the second ethylene is favored over nucleophilic attack to the second enone.[7]



Scheme 2.4. A plausible mechanism

2.3 Conclusion

In chapter 2, a nickel-catalyzed co-trimerization of enones and ethylene was demonstrated. At low temperature, a 1,5-diketone, a co-trimer of two enones with one molecule of ethylene, was obtained as a major product. At higher temperature and under high ethylene pressure, two molecules ethylene reacted with enones to afford 1,6-enones predominantly. In this reaction ethylene was incorporated as a C4 building block.

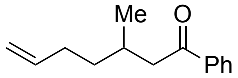
2.4 Experimental Section

General: All manipulations were conducted under a nitrogen atmosphere using standard Schlenk or dry box techniques. ^1H, ^{31}P, and ^{13}C nuclear magnetic resonance spectra were recorded on JEOL GSX-270S, JEOL AL-400, and Brucker DPX 400 spectrometers. The chemical shifts in ^1H nuclear magnetic resonance spectra were recorded relative to Me_4Si or residual protiated solvent ($CHCl_3$ (δ 7.27) or C_6D_5H (δ 7.16)). The chemical shifts in the ^{13}C spectra were recorded relative to Me_4Si. The chemical shifts in the ^{31}P spectra were recorded using 85% H_3PO_4 as external standard. Assignment of the resonances in ^1H and ^{13}C NMR spectra was based on ^1H-^1H COSY, HMQC, and HMBC experiments. GC yields were determined using tetradecane as an internal standard.

Materials: The degassed and distilled toluene used in this work was commercially available. C_6D_6 was distilled from sodium benzophenone ketyl. All commercially available reagents were distilled and degassed prior to use. (*E*)-1-phenylbut-2-en-1-one (**1a**) and 2-methyl-1-phenylprop-2-en-1-one (**1b**) were prepared by the methods in the literature.[8,9]

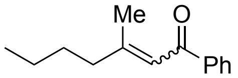
Procedure for Ni-catalyzed co-trimerization of 1a with ethylene (table 2.1, run3)
To a solution of Ni(cod)$_2$ (11 mg, 0.04 mmol) and PCy$_3$ (45 mg, 0.16 mmol) in toluene (10 mL) was added **1a** (58.5 mg, 0.40 mmol) at room temperature. The toluene solution was treated with ethylene (30 atm). The reaction mixture was heated at 100 °C and was stirred for 12 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel PTLC (Wakogel B-5F) to afford products (49.6 mg, colorless oil) as mixture of **2a** (43%) and **2'a** (18%, *E,Z* mixture), products yield was estimated by ^{1}H NMR analysis, and 8.5 mg of **3a** (13%) as a colorless oil.

3-Methyl-1-phenylhept-6-en-1-one (2a)



Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.98 (d, J = 6.8 Hz, 3H), 1.37 (m, 2H), 1.52 (m, 2H), 2.17 (m, 1H), 2.78 (dd, J = 8.0, 16.0 Hz, 1H), 2.97 (dd, J = 5.6, 16.0 Hz, 1H), 4.96 (dd, J = 1.2, 10.8 Hz, 1H), 5.03 (ddt, J = 1.6, 1.6, 17.2 Hz, 1H), 5.82 (ddt, J = 6.6, 10.2, 17.0 Hz, 1H), 7.50 (m, 3H), 7.95 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, CDCl$_3$): δ 20.0, 29.5, 31.4, 36.4, 46.0, 114.6, 128.2, 128.7, 133.0, 137.6, 138.8, 200.3. HRMS Calcd for $C_{14}H_{18}O$: 202.1358, Found 202.1358.

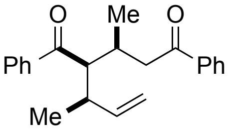
3-Methyl-1-phenylhept-2-en-1-one (*E,Z* mixture, 2'a)



Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.85-1.00 (m, 6H), 1.30-1.60 (m, 8H), 2.02 (d, J = 1.2 Hz, 3H), 2.21 (d, J = 1.2 Hz, 3H), 2.00-2.30 (m, 2H), 2.63 (m, 2H), 6.72

(s, 1H), 6.74 (q, J = 1.2 Hz, 1H), 7.42-7.50 (m, 4H), 7.50-7.59 (m, 2H), 7.91-7.98 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.1, 14.1, 19.9, 22.5, 23.1, 25.8, 29.8, 29.9, 30.6, 34.1, 41.4, 120.6, 121.3, 128.3, 128.3, 128.5, 128.6, 132.4, 139.5, 139.6, 160.7, 161.1, 191.4, 191.9. HRMS Calcd for $C_{14}H_{18}O$: 202.1358, Found 202.1340, 202.1342.

2-(but-3-en-2-yl)-3-methyl-1,5-diphenylpentane-1,5-dione (3a)

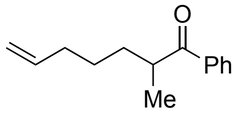


Spectral data: ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 7.2 Hz, 3H), 2.81 (m, 3H), 3.20 (dd, J = 1.6, 15.2 Hz, 1H), 3.59 (dd, J = 6.0, 8.0 Hz, 1H), 4.89 (dd, J = 1.2, 10.2 Hz, 1H), 4.98 (dd, J = 1.2, 17.0 Hz, 1H), 5.77 (ddd, J = 8.0, 10.4, 17.0 Hz, 1H), 7.52 (m, 6H), 7.98 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 18.5, 19.2, 30.1, 38.8, 41.6, 55.1, 115.0, 128.3, 128.4, 128.7, 128.8, 133.1, 133.1, 137.4, 139.8, 141.2, 200.1, 204.9. HRMS Calcd for $C_{22}H_{24}O_2$: 320.1776, Found: 320.1772, 320.1762.

Procedure for Ni-catalyzed co-trimerization of 1a with ethylene (Scheme 2.4)

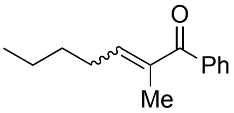
To a solution of Ni(cod)$_2$ (11 mg, 0.04 mmol) and PCy_3 (45 mg, 0.16 mmol) in toluene (5 mL) was added **1b** (58.5 mg, 0.40 mmol) at room temperature. The toluene solution was treated with ethylene (30 atm). The reaction mixture was heated at 100 °C and was stirred for 18 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel PTLC (Wakogel B-5F) to afford 52.3 mg of **2b** (65%) as a colorless oil and 7.6 mg of **2'b** (9%, *E,Z* mixture) as a colorless oil.

2-Methyl-1-phenylhept-6-en-1-one (2b)



Spectral data: ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, J = 6.8 Hz, 3H), 1.46 (m, 3H), 1.86 (m, 1H), 2.08 (m, 2H), 3.49 (m, 1H), 4.97 (dd, J = 0.8, 10.4 Hz, 1H), 5.02 (dd, J = 1.6, 17.2 Hz, 1H), 5.80 (ddt, J = 6.8, 10.4, 17.2 Hz, 1H), 7.49 (dd, J = 7.2, 7.2 Hz, 2H), 7.58 (m, 1H), 7.99 (d, J = 8.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 17.4, 26.8, 33.3, 33.9, 40.6, 114.8, 128.4, 128.7, 133.0, 136.8, 138.6, 204.5. HRMS Calcd for $C_{14}H_{18}O$: 202.1358, Found: 202.1354.

2-Methyl-1-phenylhept-2-en-1-one (*E*,*Z* mixture, 3b)



Spectral data: ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (d, J = 7.2 Hz, 3H), 1.33-1.45 (m, 4H), 1.98 (d, J = 1.2 Hz, 3H), 2.29 (dt, J = 7.2, 7.2 Hz, 2H), 6.31 (dt, J = 1.6, 7.2 Hz, 1H), 7.42 (m, 2H), 7.51 (m, 1H), 7.63 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 12.6, 14.0, 22.7, 29.0, 30.9, 128.2, 129.4, 131.4, 136.6, 139.1, 147.0, 199.2. HRMS Calcd for $C_{14}H_{18}O$: 202.1358, Found: 202.1352, 202.1354.

2.4 References and Notes

(1) (a) A.H. Tullo, *Chem. Eng. News* **2012**, *90*(10), 10; (b) J. Baker, “GPCA: Ethylene continues expansion in 2012”, can be found under http://www.icis.com/Articles/2012/11/22/9617145/gpca-ethylene-continues-expansion-in-2012.html, **2012**.

(2) For review, see: (a) RajanBabu, *Chem. Rev.* **2003**, *103*, 2845; (b) V. Saini, B. J. Stokes, M. S. Sigman, *Angew. Chem. Int. Ed.* **2013**, *52*, 11206.

(3) J. X. McDermott, J. F. White, G. M. Whitesides, *J. Am. Chem. Soc.* **1976,** *98,* 6521.

(4) Chromium-catalyzed trimeriztion of ethylene via metallacycloheptane: T. Agapie, S. J. Schofer, J. A. Labinger, J. E. Bercaw, *J. Am. Chem. Soc.* **2004,** *126,* 1304.

(5) H. Hoberg, E. Hernandez, *J. Chem. Soc., Chem. Commun.* **1986,** 544.

(6) S. Ogoshi, T. Haba, M. Ohashi, *J. Am. Chem. Soc.* **2009,** *131,* 10350.

(7) It cannot be ruled out that the generation pathways of **2** and **2’** involves the oxidative cyclization of two ethylene at the nickel(0) center, followed by insertion of an enone to afford intermediate **B**.

(8) M. R. Pitts, J. R. Harrison, C. J. Moody, *J. Chem. Soc., Perkin Trans. 1,* **2001,** 955.

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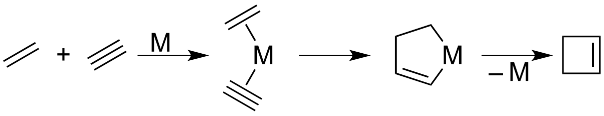
Chapter 3

Nickel-Catalyzed [2 + 2] Cycloaddition of 1,3-Enynes with Alkenes

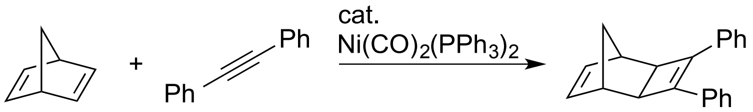
3.1 Introduction

Cyclobutene is a very attractive molecule because of its high reactivity for versatile transformations deriving from the ring strain. The [2 + 2] cycloaddition of alkenes with alkynes is the most straightforward method for preparation of cyclobutene derivatives, which is thermally forbidden and photochemically allowed according to the Woodward–Hofmann rules.[1] Lewis-acid-catalyzed[2] and transition-metal-catalyzed[3–11] reactions are the alternative methods under thermal conditions. In former case, a combination of electoron-rich alkenes or alkynes with electron-poor counterparts is usually required. Transition-metal-catalyzed reaction can be classified into two types in terms of the reaction mechanism. One is a π-acid-metal-catalyzed reaction, in which 1,n-enynes converted into bicyclic cyclobutenes.[3] This π-acid catalysis is proposed to proceed via non-classical cationic pathway where an alkylidene-metal species is formed through activation of alkyne by a π-acidic metal. As such transition metals, Pt(II), Au(I) and Rh(II) are utilized. Another reaction type involves oxidative cyclization of alkenes with alkynes at the metal center to form a metallacyclopentene, followed by reductive elimination (Scheme 3.1).

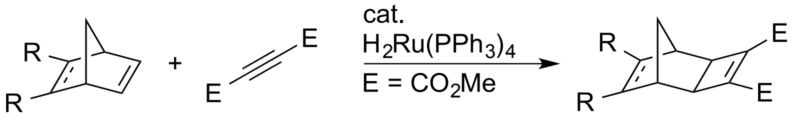


Scheme 3.1. [2 + 2] cycloaddition of alkenes with alkynes via oxidative cyclization

The first example of the latter type of [2 + 2] cycloaddition is the nickel-catalyzed reaction of norbornadiene with diphenyl acetylene reported by Schrauzer and Glockner in 1964 (Scheme 3.2).[4] In 1976, Mitsudo reported the Ru-catalyzed norbornene derivatives with acetylene dicarboxylate (Scheme 3.3).[5]

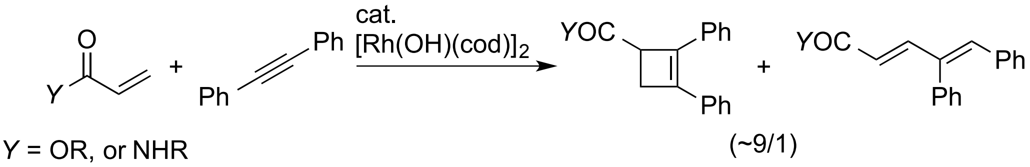


Scheme 3.2. Nickel-catalyzed [2 + 2] cycloaddition of norbornadiene with diphenyl acetylene



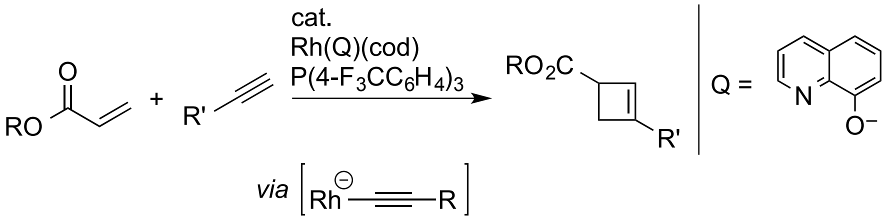
Scheme 3.3. Ruthenium-catalyzed [2 + 2] cycloaddition of norbornenes with acetylene dicarboxylate

After these pioneering works, many catalyst systems for [2 + 2] cycloaddition of strained bicyclic alkenes with alkynes has been developed.[6,7] However, intermolecular [2 + 2] cycloaddition of less-strained alkene with alkyne is still limited to a handful of examples, because insertion of another π-component or β-H elimination at metallacyclopentene occurs much easier than thermodynamically unfavorable formation of cyclobutene via reductive elimination. Baba reported the rhodium-catalyzed [2 + 2] cycloaddition of acrylates or acrylamides with diphenyl acetylene with a concomitant formation of linear 1,3-dienes (Scheme 3.4).[8]



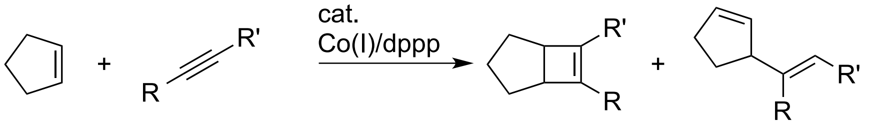
Scheme 3.4. Rhodium-catalyzed [2 + 2] cycloaddition of acrylates or acrylamides with diphenyl acetylene

Kakiuchi showed that 8-quinolinolato-rhodium efficiently catalyzed the [2 + 2] cycloaddition of acrylates with terminal alkynes, in which nucleophilic alkynyl-rhodium complex is proposed as a key intermediate (Scheme 3.5).[9]



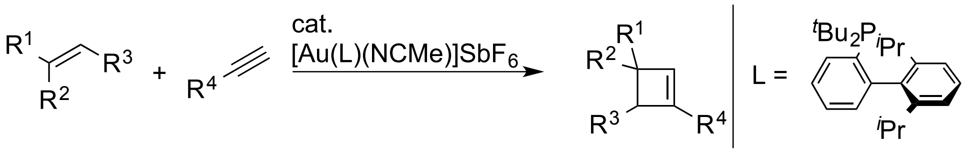
Scheme 3.5. 8-Quinolinolato-rhodium catalyzed [2 + 2] cycloaddition of acrylates with terminal alkynes

As for electronically unactivated alkenes, cobalt-catalyzed and gold-catalyzed reactions has been reported. Hilt described that, in the presence of Co(I)/dppp catalyst, cyclopentene reacts with internal alkynes to afford a mixture of cyclobutenes and Alder–ene products via cobaltacyclopentene intermediate (Scheme 3.6).[10] Although the mechanistic insights has not been mentioned, Hilt also showed that the reaction of a 1,3-enyne, (cyclohex-1-en-1-ylethynyl)benzene, provides [2 + 2] cycloadduct selectively.



Scheme 3.6. Co(I)/dppp catalyzed [2 + 2] cycloaddition of cyclopentene with alkynes

A cationic Au(I) complex with a bulky phosphine ligand developed by Echavarren efficiently catalyzed the [2 + 2] cycloaddition of di- or tri-substituted alkenes with terminal alkynes (Scheme 3.7).[11] In this case, alkenes should be deactivated in order to suppress further reaction of products and oligomerization of alkenes. This reaction is proposed to proceed via a π-acidic activation of alkynes by a cationic Au(I) complex.

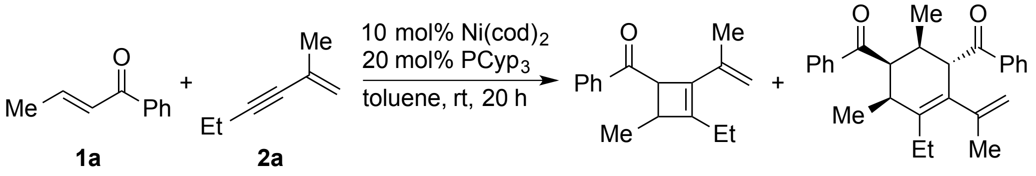


Scheme 3.7. Gold-catalyzed [2 + 2] cycloaddition of highly substituted alkenes with terminal alkynes

Therefore, the reaction system applicable to more diverse range of alkenes is desired. In this chapter, I describe the nickel-catalyzed intermolecular [2 + 2] cycloaddition of less-strained alkenes with 1,3-enynes. The mechanistic studies based on stoichiometric reactions are also discussed.

3.2 Results and Discussion

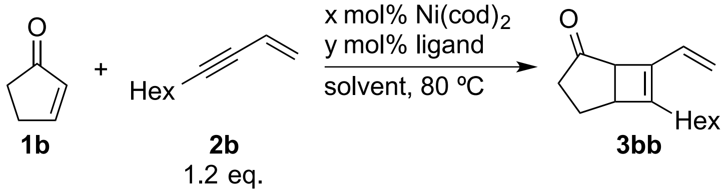
During the course of the study on nickel-catalyzed [2 + 2 + 2] cycloaddition of two enones with one alkyne descried in Chapter 2, a trace amount of cyclobutene derivative **3aa** was obtained when 2-methyl-1-hexen-3-yne (**2a**) was used as an alkyne component (eq. 3.1).



1a **2a** 1 eq. **3aa**: trace **4aa**: 92% (8/2 regiosel.) (3.1)

According to this observation, I assumed that 1,3-enyne is the key substrate for [2 + 2] cycloaddition. Initially, the reaction of cyclopentenone (**1b**) was investigated, because cyclic enones did not afford cyclohexene product under Ni/PCyp$_3$ catalyst system (Table 3.1). In the presence of a catalytic amount of Ni(cod)$_2$ and PCyp$_3$ at 80 ºC, [2 + 2] cycloaddition of **1b** with 1-decen-3-yne (**2b**) occurred to give the desired cyclobutene **3bb** in 20% yield (run 1). However, the major product in this reaction was a mixture of [2 + 2 + 2] cycloadducts of **1b** with two molecules of **2b**. The use of PCy$_3$ as ligand did not improved the yield and selectivity (run 2). On the other hand, when utilizing IPr as a ligand, **3bb** was obtained on 80% yield and no generation of [2 + 2 + 2] cycloadducts was observed (run 3). The catalyst loading could be reduced to 5 mol% by prolonging the reaction time without significant loss of the yield (run 4). As for solvent, dioxane gave the best result to afford **3bb** in 80% yield (run 5). Thus, the conditions in run 5 were used for further investigations.

Table 3.1. Optimization of reaction conditions

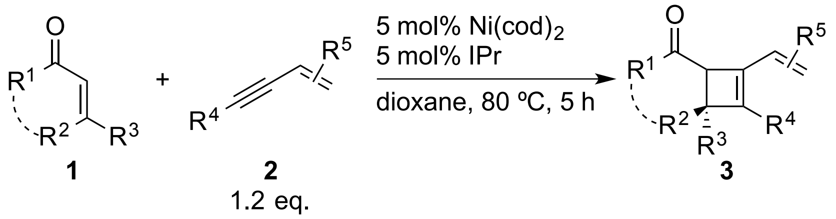


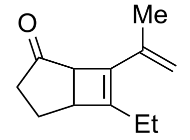
run	ligand	x (mol%)	y (mol%)	solvent	time (h)	GC yield (%)
1	PCyp$_3$	10	20	toluene	2	20
2	PCy$_3$	10	20	toluene	2	12
3	IPr	10	10	toluene	2	80
4	IPr	5	5	toluene	5	76
5	IPr	5	5	dioxane	5	80(76)[a]

[a] Isolated yield in parentheses.

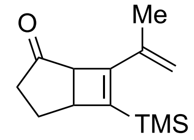
The scope of substrates is summarized in Table 3.2. Under optimized conditions, **1b** reacted with **1a** to afford cyclobutene **3ba** in 73% yield. The reaction of 1,3-enyne **2c** bearing TMS group was very slow to give corresponding product **3bc** in 33% yield. In the reactions of 1-phenyl-3-buten-1-yne (**2d**) and (*E*)-1-phenyl-1-3-penten-1-yne ((*E*)-**2e**), slow addition of an enyne via a syringe drive was required to suppress the oligomerization of enynes. In addition, the reaction of **1b** with **2d** was conducted in toluene with 10 mol% catalyst loading to afford **3bd** in 64% yield. The reaction of (*E*)-**2e** with **1b** gave (*E*)-**3be** in 55% yield while (*Z*)-**2e** reacted with **1b** to afford (*Z*)-**3be** in 88% yield, and no *E*/*Z*-isomerization was observed during these reactions.

Table 3.2. Scope and limitations of substrate

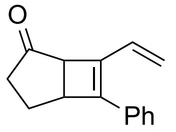




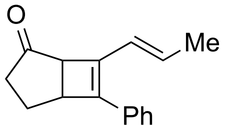
3ba: 73%



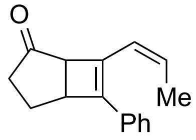
3bc: 33%



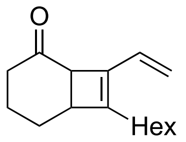
3bd: 64%[a,b]



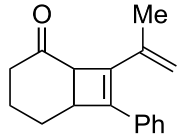
(*E*)-**3be**: 55%[a]



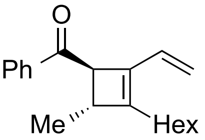
(*Z*)-**3be**: 88%



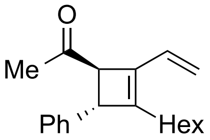
3cb: 68%[c]



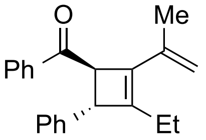
3cf: 77%



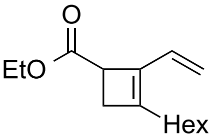
3ab: 60%



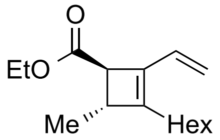
3db: 59%[d]



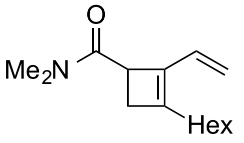
3ea: 60%[e]



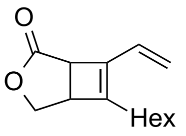
3fb: 91%



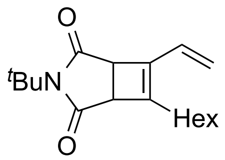
3gb: 57%[f]



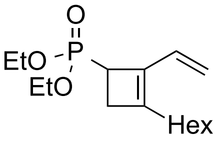
3hb: 65%



3ib: 58%



3jb: 69%



3kb: 79%

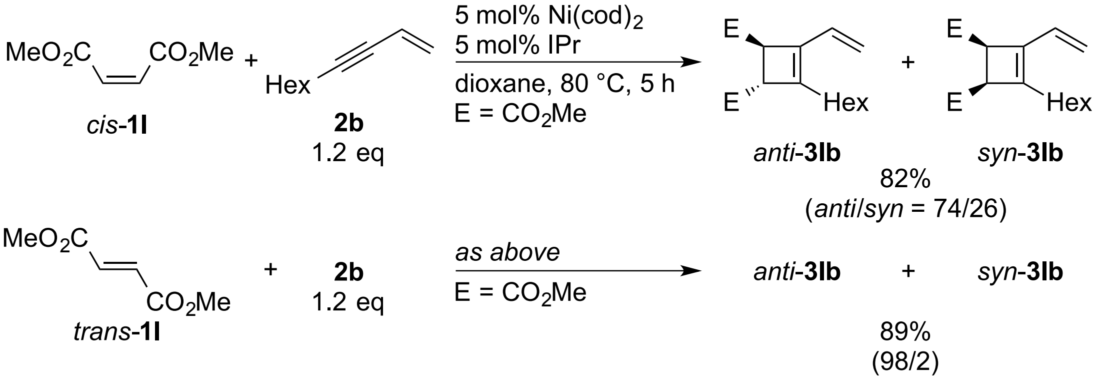
---

[a]With slow addition of **2**. [b]In toluene with a 10 mol % catalyst loading. [c]2 equiv of **2b** was used. [d]In THF with a 10 mol % catalyst loading. [e]The reaction was performed at 60 °C using 10 mol % Ni(cod)$_2$ and 20 mol % PCyp$_3$ as the catalyst. [f]The reaction was performed with 2 equiv of **1g** and 1 equiv of **2b**.

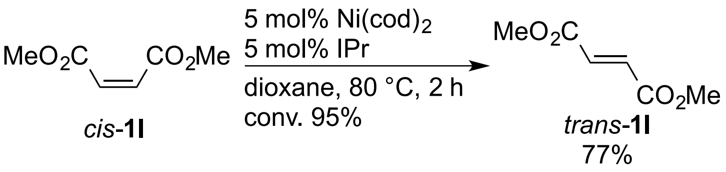
2-Cyclohexenone (**1c**) also reacted with **2b** and 3-methyl-1-phenyl-3-buten-1-yne (**2f**) to give **3cb** (68%) and **3cf** (77%), respectively. Acyclic enones **1a**, (*E*)-benzalacetone (**1d**), and (*E*)-chalcone (**1e**) are also applicable to this reaction, and **3ab**, **3db** and **3ea** were obtained in moderate yields. Only in the case of the reaction of **1a**, the [2 + 2 + 2] cycloadduct of two molecules of **1a** with **2d** was also obtained as a byproduct. The reaction of **1e** was conducted with PCyp$_3$ because the reaction proceeded faster than with IPr. Notably, ethyl acrylate (**1f**) underwent [2 + 2] cycloaddition with **2b**, to give **3fb** in 91% yield although **1f** reacts with simple internal alkyne to give a 2:1 linear trimerized product under similar reaction conditions.[12] In addition, nickel-catalyzed [2 +

2 + 2] cycloaddition, 1:2 trimerization and 1:1 dimerization of acrylates with alkynes have been reported.[13] However, such undesired byproducts were not observed at all in the present reaction. Other α,β-unsaturated carbonyls, (*E*)-ethyl crotonate (**1g**), *N*,*N*-dimethylacrylamide (**1h**), γ-crotonolactone (**1i**) and N-*tert*-butylmaleimide (**1j**), all were reacted with **1b** to give the corresponding cyclobutenes **3gb**, **3hb**, **3ib** and **3jb** in good yields. Furthermore, diethyl vinylphosphonate (**1k**) could be applied to this [2 + 2] cycloaddition to afford **3kb** in 79% yield.

To compare the reactivity between *cis*- and *trans*-alkenes, the reactions of dimethyl maleate (*cis*-**1l**) and dimethyl fumarate (*trans*-**1l**) were examined (Scheme 3.8). Under the optimized conditions, *trans*-**1l** reacted with **2b** to give *anti*-**3lb** selectively (89%, *anti*/*syn* = 98/2). On the other hand, the reaction of *cis*-**1l** with **2b** afforded a mixture of *anti*-**3lb** and *syn*-**3lb** in 82% yield (*anti*/*syn* = 74/26) due to the competitive *E*/*Z* isomerization of (*Z*)-**1l**. A control experiment showed that *cis*-**1l** was easily isomerized into *trans*-**1l** under the catalytic conditions (Scheme 3.9).

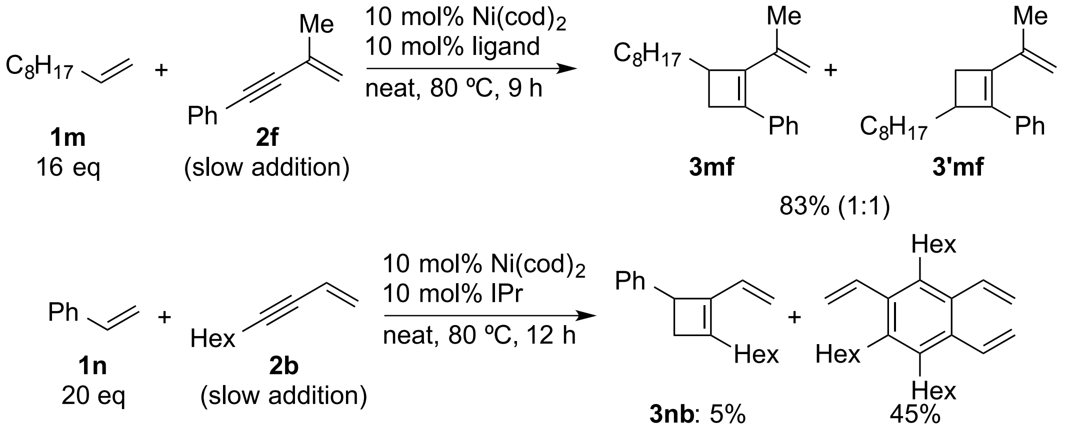


Scheme 3.8. Comparing the reactivity of *cis*- and *trans*-**1l**



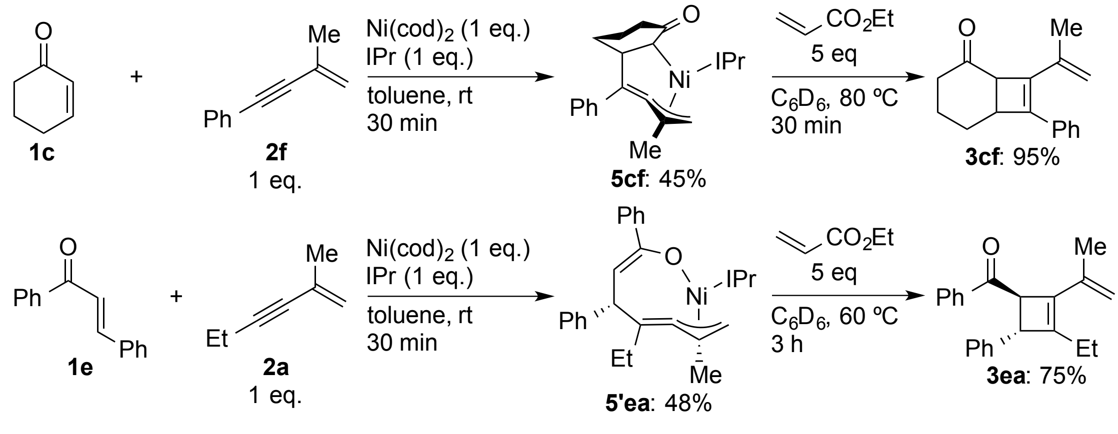
Scheme 3.9. Isomerization of *cis*-**1l** to *trans*-**1l**

Next, the reaction of electronically unactivated alkenes was investigated (Scheme 3.10). Since unactivated alkenes are less reactive than electron-deficient alkenes in the nickel-catalyzed reaction, the reaction conducted using an alkene as solvent and with slow addition of a 1,3-enyne via a syringe drive. The reaction of 1-decene (**1m**) with **2f** gave a regioisomeric mixture of **3mf** and **3'mf** in 82% yield. On the other hand, the reaction of styrene (**1n**) with **2b** afforded only a small amount of desired cyclobutene, and the major product was [2 + 2 + 2] cycloadducut of **2b**.



Scheme 3.10. [2 + 2] cycloaddition of unactivated alkenes with 1,3-enynes

To elucidate the reaction mechanisms, the stoichiometric reactions were conducted (Scheme 3.11). Treatment of **1c** with **2f**, Ni(cod)$_2$ and IPr gave nickelacycle **5cf** in 45% isolated yield. The structure of complex **5cf** was confirmed by X-ray diffraction analysis (Figure 3.1, left). Carbon atoms **C1**, **C2** and **C3** derived from 1.3-enyne **2f** were coordinated to nickel-center in η^3-butadienyl fashion and **C6** bound to nickel as a *C*-enolate. By heating nickelacycle **5cf** in the presence of ethyl acrylate, the corresponding [2 + 2] cycloadduct **3cf** was obtained in 95% yield, indicating that the η^3-butadienyl nickelacycle is the intermediate for this [2 + 2] cycloaddition. The reaction of acyclic enone **1e** with **2a** also generated η^3-butadienyl nickelacycle **5'ea** (Figure 3.1, right). In contrast to the complex **5cf**, the oxygen atom derived from **1e** coordinated to nickel in *O*-enolate fashion. In the presence of ethyl acrylate at 60 ºC,



Scheme 3.11. Synthesis and reactivity of η^3-butadienyl nickelacycles

nickelacycle **5'ea** was also converted to the corresponding cyclobutene **3ea** in 75% yield.

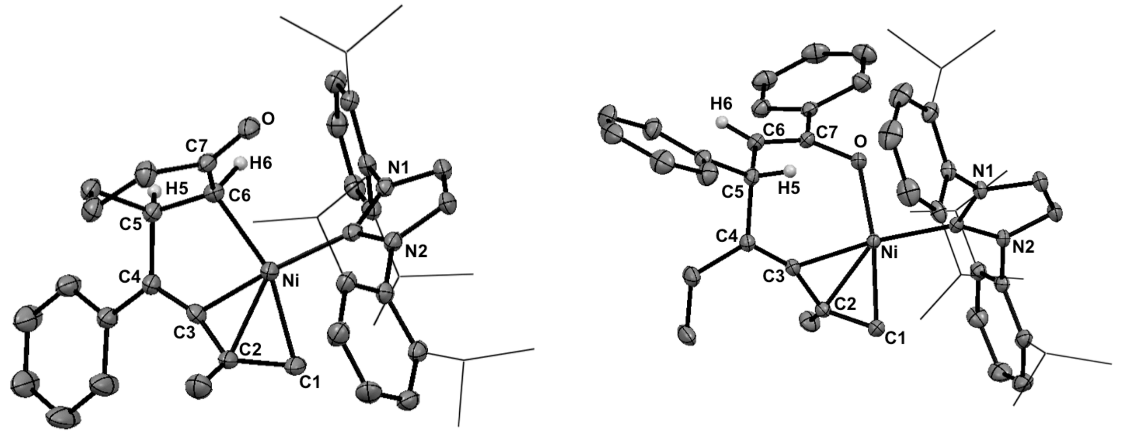
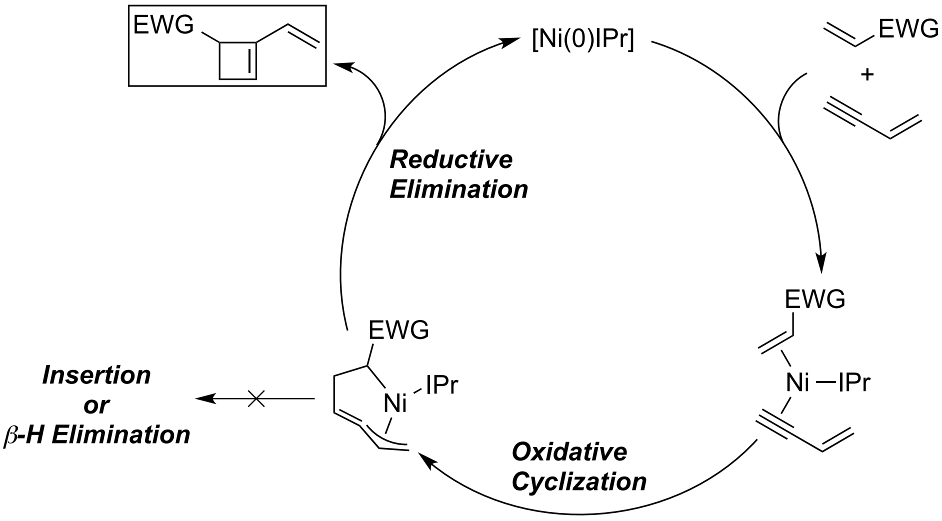


Figure 3.1. Molecular structure of complex **5cf** (left) and **5'ea** (right) with thermal ellipsoids set at the 30% probability level. Hydrogen atoms except for **H5** and **H6**, and solvated molecules have been omitted for clarity.

A proposed reaction mechanism is depicted in Scheme 3.12. An alkene and a 1,3-enyne coordinate to nickel(0) center followed by oxidative cyclization to generate η^3-butadienyl nickelacycle **A**.[14] The η^3-coordination might prevent the undesired path ways, such as β-H elimination and insertion of another π-substrate, by occupying the vacant site of the nickel(II) species. Then, reductive elimination takes place to afford the cyclobutene and regenerates the nickel(0) species. The *O*-enolate nickelacycle might be the resting state when using acyclic enones.



Scheme 3.12. A plausible mechanism

3.3 Conclusion

In chapter 3, the nickel-catalyzed intermolecular [2 + 2] cycloaddition of conjugated enynes with alkenes was developed. A diverse range of electron-deficient alkenes as well as electronically neutral 1-decene was applicable to provide cyclobutene derivatives with high chemo- and regioselectivities. The isolation of the key reaction intermediate revealed that the η^3-butadienyl coordination derived from conjugated enyne plays an important role for the selective formation of cyclobutenes.

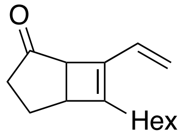
3.4 Experimental Section

General: All manipulations were conducted under a nitrogen atmosphere using standard Schlenk or dry box techniques. ^{1}H, ^{13}C, and ^{31}P nuclear magnetic resonance spectra were recorded on Brucker Avance III 400 and Varian Unity Inova 600 spectrometers. The chemical shifts in ^{1}H NMR spectra were recorded relative to residual protiated solvent ($CHCl_3$ (δ 7.27), C_6D_5H (δ 7.16), or toluene-d_7 (δ 2.08)). The chemical shifts in the ^{13}C NMR spectra were recorded relative to deuterated solvent ($CDCl_3$ (δ 77.0), C_6D_6 (δ 128.0), or toluene-d_8 (δ 20.4)). The chemical shifts in the ^{31}P NMR spectra were recorded using 85% H_3PO_4 as external standard. Assignment of the resonances in ^{1}H and ^{13}C NMR spectra was based on ^{1}H-^{1}H COSY, HMQC, HMBC, and NOESY experiments. High-resolution mass spectrometry and elemental analyses were performed at Instrumental Analysis Center, Faculty of Engineering, Osaka University. X-ray crystal data were collected by a Rigaku RAXIS-RAPID Imaging Plate diffractometer.

Materials: $Ni(cod)_2$ was purified by recrystallization from toluene. 1,4-Dioxne, toluene, THF, C_6D_6 and toluene-d_8 were distilled from sodium benzophenone ketyl. All commercially available reagents were distilled and degassed prior to use. Enyens **2a**, **2c** and (*E*)-**2e** were prepared by Sonogashira cross-coupling. Enynes (*Z*)-**2e**[15], **2f**[16] and Enone **3c**[17] was prepared according to the literature procedures.

General procedure for the Ni-catalysed [2+2] cycloaddition of conjugated enynes with alkynes: The reaction was conducted in a pressure tight test tube equipped with a magnetic stirrer bar. To a solution of Ni(cod)$_2$ (8.3 mg, 0.03 mmol, 5 mol%) and IPr (11.7 mg, 0.03 mmol, 5 mol%) in 1,4-dioxane (2 mL) was added an alkene (0.60 mmol). The solution was stirred for 5 min and then a 1,3-enyne (0.72 mmol, 1.2 equiv.) was added to it. The reaction mixture was heated at 80 °C and stirred for indicated time. The resulting mixture was cooled to room temperature, filtered directly through a short plug of silica gel and washed with EtOAc. Volatiles were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (Wako, Wakogel® C-300).

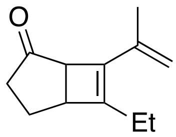
6-Hexyl-7-vinylbicyclo[3.2.0]hept-6-en-2-one (3bb)



Following the general procedure, cyclopentenone (**1b**) (49.8 mg, 0.61 mmol), dec-1-en-3-yne (**2b**) (100.5 mg, 0.74 mmol), Ni(cod)$_2$ (8.6 mg, 0.03 mmol) and IPr (12.2 mg, 0.03 mmol) were stirred at 80 °C for 5 hrs. Purification by column chromatography (hexane/EtOAc = 95/5) gave 100.0 mg of **3bb** (76%) as a pale yellow oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.19-1.40 (m, 6H), 1.50 (m, 2H), 1.81-2.03 (m, 2H), 2.03-2.29 (m, 3H), 2.76 (m, 1H), 3.12-3.28 (m, 2H), 5.08 (d, *J* = 10.8 Hz, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 6.33 (dd, *J* = 10.8, 17.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 14.0, 21.5, 22.5, 27.1, 27.8, 29.3, 31.6, 34.4, 41.4, 50.5, 115.8, 127.1, 138.0, 148.7, 216.7. HRMS Calcd for $C_{15}H_{22}O$: 218.1671, Found: 218.1673.

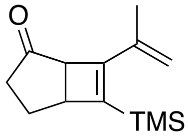
6-Ethyl-7-(prop-1-en-2-yl)bicyclo[3.2.0]hept-6-en-2-one (3ba)



Following the general procedure, **1b** (49.8 mg, 0.61 mmol), 2-methylhex-1-en-3-yne (**2a**) (67.7 mg, 0.72 mmol), Ni(cod)$_2$ (8.2 mg, 0.03 mmol) and IPr (12.2, 0.03 mmol) were stirred at 80 °C for 6 hrs. Purification by column chromatography (Hexane/CH_2Cl_2 = 50/50) gave 77.7 mg of **3ba** (73%) as a pale yellow oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.10 (t, *J* = 7.6 Hz, 3H), 1.83-2.30 (m, 2H), 1.92 (s, 3H), 2.09 (dd, *J* = 8.4, 17.4 Hz, 1H), 2.28 (m, 1H), 2.42 (m, 1H), 2.80 (m, 1H), 3.17 (s, 1H), 3.24 (d, *J* = 6.8 Hz, 1H), 4.85 (s, 1H), 5.06 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ12.0, 20.5, 21.5, 21.7, 34.3, 40.0, 50.5, 114.4, 137.5, 138.7, 148.3, 216.8. HRMS calcd for $C_{12}H_{16}O$: 176.1201, Found: 176.1202.

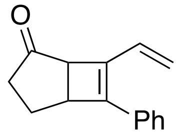
7-(Prop-1-en-2-yl)-6-(trimethylsilyl)bicyclo[3.2.0]hept-6-en-2-one (3bc)



Following the general procedure, **1b** (49.4 mg, 0.60 mmol), 1-(trimethylsilyl)-3-methyl-but-3-en-1-yne (**2c**) (99.7 mg, 0.72 mmol), $Ni(cod)_2$ (8.3 mg, 0.03 mmol) and IPr (12.4, 0.03 mmol) were stirred at 80 °C for 5 hrs. Purification by column chromatography (Hexane/EtOAc = 95/5) gave 43.8 mg of **3bc** (33%) as a pale yellow oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.20 (s, 9H), 1.86 (s, 3H), 1.93-2.15 (m, 3H), 2.83 (m, 1H), 3.22, (m, 1H), 3.42 (m, 1H), 5.01 (d, *J* = 0.4 Hz, 1H), 5.22, (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ -0.4, 19.8, 24.0, 34.5, 40.6, 54.1, 116.6, 138.3, 150.7, 156.7, 216.9. HRMS Calcd for $C_{13}H_{20}OSi$: 220.1283, Found: 220.1274.

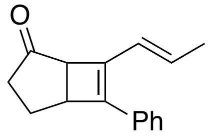
6-Phenyl-7-vinylbicyclo[3.2.0]hept-6-en-2-one (3bd)



The reaction was conducted in a septum-capped Schlenk tube. To a solution of $Ni(cod)_2$ (13.5 mg, 0.05 mmol, 10 mol%), IPr (20.3 mg, 0.05 mmol, 10 mol%) and **1b** (51.4 mg, 0.61 mmol, 1.0 equiv.) in toluene (3 mL) was added over 2 hrs via syringe-drive at 80 ºC a solution of 1-phenylbut-3-en-1-yne (**2d**) (64.4 mg, 0.50 mmol) in toluene (0.56 mL) and the mixture was further stirred at 80 ºC for 30 min. Purification by column chromatography (Hexane/EtOAc = 98/2) gave 69.1 mg of **3bd** (64% 97/3 regioisomeric ratio) as a pale yellow oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00-2.24 (m, 3H), 2.81 (dt, *J* = 18.0, 10.4, 1H), 3.41 (s, 1H), 3.72 (m, 1H), 5.34 (d, *J* = 10.4, 1H), 5.61 (d, *J* = 17.2, 1H), 6.82 (dd, *J* = 17.2, 10.4 Hz, 1H), 7.28-7.49 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 22.0, 34.6, 39.8, 50.3, 119.4, 126.7, 128.2, 128.2, 128.8, 133.9, 137.2, 142.7, 215.9. HRMS Calcd for $C_{15}H_{14}O$: 210.1045, Found: 210.1041. Most of ^{1}H resonances of the minor regioisomer of **3ac** were obscured by those of the major isomer, and thus, characteristic ^{1}H resonances are listed as follows: δ/ppm 3.48 (s, 1H), 3.62 (m, 1H), 5.42 (d, *J* = 10.4 Hz, 1H), 5.49 (d, *J* = 17.6 Hz, 1H).

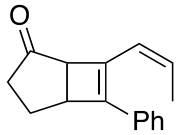
6-Phenyl-7-((*E*)-prop-1-en-1-yl)bicyclo[3.2.0]hept-6-en-2-one ((*E*)-3be)



The reaction was conducted in a septum-capped Schlenk tube. To a solution of Ni(cod)$_2$ (8.0 mg, 0.03 mmol, 5 mol%), IPr (12.7 mg, 0.03 mmol, 5 mol%) and **1b** (50.1 mg, 0.61 mmol) in 1,4-dioxane (2 mL) was added over 4 hrs via syringe-drive at 80 ºC a solution of (*E*)-1-phenylpent-3-en-1-yne ((*E*)-**2e**, 102.7 mg, 0.72 mmol, 1.2 equiv.) in 1,4-dioxane (0.72 mL) and the mixture was further stirred for 1 hr. Purification by column chromatography (Hexane/EtOAc = 95/5) gave 74.6 mg of (*E*)-**3be** (55%) as a pale yellow oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.87 (d, 7.2 Hz, 3H), 1.96-2.22 (m, 3H), 2.81 (m, 1H), 3.36 (d, 3.2 Hz, 1H), 3.68 (dd, 3.2, 7.2 Hz , 1H), 6.13 (dq, 7.2, 15.6 Hz, 1H), 6.53 (d, 15.6 Hz, 1H), 7.28 (m, 1H), 7.39 (m, 2H), 7.45 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 18.6, 22.1, 34.7, 39.7, 50.7, 123.5, 126.5, 127.6, 128.7, 132.5, 134.3, 137.2, 139.3, 216.5. HRMS Calcd for $C_{16}H_{16}O$: 224.1201, Found: 224.1203.

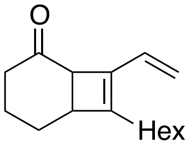
6-Phenyl-7-((*E*)-prop-1-en-1-yl)bicyclo[3.2.0]hept-6-en-2-one ((*Z*)-3be)



Following the general procedure, **1b** (51.3 mg, 0.62 mmol), (*Z*)-1-phenylpent-3-en-1-yne ((*Z*)-**2e**) (104.4 mg, 0.73 mmol), Ni(cod)$_2$ (8.1 mg, 0.03 mmol) and IPr (12.5, 0.03 mmol) were stirred at 80 °C for 5 hrs. Purification by column chromatography (Hexane/EtOAc = 95/5) gave 123.3 mg of (*Z*)-**3be** (88%) as a pale yellow oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.96 (dd, 1.2, 7.2 Hz, 3H), 1.83-2.27 (m, 3H), 2.83 (dddd, 1.2, 9.2, 12.4, 17.6 Hz, 1H), 3.51 (s, 1H), 3.77 (dd, 3.6, 7.2 Hz , 1H), 5.74 (dq, 7.2, 11.6 Hz, 1H), 6.36 (d, 11.6 Hz, 1H), 7.22-7.48 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 15.2, 21.4, 34.6, 41.4, 52.5, 121.3, 126.8, 127.8, 128.6, 131.0, 134.2, 136.5, 143.4, 215.7. HRMS Calcd for $C_{16}H_{16}O$: 224.1201, Found: 224.1201.

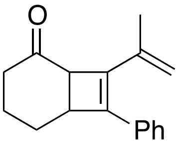
7-Hexyl-8-vinylbicyclo[4.2.0]oct-7-en-2-one (3cb)



Following the general procedure except for the use of 2 equiv. of **2b**, cylohexenone (**1c**) (57.4 mg, 0.60 mmol), **2b** (163.0 mg, 1.20 mmol), Ni(cod)$_2$ (8.2 mg, 0.03 mmol) and IPr (12.5, 0.03 mmol) were stirred at 80 °C for 5 hrs. Purification by column chromatography (Hexane/EtOAc = 95/5) gave 94.4 mg of **3cb** (68%) as a pale yellow oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.90 (t, J = 6.4 Hz, 3H), 1.21-2.29 (m, 15H), 2.50 (dd, J = 18.8, 5.2 Hz, 1H), 3.19 (s, 1H), 3.48 (s, 1H), 5.05 (d, J = 10.8 Hz, 1H), 5.37 (d, J = 17.2 Hz, 1H), 6.37 (dd, J = 10.8, 17.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 14.1, 18.0, 22.5, 24.5, 27.0, 27.4, 29.4, 31.6, 39.8, 40.4, 51.3, 115.7, 127.5, 135.4, 148.7, 212.4. HRMS Calcd for $C_{16}H_{24}O$: 232.1827, Found: 232.1825.

7-Phenyl-8-(prop-1-en-2-yl)bicyclo[4.2.0]oct-7-en-2-one (3cf)

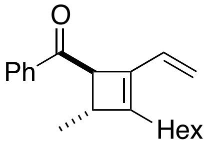


Following the general procedure, **1c** (59.0 mg, 0.61 mmol), 1-phenyl-3-methyl-but-3-en-1-yne (**2f**) (104.1 mg, 0.73 mmol), Ni(cod)$_2$ (8.8 mg, 0.03 mmol) and IPr (12.7, 0.03 mmol) were stirred at 80 °C for 5 hrs. Purification by column chromatography (Hexane/CH_2Cl_2 = 70/30) gave 112.0 mg of **3cf** (77%) as a white solid.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.56-1.72 (m, 2H), 1.87 (s, 3H), 1.85-2.04 (m, 2H), 2.23 (ddd, J = 7.2, 11.2, 19.2 Hz, 1H), 2.61 (dd, J = 6.0, 19.2 Hz, 1H), 3.60 (s, 2H), 5.02 (s, 1H), 5.34 (s, 1H), 7.26-7.40 (m, 5H). ^{13}C{^{1}H} NMR (100

MHz, $CDCl_3$): δ 17.9, 21.2, 24.4, 39.6, 40.2, 52.4, 116.7, 127.7, 127.8 128.3, 134.5, 137.7, 138.3, 143.8, 212.4. HRMS Calcd for $C_{17}H_{18}O$: 238.1358, Found: 238.1364.

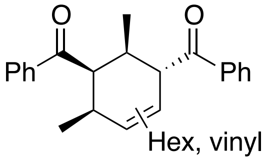
(3-Hexyl-4-methyl-2-vinylcyclobut-2-en-1-yl)(phenyl)methanone (3ab)



Following the general procedure, 1-phenylbut-2-en-1-one (**1a**) (85.8 mg, 0.59 mmol), **2b** (100.7 mg, 0.74 mmol), Ni(cod)$_2$ (9.0 mg, 0.03 mmol) and IPr (12.8, 0.03 mmol) were stirred at 80 °C for 5 hrs. Purification by column chromatography (Hexane/CH_2Cl_2 = 70/30) gave 99.3 mg of **3ab** (60%) as colorless oil.

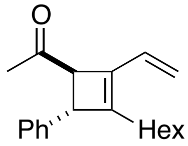
Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 7.2 Hz, 3H), 1.24-1.40 (m, 6H), 1.36 (d, J = 7.2 Hz, 3H), 1.45 (m, 2H), 2.16 (m, 1H), 2.26 (m, 1H), 2.70 (q, J = 7.2 Hz, 1H), 4.07 (s, 1H), 4.87 (d, J = 17.2 Hz, 1H), 5.02 (d, J = 10.4 Hz, 1H), 6.52 (dd, J = 10.4, 17.2 Hz, 1H), 7.49 (m, 2H), 7.58 (m, 1H), 8.02 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.1, 17.7, 22.5, 27.1, 27.4, 29.3, 31.6, 41.9, 52.6, 114.1, 128.1, 128.3, 128.6, 132.9, 135.5, 137.1, 149.9, 199.5. HRMS Calcd for $C_{20}H_{26}O$: 282.1984, Found: 282.1986.

A regioisomeric mixture of [2+2+2] cycloadduct (35.4 mg, 28%, major/minor = 75/25) was also obtained.



Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, 6.8 Hz, 1H, $3H_{maj}$), 0.91 (t, 6.4 Hz, 1H, $3H_{min}$), 0.94-1.02 (m, $3H_{maj}$, $3H_{min}$), 1.19-1.71 (m, $11H_{maj}$, $12H_{min}$), 2.25-2.35 (m, $1H_{maj}$, $1H_{min}$), 2.38-2.66 (m, $2H_{maj}$, $1H_{min}$), 2.93 (m, $1H_{min}$), 3.20 (m, $1H_{maj}$), 3.79-3.86 (m, $1H_{maj}$, $1H_{min}$), 4.14 (s, $1H_{maj}$), 4.38 (s, $1H_{min}$), 4.85 (d, 17.2 Hz, $1H_{min}$), 4.91 (d, 11.2 Hz, $1H_{min}$), 5.09 (d, 17.6 Hz, $1H_{maj}$), 5.16 (d, 11.6 Hz, $1H_{maj}$), 6.67 (dd, 11.6, 17.6 Hz, $1H_{maj}$), 6.83 (dd, J = 11.2, 17.2 Hz, $1H_{min}$), 7.40-7.63 (m, $6H_{maj}$, $6H_{min}$), 7.80-7.90 (m, $2H_{maj}$, $2H_{min}$), 8.03 (m, $2H_{maj}$), 8.06 (m, $2H_{min}$). HRMS Calcd for $C_{30}H_{36}O_2$: 428.2715, Found: 428.2713 and 428.2718.

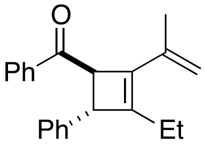
1-(-3-Hexyl-4-phenyl-2-vinylcyclobut-2-en-1-yl)ethanone (3db)



To a solution of Ni(cod)$_2$ (14.3 mg, 0.05 mmol, 10 mol%) and IPr (22.5 mg, 0.06 mmol, 10 mol%) in THF (2 mL) was added (*E*)-benzalacetone (**1d**) (72.6 mg, 0.50 mmol). The solution was stirred for 5 min and then **2b** (76.0 mg, 0.56 mmol) was added. The reaction mixture was heated at 80 °C and stirred for 2 hrs. The resulting mixture was cooled to room temperature, filtered directly through a short pad of silica gel and washed with EtOAc. Volatiles were removed under reduced pressure. The residue was purified by column chromatography (Hexane/CH_2Cl_2 = 70/30) to give 83.1 mg of **3db** (59%) as a pail yellow oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.17-1.50 (m, 8H), 2.07 (m, 1H), 2.18 (s, 3H), 2.29 (m, 1H), 3.46 (s, 1H), 3.69 (s, 1H), 5.04 (d, *J* = 17.6 Hz, 1H), 5.15 (d, *J* = 10.4 Hz, 1H), 6.56 (dd, *J* = 17.6, 10.4 Hz, 1H), 7.18-7.35 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 26.9, 27.5, 29.2, 29.7, 31.5, 49.6, 60.0, 115.3, 127.1, 127.2, 128.0, 128.6, 138.3, 140.2, 148.9, 208.5. HRMS Calcd for $C_{20}H_{26}O$: 282.1984, Found: 282.1975.

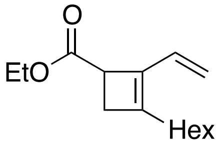
(-3-Ethyl-4-phenyl-2-(prop-1-en-2-yl)cyclobut-2-en-1-yl)(phenyl)methanone (3ea)



(*E*)-Chalcone (**1e**) (125.4 mg, 0.60 mmol) was added to a solution of Ni(cod)$_2$ (16.3 mg, 0.06 mmol, 10 mol%) and PCyp$_3$ (31.1 mg, 0.13 mmol, 10 mol%) in 1,4-dioxane (2 mL). The solution was stirred for 5 min and then **2a** (71.3 mg, 0.76 mmol, 1.2 equiv.) was added. The reaction mixture was heated at 60 °C and stirred for 24 hrs. The resulting mixture was cooled to room temperature, filtered directly through a short pad of silica gel and washed with EtOAc. Volatiles were removed under reduced pressure. The residue was purified by column chromatography (Hexane/CH_2Cl_2 = 70/30) to give 109.5 mg of **3ea** (60%) as a white solid. Single crystals suitable for X-ray diffraction analysis were obtained by recrystallization from hexane under a nitrogen atmosphere at –30 °C.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.93 (t, *J* = 7.6 Hz, 3H), 2.09 (s, 1H), 2.17 (dt, *J* = 7.6, 7.6 Hz, 1H), 2.54 (dt, *J* = 7.6, 7.6 Hz, 1H), 3.68 (s, 1H), 4.29 (s, 1H), 4.68 (s, 1H), 4.92 (s, 1H), 7.25-7.40 (m, 7H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 11.7, 20.9, 21.5, 50.2, 54.6, 113.8, 127.2, 127.5, 128.3, 128.5, 128.7, 132.9, 136.7, 138.3, 138.5, 140.7, 147.5, 198.6. HRMS Calcd for $C_{22}H_{22}O$: 302.1671, Found: 302.1699.

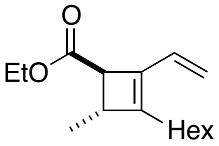
Ethyl 3-hexyl-2-vinylcyclobut-2-enecarboxylate (3fb)



Following the general procedure, ethyl acrylate (**1f**) (60.2 mg, 0.60 mmol), **2b** (97.8 mg, 0.72 mmol), Ni(cod)$_2$ (8.3 mg, 0.03 mmol) and IPr (12.3, 0.03 mmol) were stirred at 80 °C for 5 hrs. Purification by column chromatography (Hexane/EtOAc = 95/5) gave 129.6 mg of **3fb** (91%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.22-1.37 (m, 9H), 1.40-1.51 (m, 2H), 2.18 (t, *J* = 7.2 Hz, 2H), 2.48-2.60 (m, 2H), 3.57 (dd, *J* = 1.6, 4.0 Hz, 1H), 4.17 (m, 2H), 5.02 (d, *J* = 10.4 Hz, 1H), 5.13 (d, *J* = 17.6 Hz, 1H), 6.37 (dd, *J* = 10.4, 17.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 14.1, 14.2, 22.5, 26.9, 28.8, 29.1, 31.6, 31.8, 41.4, 60.3, 113.7, 127.9, 136.8, 147.1, 173.9. HRMS Calcd for $C_{15}H_{24}O_2$: 236.1776, Found: 236.1778.

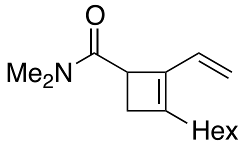
Ethyl 3-hexyl-4-methyl-2-vinylcyclobut-2-enecarboxylate (3gb)



Following the general procedure except for the use of 2 equiv. of **1g**, (*E*)-ethyl crotonate (**1g**) (145.6 mg, 1.27 mmol) and **2b** (86.2 mg, 0.63 mmol), Ni(cod)$_2$ (8.4 mg, 0.03 mmol) and IPr (12.5, 0.03 mmol) were stirred at 80 °C for 10 hrs. Purification by column chromatography (Hexane/EtOAc = 95/5) gave 90.7 mg of **3gb** (57%) as a pale yellow oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.89 (t, *J* = 6.8, 3H), 1.20 (d, *J* = 6.8, 3H), 1.21-1.57 (m, 14H), 2.03-2.90 (m, 2H), 2.84 (q, *J* = 6.8, 1H), 3.07 (s, 1H), 4.16 (m, 2H), 5.02 (d, *J* = 10.8 Hz, 1H), 5.09 (d, *J* = 17.6 Hz, 1H), 6.41 (dd, *J* = 17.6, 10.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.1, 14.3, 17.3, 22.5, 27.0, 27.3, 29.2, 31.6, 40.0, 49.7, 60.2, 113.6, 128.3, 134.8, 151.3, 173.7. HRMS Calcd for $C_{16}H_{26}O_2$: 250.1933, found: 250.1929.

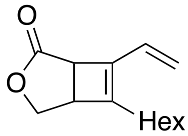
3-Hexyl-*N*,*N*-dimethyl-2-vinylcyclobut-2-enecarboxamide (3hb)



Following the general procedure, *N*,*N*-dimethylacrylamide (**1h**) (50.9 mg, 0.60 mmol), **2b** (98.1 mg, 0.72 mmol), Ni(cod)$_2$ (8.2 mg, 0.03 mmol) and IPr (12.8, 0.03 mmol) were stirred at 80 °C for 5 hrs. Purification by column chromatography (Hexane/EtOAc = 67/33) gave 91.7 mg of **3hb** (65%) as a colorless oil.

Spectral data: ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.17-1.35 (m, 6H), 1.43 (m, 2H), 2.16 (t, *J* = 7.2 Hz, 2H), 2.36 (d, *J* = 13.2 Hz, 1H), 2.63 (dd, *J* = 13.2, 4.8 Hz, 1H), 2.94 (s, 3H), 3.04 (s, 3H), 3.79 (d, *J* = 4.8 Hz, 1H), 4.91-5.07 (m, 2H), 6.40 (dd, *J* = 17.2, 10.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 26.9, 28.7, 29.1, 31.5, 32.9, 35.3, 36.6, 39.3, 133.6, 128.2, 137.5, 145.1, 172.6. HRMS Calcd for $C_{15}H_{25}NO$: 235.1936, Found: 235.1935.

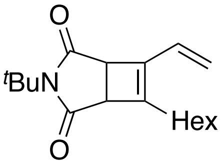
6-Hexyl-7-vinyl-3-oxabicyclo[3.2.0]hept-6-en-2-one(3ib)



To a solution of Ni(cod)$_2$ (8.2 mg, 0.03 mmol) and IPr (12.9, 0.03 mmol) in dioxane (1.5 mL) was added a solution of γ-crotonolactone (**1i**) (52.0 mg, 0.62 mmol) and **2b** (98.2 mg, 0.72 mmol) in dioxane (0.5 mL). The reaction mixture was heated at 80 °C and stirred for 5 hrs. The resulting mixture was cooled to room temperature, filtered directly through a short pad of silica gel and washed with EtOAc. Volatiles were removed under reduced pressure. The residue was purified by column chromatography (Hexane/CH_2Cl_2 = 70/30) to give 79.1 mg of **3ib** (58%) as a pale yellow oil.

Spectral data: ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.20-1.38 (m, 6H), 1.39-1.56 (m, 2H), 2.11-2.30 (m, 2H), 3.41 (m, 1H), 3.66 (d, *J* = 4.0 Hz, 1H), 4.30 (m, 2H), 5.24 (d, *J* = 10.4 Hz, 1H), 5.53 (d, *J* = 17.6 Hz, 1H), 6.35 (dd, *J* = 10.4, 17.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 27.2, 27.6, 29.2, 31.5, 39.3, 42.6, 68.2, 117.7, 126.5, 140.3, 146.7, 175.5. HRMS Calcd for $C_{14}H_{20}O_2$: 220.1463, Found: 220.1467.

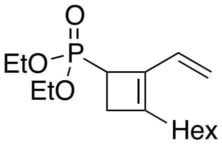
3-(*tert*-Butyl)-6-hexyl-7-vinyl-3-azabicyclo[3.2.0]hept-6-ene-2,4-dione (3jb)



Following the general procedure, *N*-*tert*-butylmaleimide (**1j**) (93.3 mg, 0.61 mmol), **2b** (98.1 mg, 0.72 mmol), Ni(cod)$_2$ (8.2 mg, 0.03 mmol) and IPr (14.1, 0.04 mmol) were stirred at 80 °C for 5 hrs. Purification by column chromatography (Hexane/EtOAc = 98/2) gave 121.3 mg of **3jb** (69%) as a pale yellow oil.

Spectral data: ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.20-1.32 (m, 6H), 1.44-1.57 (m, 2H), 1.51 (s, 9H), 2.23 (t, *J* = 7.6 Hz, 2H), 3.39 (d, *J* = 3.2 Hz, 1H), 3.60 (d, *J* = 3.2 Hz, 1H), 5.25 (d, *J* = 10.8 Hz, 1H), 5.58 (d, *J* = 17.2 Hz, 1H), 6.33 (dd, *J* = 10.8, 17.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 26.9, 28.2, 28.3, 29.0, 31.4, 43.5, 45.2, 57.9, 118.2, 126.6, 141.3, 145.7, 176.3, 176.5. HRMS Calcd for $C_{18}H_{27}NO_2$: 289.2042, Found: 289.2041.

Diethyl (3-hexyl-2-vinylcyclobut-2-en-1-yl)phosphonate (3kb)

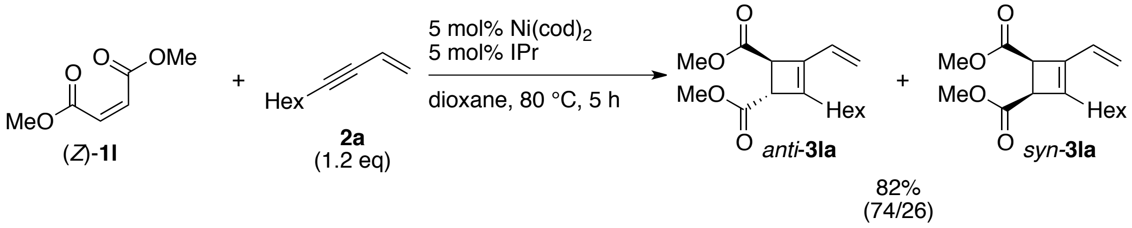


Following the general procedure, diethyl vinylphosphonate (**1k**) (95.1 mg, 0.58 mmol), **2b** (100.4 mg, 0.73 mmol), Ni(cod)$_2$ (8.1 mg, 0.03 mmol) and IPr (12.3, 0.03 mmol) were stirred at 80 °C for 5 hrs. Purification by column chromatography (Hexane/EtOAc = 50/50) gave 137.8 mg of **3kb** (79%) as a pale yellow oil.

Spectral data: ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.20-1.37 (m, 12H), 1.43 (m, 2H), 2.16 (m, 2H), 2.56 (m, 2H), 3.23 (ddd, *J* = 1.0, 10.4 Hz, J_{HP} = 4.4 Hz, 1H), 4.00-4.18 (m, 4H), 5.11 (d, *J* = 11.2 Hz, 1H), 5.51 (d, *J* = 17.2 Hz, 1H), 6.36

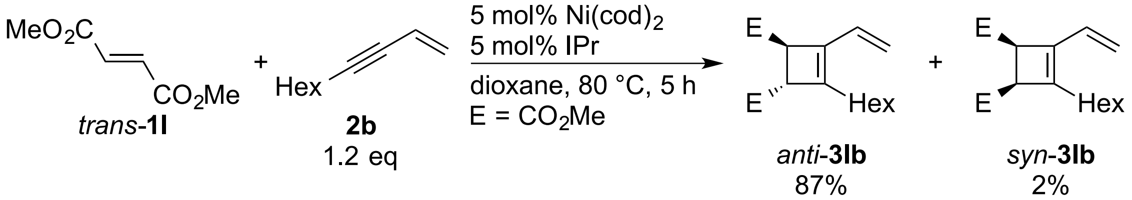
(dd, J = 11.2, 17.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.0, 16.5 (d, J_{CP} = 3.8 Hz), 16.5 (d, J_{CP} = 3.8 Hz), 22.5, 27.1(d, J_{CP} = 3.1 Hz), 28.6, 29.1, 30.0 (d, J_{CP} = 7.7 Hz), 31.6, 35.0 (d, J_{CP} = 148.6 Hz), 61.4 (d, J_{CP} = 6.1 Hz), 62.0 (d, J_{CP} = 6.1 Hz), 115.4, 127.8, 135.1 (d, J_{CP} = 10.0 Hz), 146.9 (d, J_{CP} = 16.9 Hz). $^{31}P\{^1H\}$ NMR (109 MHz, $CDCl_3$): δ 30.5 (s). HRMS Calcd for $C_{16}H_{29}O_3P$: 300.1854, Found: 300.1865.

Nickel-Catalyzed [2+2] cycloaddition of dimethyl maleate (*cis*-**1l**) with 2a



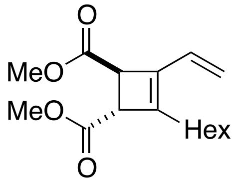
Following the general procedure, dimethyl maleate (*cis*-**1l**) (86.5 mg, 0.60 mmol), **2b** (97.9 mg, 0.72 mmol), Ni(cod)$_2$ (8.1 mg, 0.03 mmol) and IPr (12.3, 0.03 mmol) were stirred at 80 °C for 5 hrs. Purification by column chromatography (Hexane/EtOAc = 95/5) gave 100.6 mg of *anti*-**3lb** (60%) as a colorless oil and 37.7 mg of *syn*-**3lb** (22%) as a colorless oil.

Nickel-Catalyzed [2+2] cycloaddition of dimethyl fumarate (*trans*-**1l**) with 2b



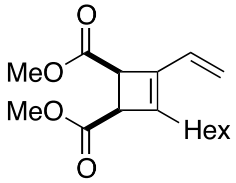
Following the general procedure, dimethyl fumarate (*trans*-**1l**) (86.0 mg, 0.60 mmol), **2b** (96.8 mg, 0.71 mmol), Ni(cod)$_2$ (8.3 mg, 0.03 mmol) and IPr (12.4, 0.03 mmol) were stirred at 80 °C for 5 hrs. Purification by column chromatography (hexane/EtOAc = 95/5) gave 146.1 mg of *anti*-**3lb** (87%) as a colorless oil and 3.2 mg of *syn*-**3lb** (2%) as a colorless oil.

anti-(1*R**,2*R**)-Dimethyl 3-hexyl-4-vinylcyclobut-3-ene-1,2-dicarboxylate (*anti*-3lb)



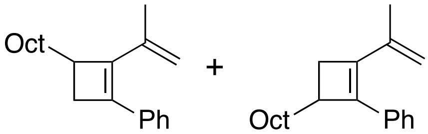
Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.22-1.38 (m, 6H), 1.40-1.56 (m, 2H), 2.11-2.32 (m, 2H), 3.67 (s, 1H), 3.72 (s, 3H), 3.72 (s, 3H), 3.82 (s, 1H), 5.15 (d, *J* = 11.2 Hz, 1H), 5.23 (d, *J* = 17.2 Hz, 1H), 6.39 (dd, *J* = 17.2, 11.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 26.7, 28.0, 29.0, 31.5, 44.8, 46.7, 52.0, 52.0, 116.2, 127.4, 138.8, 144.4, 171.9, 172.4. HRMS Calcd for $C_{16}H_{24}O_4$: 280.1675, Found: 280.1675.

syn-Dimethyl 3-hexyl-4-vinylcyclobut-3-ene-1,2-dicarboxylate (*syn*-3lb)



Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.23-1.57 (m, 8H), 2.23-2.40 (m, 2H), 3.69 (s, 3H), 3.69 (s, 3H), 3.73 (d, *J* = 5.2 Hz, 1H), 3.91 (d, *J* = 5.2 Hz, 1H), 5.15 (d, *J* = 11.2 Hz, 1H), 5.16 (d, *J* = 17.2 Hz, 1H), 6.41 (dd, *J* = 17.2, 11.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 26.8, 27.9, 29.2, 31.5, 45.3, 45.9, 51.8, 51.9, 116.0, 127.3, 137.9, 144.1, 171.1, 171.7. HRMS Calcd for $C_{16}H_{24}O_4$: 280.1675, Found: 280.1676.

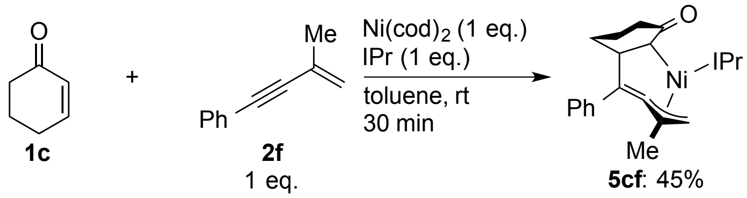
(3-Octyl-2-(prop-1-en-2-yl)cyclobut-1-en-1-yl)benzene (3mf) and (4-Octyl-2-(prop-1-en-2-yl)cyclobut-1-en-1-yl)benzene (3’mf)



The reaction was conducted with septum-capped test-tube. Ni(cod)$_2$ (12.8 mg, 0.05 mmol, 10 mol%) and IPr (19.1 mg, 0.05 mmol, 10 mol%) were dissolved in 1-decene **2m** (1.5 mL, 8 mmol, 16 equiv.). The reaction mixture was heated to 80 ºC and stirred for 5 minutes. A solution of **2f** (71.1 mg, 0.50 mmol, 1 equiv.) in 1,4-dioxane (0.60 mL) was added via syringe-drive over 8 hrs and the mixture was further stirred for 1 hr at 80 ºC. The reaction mixture was cooled to room temperature and filtered through short pad of silica gel with EtOAc as eluent. Purification by column chromatography (Hexane) gave 116.8 mg of a mixture of **3mf** and **3'mf** (83%, 50/50) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 6.8 Hz, 3H), 1.10-1.50 (m, 26H), 1.70 (m, 1H, **3mf**), 1.82 (m, 1H, **3'mf**), 1.87 (s, 3H, **3mf**), 1.91 (s, 3H, **3'mf**), 2.17 (dd, *J* = 13.2, 1.6 Hz, 1H, **3mf**), 2.27 (dd, *J* = 13.2, 1.6 Hz, 1H, **3'mf**), 2.66 (dd, *J* = 13.2, 4.8 Hz, 1H, **3nf**), 2.75 (dd, *J* = 13.2, 4.8 Hz, 1H, **3'mf**), 2.86 (m, 1H, **3'mf**), 2.99 (m, 1H, **3mf**), 4.93 (s, 1H, **3'mf**), 5.02 (s, 1H, **3mf**), 5.07 (s, 1H, **3'mf**), 5.10 (s, 1H, **3mf**), 7.18-7.47 (m, 10H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.1, 14.1, 20.7 (**3'mf**), 21.1(**3mf**), 22.7, 22.7, 27.0, 27.2, 29.3, 29.3, 29.6, 29,7, 29.8, 29.9, 31.9, 31.9, 32.8, 32.9, 33.0, 33.4, 39.4 (**3mf**), 39.7 (**3'mf**), 113.5 (**3'mf**), 114.2 (**3mf**), 126.8, 126.9, 127.0, 127.7, 127.9, 128.0, 136.0, 136.4, 137.1 (**3mf**), 138.9 (**3'mf**), 139.5 (**3mf**), 140.2 (**3'mf**), 143.9 (**3'mf**), 145.0 (**3mf**). HRMS Calcd for $C_{21}H_{30}$: 282.2348, Found: 282.2339 and 282.2340.

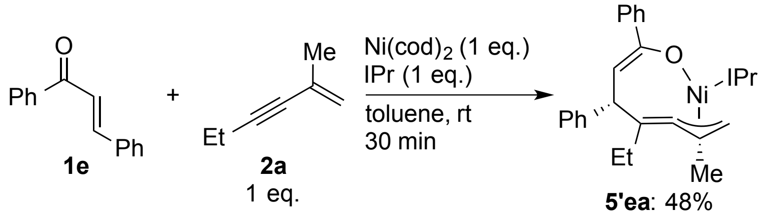
Isolation of complex 5cf



To a toluene solution of Ni(cod)$_2$ (53.9 mg, 0.20 mmol) and IPr (76.8 mg, 0.20 mmol) was added a toluene solution of **1c** (19.1 mg, 0.20 mmol) and **2f** (29.0 mg, 0.20 mmol) at room temperature. Resulting dark brown mixture was stirred for 30 min and then volatiles were removed *in vacuo* to give dark brown solids. The solids were dissolved in pentane and recrystallized at –30 °C to give **5cf** (67.1 mg, 45%) as an orange solid. Single crystals suitable for X-ray diffraction analysis were obtained by recrystallization from hexane at –30 °C.

Complex **5cf** was observed as two isomers (77/23) at –60 °C on NMR spectroscopies and the most of resonances were complicated to identify. Thus, the characteristic resonances of the major isomer of **5cf** were listed as follows; ^{1}H NMR (400 MHz, toluene-d_8, –60 °C): δ 1.79 (s, 1H, η^3-(CC(CH$_3$)C*H*$_2$)), 2.05 (s, 1H, η^3-(CC(CH$_3$)C*H*$_2$)), 2.26 (m, 1H, CH$_2$C*H*$_2$C=O), 2.80 (m, 1H, CH$_2$C*H*$_2$C=O), 3.71 (m, 1H, -C*H*CH(Ni)C=O), 3.88 (d, *J* = 6.6 Hz, 1H, -CHC*H*(Ni)C=O) 6.46 (s, 1H, -NC*H*=C*H*N-), 6.51 (s, 1H, -NC*H*=C*H*N-). ^{13}C{^{1}H} NMR (100 MHz, toluene-d_8, –60 ºC): δ 22.9 (η^3-(CC(*C*H$_3$)CH$_2$), 37.1 (CH$_2$*C*H$_2$C=O), 48.4 (η^3-(CC(CH$_3$)*C*H$_2$)), 52.7 (-*C*HCH(Ni)C=O), 53.5 (-CH*C*H(Ni)C=O), 97.5 (η^3-(C*C*(CH$_3$)CH$_2$)), 180.7 (η^3-(*C*C(CH$_3$)CH$_2$)), 192.9 (-N*C*N-), 205.9 (*C*=O). Anal. Calcd for $C_{44}H_{54}N_2NiO$: C, 77.08; H, 7.94; N, 4.09. Found: C, 76.41; H, 7.64; N, 4.01.

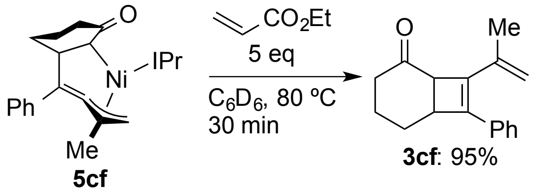
Isolation of complex 5’ea



To a toluene solution of Ni(cod)$_2$ (26.1 mg, 0.09 mmol) and IPr (39.3 mg, 0.10 mmol) was added a toluene solution of **1e** (22.8 mg, 0.11 mmol) and **2a** (13.4 mg, 0.14 mmol) at room temperature. Resulting dark brown mixture was stirred for 30 min and then volatiles were removed *in vacuo* to give dark brown solids. The solids were dissolved in pentane and recrystallized at –30 °C to give **5’ea** (34.0 mg, 48%) as a yellow solid. Single crystals suitable for X-ray diffraction analysis were obtained by recrystallization from pentane at –30 °C.

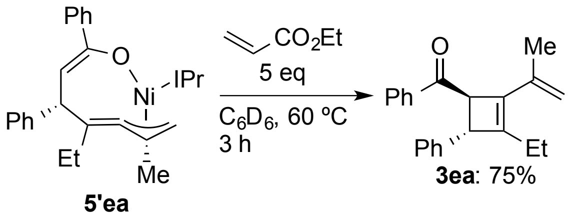
Spectral data: ^{1}H NMR (400 MHz, C$_6$D$_6$, rt): δ 0.79 (t, *J* = 7.2 Hz, 3H, -CH$_2$C*H*$_3$), 0.92 (s, 1H, η^3-(CC(CH$_3$)C*H*$_2$)), 1.08 (m, 12H, ^{i}*Pr*), 1.17 (d, *J* = 6.8 Hz, 6H, ^{i}*Pr*), 1.23 (s, 1H, η^3-(CC(CH$_3$)C*H*$_2$)), 1.24 (d, *J* = 6.8 Hz, 6H, ^{i}*Pr*), 1.45 (s, 3H, η^3-(CC(C*H*$_3$)CH$_2$)), 1.68 (dq, *J* = 16.4, 7.2 Hz, 1H, -C*H*$_2$CH$_3$), 2.04 (dq, *J* = 16.4, 7.2 Hz, 1H, -C*H*$_2$CH$_3$), 2.87 (m, 2H, ^{i}*Pr*), 3.76 (m, 2H, ^{i}*Pr*), 4.29 (d, *J* = 7.6 Hz, 1H, -C*H*(Ph)-), 5.80 (d, *J* = 7.6 Hz , 1H, -C*H*=C(Ph)O-), 6.66 (s, 2H, -NC*H*=C*H*N-), 7.07 (d, *J* = 7.2 Hz, 2H, *Ar*), 7.14-7.37 (m, 10H, *Ar*, *Ph*), 7.44 (d, *J* = 7.6 Hz, 2H, *Ph*), 7.88 (d, *J* = 7.6 Hz, 2H, *Ph*). ^{13}C{^{1}H} NMR (100 MHz, C$_6$D$_6$, rt): δ 12.6 (-CH$_2$*C*H$_3$), 22.1 (η^3-(CC(*C*H$_3$)CH$_2$)), 22.2 (^{i}*Pr*), 23.0 (^{i}*Pr*), 25.6 (^{i}*Pr*), 25.6 (-*C*H$_2$CH$_3$), 26.6 (^{i}*Pr*), 28.7 (^{i}*Pr*), 28.9 (^{i}*Pr*), 35.5 (η^3-(CC(CH$_3$)*C*H$_2$), 43.6 (-*C*H(Ph)-), 94.4 (η^3-(C*C*(CH$_3$)CH$_2$), 100.4 (-*C*H=C(Ph)O-), 123.9 (-N*C*H=*C*HN-), 124.0, 124.1 (-CH(Ph)*C*(CH$_2$CH$_3$)=C-), 124.3, 125.5, 125.7 (*Ph*), 125.8, 127.1, 127.3, 128.5, 128.9, 129.9, 130.3, 129.9, 137.3 (*Ar*), 144.1 (*Ph*), 145.3 (*Ar*), 146.1 (*Ar*), 146.8 (*Ar*), 161.6 (-CH=*C*(Ph)O-), 171.8 (η^3-(*C*C(CH$_3$)CH$_2$)), 194.1 (-N*C*N-), some peaks attributed to the aromatic ring(s) might be obscured by solvent signal. Anal. Calcd for $C_{44}H_{54}N_2NiO$: C, 77.08; H, 7.94; N, 4.09. Found: C, 77.99; H, 8.05; N, 3.82.

Generation of 3cf from complex 5cf



A solution of complex **5cf** (7.2 mg, 0.01 mmol) and ethyl acrylate (5.0 mg, 0.05 mmol) in C_6D_6 (0.5 mL) was heated at 80 ºC for 30 min. The reaction was monitored by means of ^1H NMR spectroscopy with 1,3,5-trioxane as an internal standard. The product **3cf** was generated in 95% yield.

Generation of 3db from complex 5’ea



A solution of complex **5’ea** (7.2 mg, 0.01 mmol) and ethyl acrylate (5.0 mg, 0.05 mmol) in C_6D_6 (0.5 mL) was heated at 60 ºC for 3 hrs. The reaction was monitored by means of ^1H NMR spectroscopy with 1,3,5-trioxane as an internal standard. The product **3ea** was generated in 75% yield.

3.5 Reference and Notes

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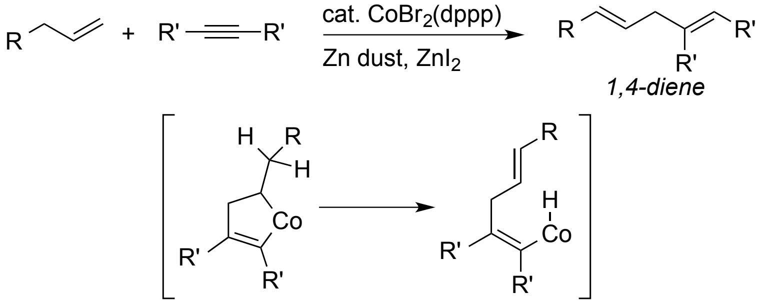
Chapter 4

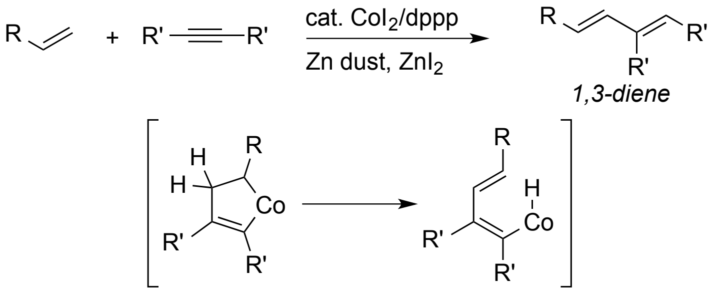
Cobalt-Catalyzed Cross-Dimerization of Simple Alkenes with 1,3-Enynes

4.1 Introduction

Low-valent cobalt complexes are effective catalysts for the dimerization of electronically unbiased unsaturated hydrocarbons, such as alkenes, alkynes, 1,3-dienes, and many other compounds.[1,2] Hilt and Cheng have independently developed the cross-dimerization of simple alkenes with internal alkynes in the presence of Co(I)/dppp catalyst to give linear dienes.[3,4]



Scheme 4.1. Cobalt-catalyzed dimerization of alkenes with alkynes to afford 1,4-dienes



Scheme 4.2. Cobalt-catalyzed dimerization of alkenes with alkynes to afford 1,3-dienes

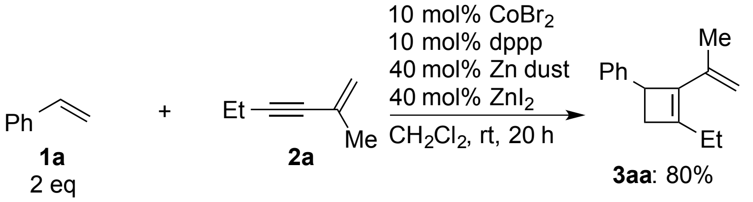
In Hilt's report, the reaction of alkynes with alkenes bearing allylic hydrogen afforded 1,4-dienes via *exo*-cyclic β-H elimination on the corresponding cobaltacycle intermediate (Scheme 4.1). On the other hand, Cheng described that the reaction of alkenes with no allylic hydrogen gave 1,3-dienes via *endo*-cyclic β-H elimination on the cobaltacycle (Scheme 4.2). Both reactions required only a slight excess amount of either alkenes or alkynes.

As described in Chapter 3, nickel-catalyzed [2 + 2] cycloaddition of unactivated alkenes with 1,3-enynes required highly excess amount of alkenes and slow addition of

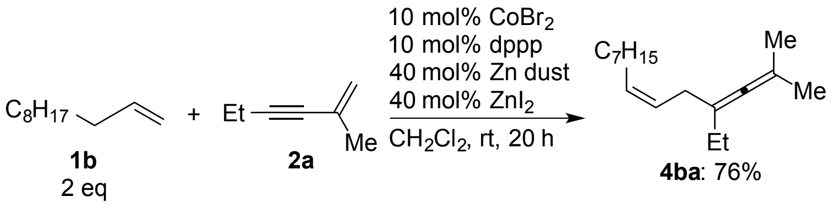
1,3-enynes to control the concentration due to low coordination ability of such alkenes. Thus, I next focused on the cobalt catalyst which efficiently catalyzes the dimerization of unactivated alkenes with alkynes. I assumed that the oxidative cyclization of a 1,3-enyne with a simple alkene at a cobalt center could occur selectively to give η^3-butadienyl cobaltacycle as with nickel catalysis, then reductive elimination would proceed in preference to the β-H elimination to give a cyclobutene derivative. Actually, there are two examples appeared in literature showing that 1,3-enyne facilitate [2 + 2] cycloaddition of norbornadiene or cyclopentene over competing homo-Diels–Alder reaction or Alder–ene reaction.[5,6]

4.2 Results and Discussion

Based on the reaction conditions developed by Hilt and Cheng, the reactions of two types of alkenes were examined. In the presence of $CoBr_2$, dppp, Zn dust and ZnI_2, a treatment of styrene (**1a**) with 2-methyl-1-hexen-3-yne (**2a**) gave the desired cyclobutene **3aa** in 80% yield (eq. 4.1). In contrast to the nickel-catalyzed reaction, this reaction proceeded even at room temperature. On the other hand, 1-decene (**1b**) reacted with **2a** to give tetra-substituted allene **4ba** as a major product with concomitant formation of a small amount of unidentified isomers in 76% yield, and no cyclobutene product was observed (eq. 4.2). From the viewpoint of the reaction mechanism, generating allene **4ba** might involve a β-H elimination pathway (*vide infra*).



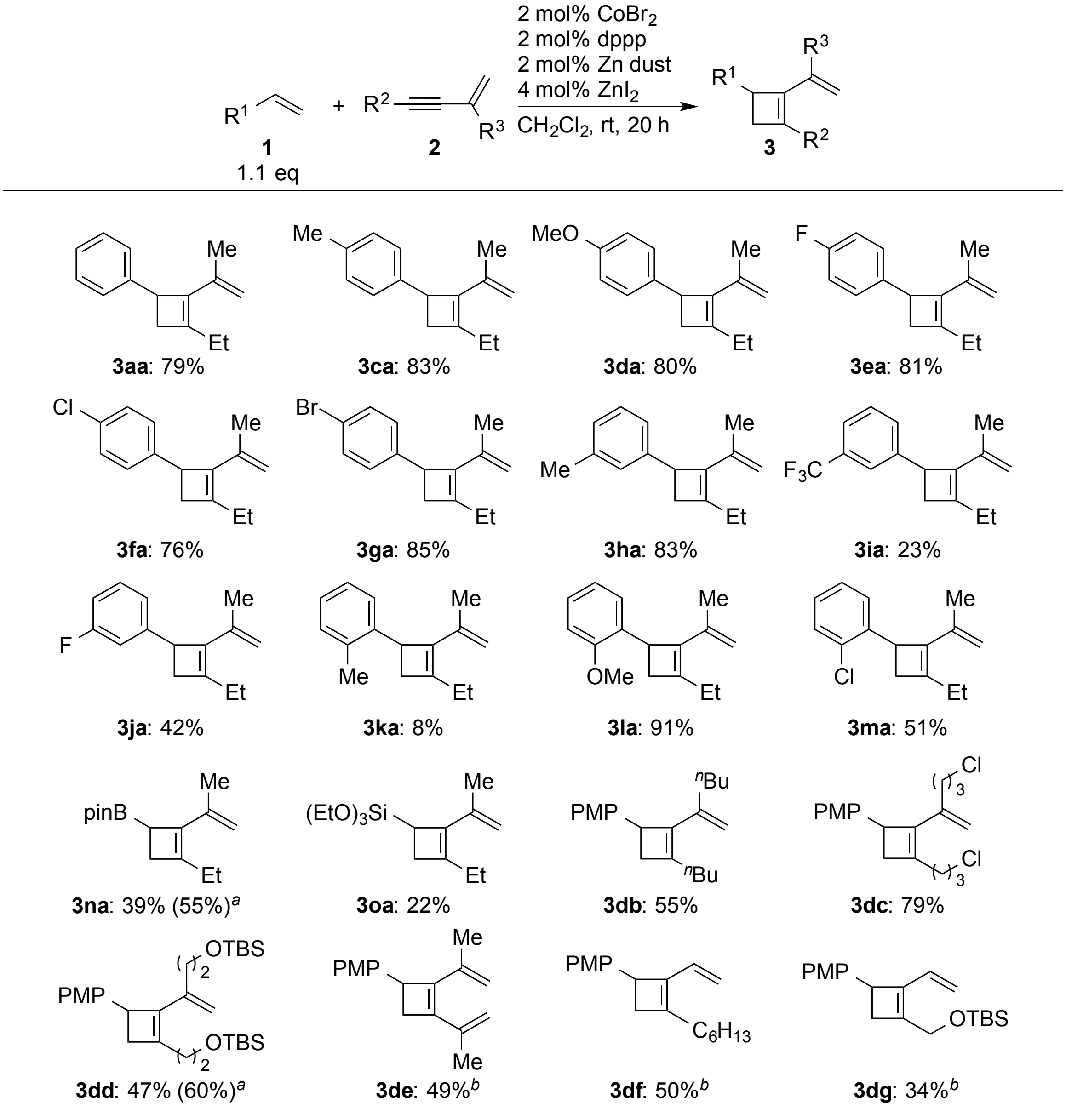
(4.1)



(4.2)

According to these preliminary results, the [2 + 2] cycloaddition of styrene derivatives with 1,3-enynes was investigated (Table 4.1). After some optimizations, the reaction conditions were selected as follows: 2 mol% of $CoBr_2$, dppp, Zn dust, ZnI_2 (1:1:1:2) as the catalyst precursor and CH_2Cl_2 as the solvent. Under these conditions, cyclobutene **3** was obtained in 79% isolated yield. In the reaction of *p*-substituted styrenes, methyl-, methoxy-, fluoro-, chloro- and bromo-functionalities were compatible

Table 4.1. Cobalt-catalyzed [2 + 2] cycloaddition of alkenes with 1,3-enynes

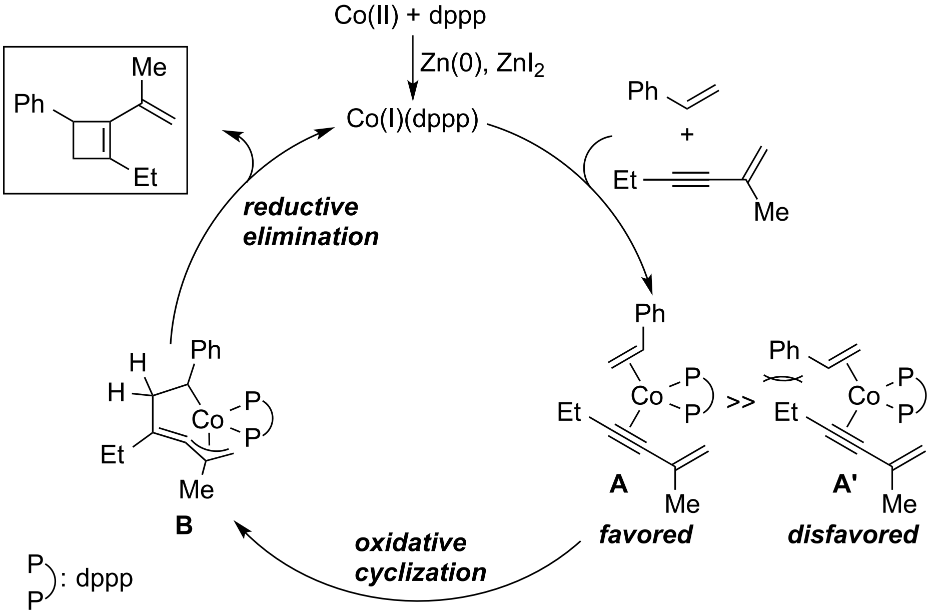


3aa: 79%
3ca: 83%
3da: 80%
3ea: 81%
3fa: 76%
3ga: 85%
3ha: 83%
3ia: 23%
3ja: 42%
3ka: 8%
3la: 91%
3ma: 51%
3na: 39% (55%)[a]
3oa: 22%
3db: 55%
3dc: 79%
3dd: 47% (60%)[a]
3de: 49%[b]
3df: 50%[b]
3dg: 34%[b]

[a]NMR yields are shown in parentheses. [b]Reaction was conducted with 5 mol% catalyst loading.

to afford the desired cyclobutenes **3ca**–**3ga** in high yields. Electron-rich *m*-methylstyrene (**1h**) reacts with **1a** to give **3ha** in high yield, while electron-deficient *m*-fluorostyrene (**1i**) and *m*-trifluoromethylstyrene (**1j**) diminished the reactivity to afford **3ia** and **3ja** in low yield probably due to their low coordination ability. The reaction of *o*-methylstyrene (**1k**) gave **3ka** only in 8% yield, which might be caused by steric bulkiness of **1k**. On the other hand, *o*-methoxy- and *o*-chloro-substituents did not hamper the reaction probably due to the chelation of the oxygen and chlorine atoms at the oxidative cyclization step. In addition, vinylboronate **1l** and vinylsilane **1m** were also applicable to this reaction. As for 1,3-enynes, longer alkyl chain (**2b**), chloro- (**2c**) and siloxy substituent (**2d**) were intact under these reaction conditions. The reaction of bisalkenylacetylene (**2e**) also took place with 5 mol% catalyst, and **3de** was obtained in 49% selectively. Although homo-dimerization of the enynes competed, 1,3-enynes baring a vinyl group (**2f** and **2g**) were applicable to afford **3df** and **3dg**, respectively.

A plausible mechanism for cobalt-catalyzed [2 + 2] cycloaddition is depicted in Scheme 4.3. Initially, a cobalt(II) salt is reduced by zinc metal with zinc iodide into cobalt(I) species, at which an alkenes and a 1,3-enyne coordinated simultaneously to form intermediate **A**.[7] In this step, the coordination of the alkene might occur regioselectively to avoid a steric repulsion with alkyne substituent. Then, oxidative cyclization of **A** gives rise to a generation of an η^3-butadienyl cobaltacycle **B**. As with

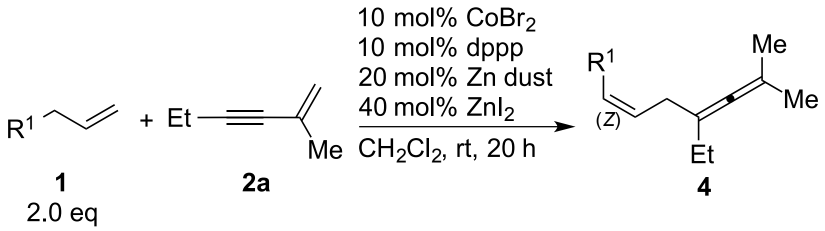


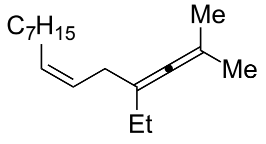
Scheme 4.3. A plausible mechanism for cobalt-catalyzed [2 + 2] cycloaddition

nickel-catalyzed reaction, *endo*-cyclic β-hydrogen elimination on intermediate **B** might be suppressed by the η^3-butadienyl coordination. Thus, the reductive elimination from **B** occurs to give cyclobutene **3**.

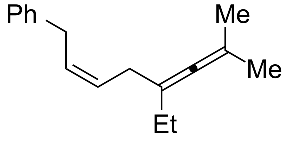
I next investigated the synthesis of allenes via 1,4-hydroallylation (Table 4.2). As the catalyst system, $CoBr_2$, dppp, Zn dust and ZnI_2 (1:1:2:4) were used. Under these conditions, allene **4ba** was obtained in 88% yield. Other aliphatic alkenes containing a phenyl, phthalimido or acetoxy group were tolerated to this reaction to give the corresponding allenes **4pa**–**4ra** in good yields. When a 1,5-diene containing different alkenyl groups was used as a substrate, the less-substituted alkenyl moiety reacted to give **4sa**.

Table 4.2. Cobalt-catalyzed1,4-hydroallylation of alkenes to 1,3-enynes

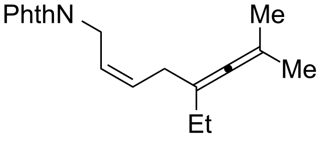




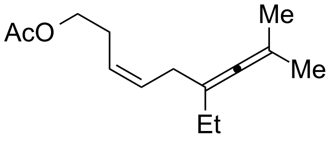
4ba: 88%



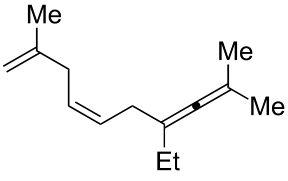
4pa: 70%



4qa: 68%

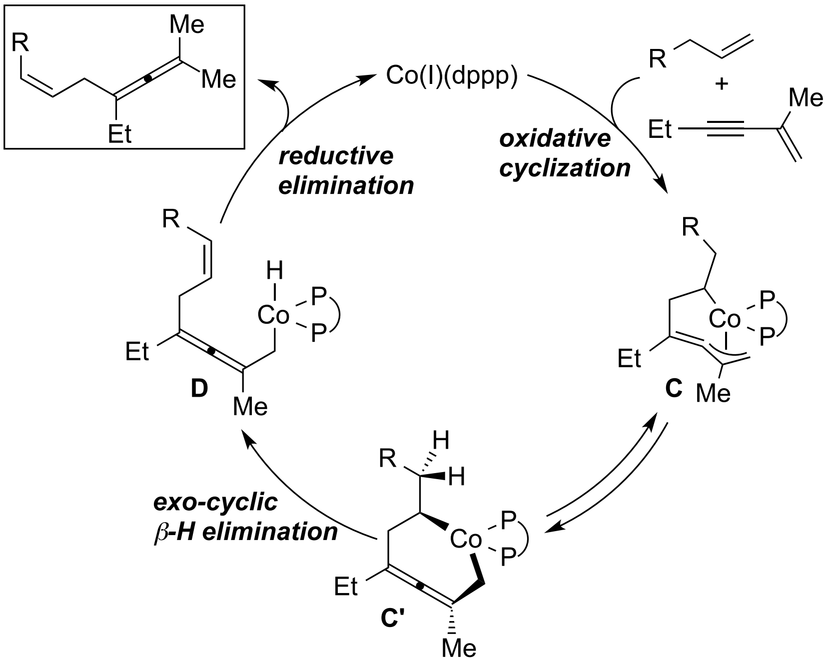


4ra: 65%



4sa: 86%

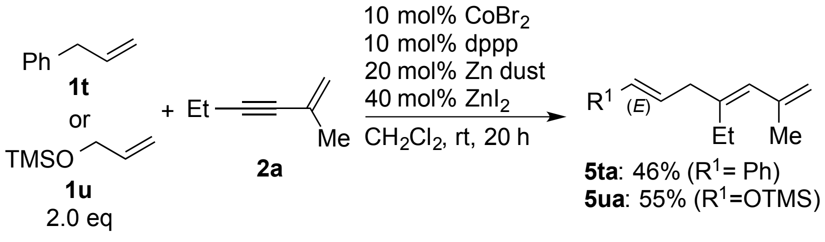
The possible reaction mechanism for 1,4-hydroallylation is depicted in Scheme 4.4. As described in Scheme 4.3, this reaction is also initiated by the oxidative cyclization of alkene with 1,3-enyne to form an η^3-butadienyl cobalt complex **C**. Although it was omitted for clarity in scheme 4.3, intermediate **C** could be in equilibrium with seven-membered η^1-2,3-butadien-1-yl cobaltacycle **C'**. The β-H elimination from **C'** takes place at more facile *exo*-cyclic methylene moiety rather than *endo*-cyclic position to give a Co–H species **D**. Then, reductive elimination from **D** affords the



Scheme 4.4. A possible mechanism for cobalt-catalyzed1,4-hydroallylation

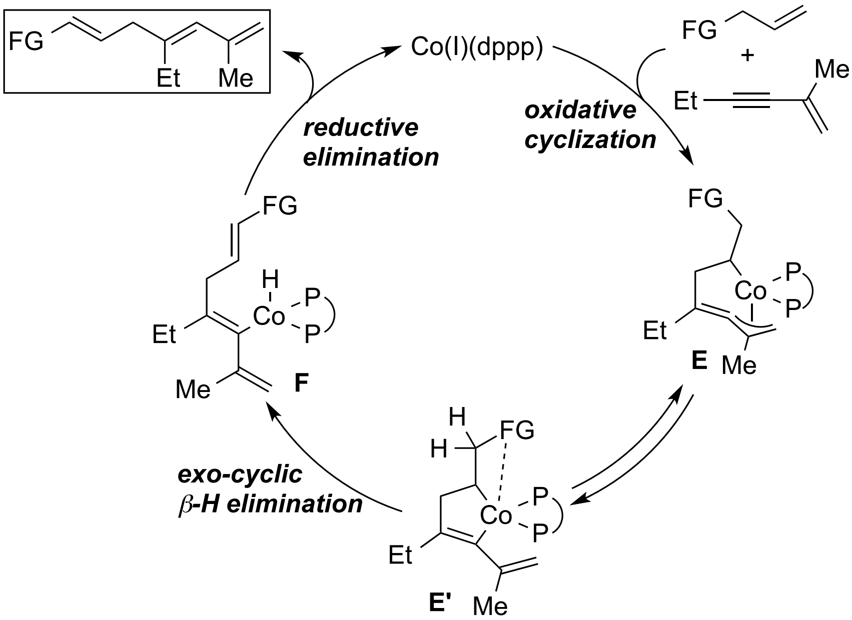
corresponding allene. The *Z*-configuration of alkenyl moiety might be caused by the steric interaction of R group in **C'** with dppp ligand.

In contrast, alkenes with functional groups at the allylic position were found to undergo 1,2-hydroallylation to 1,3-enynes. Allylbenzene (**1t**) and allyloxy-trimethylsilane (**1u**) reacted with **2a** to give 1,3,6-trienes **5ta** and **5ua** in moderate yield (Scheme 4.5). In addition, the configuration of the separated alkenyl groups in **5ta** and **5ua** were exclusively *E*.

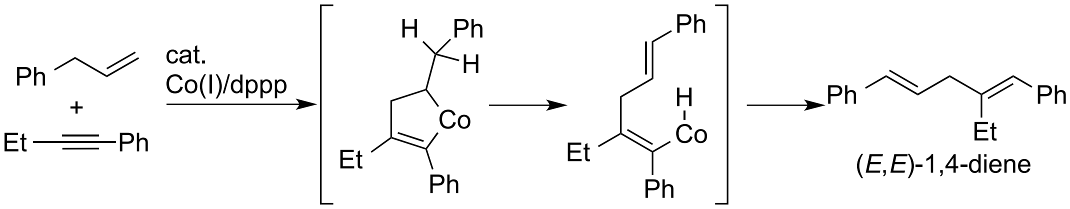


Scheme 4.5. Cobalt-catalyzed 1,2-hydrovinylation of a 1,3-enyne with alkenes

The possible mechanism is illustrated in Scheme 4.6. Initially, oxidative cyclization of alkenes and 1,3-enyne with cobalt(I) species takes place to give η^3-coordinated cobaltacycle **E**. The intermediate **E** isomerized into five-membered cobaltacycle **E'** by an intramolecular coordination of the allylic functional group (Ph or OTMS). Then, *exo*-cyclic β-H elimination affords a Co–H intermediate **F**, which undergoes reductive elimination to provide the 1,3,6-triene. Since the cobalt-catalyzed cross-dimerization of alkenes with internal alkynes gave (*E*,*E*)-1,4-diene predominantly via cobaltacyclopentene intermediate (Scheme 4.7), this 1,2-hydroallylation might also involve the five-membered cobaltcycle.[3]



Scheme 4.6. A possible mechanism for cobalt-catalyzed1,2-hydroallylatio



Scheme 4.7. Cobalt-catalyzed1,2-hydroallylation of allylbenzene with internal alkyne

4.3 Conclusion

In chapter 4, a cobalt-catalyzed cross-dimerization of simple alkenes with 1,3-enyne was described. A [2 + 2] cycloaddition occurred utilizing alkenes with no allylic hydrogen atom while aliphatic alkenes underwent hydroallylation. These reactions are highly chemo- and regio-selective and can provide synthetically useful, but relatively less-accessible cyclobutenes or allenes.

4.4 Experimental Section

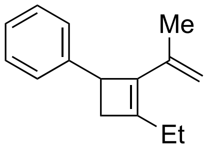
General: All manipulations were conducted under nitrogen atmosphere using standard Schlenk or dry box techniques. ^{1}H, ^{13}C and ^{19}F nuclear magnetic resonance spectra were recorded on Brucker Avance III 400. The chemical shifts in ^{1}H NMR spectra were recorded relative to residual protonated solvent ($CHCl_3$ (δ 7.27)). The chemical shifts in ^{13}C NMR spectra were recorded relative to deuterated solvent ($CDCl_3$ (δ 77.0)). The chemical shifts in ^{19}F NMR spectra were recorded relative to α,α,α-trifluorotoluene (δ –65.64). Assignment of the resonances in ^{1}H and ^{13}C NMR spectra was based on ^{1}H-^{1}H COSY, HMQC, HMBC, and NOESY experiments. Medium-pressure column chromatography was carried out on a Biotage Flash Purification System Isolera, equipped with a 254 and 280 nm UV detector. Analytical gas chromatography (GC) was carried out on a Shimadzu GC-2014 gas chromatograph, equipped with a flame ionization detector. High-resolution mass spectra (HRMS) were obtained on a JEOL JMS-DX303 instrument at Instrumental Analysis Center, Faculty of Engineering, Osaka University.

Materials: Cobalt(II) bromide and zinc dust was purchased from Wako Pure Chemical Industries, Ltd. 1,3-Bis(diphenylphosphino)propane (dppp) was purchased from Tokyo Kasei Kogyo Co., Ltd. Zinc iodide was purchased from Kanto Chemical Co., Inc. These reagents were used as received. Dichloromethane (CH_2Cl_2) was distilled over CaH_2. All commercially available reagents were degassed and stored under N_2 atmosphere. Enyens **2b**–**2d** were synthesized by Pd-catalyzed dimerization of terminal alkynes.[8] Enyne **2e** was prepared by literature procedure.[9] Enynes **2f** and **2g** were prepared by Sonogashira cross-coupling of terminal alkynes with vinylbromide.

Cobalt-catalyzed [2 + 2] cycloaddition of alkenes with 1,3-enynes

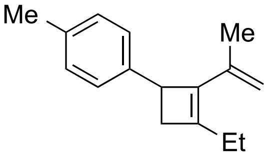
General procedure A: In a screw-capped vial, Zn dust (2.0 mg, 0.03 mmol, 2 mol%), ZnI_2 (19.2 mg, 0.06 mmol, 4 mol%), $CoBr_2$ (6.6 mg, 0.03 mmol, 2 mol%) dppp (12.4 mg, 0.03 mmol, 2 mol%), and CH_2Cl_2 (1.5 mL) were stirred for 10 min at room temperature. Alkene (1.7 mmol, 1.1 eq.) and 1,3-enyne (1.5 mmol) were added to the resulting suspension. The vial was sealed and the reaction mixture was stirred at room temperature for 20 hrs. The resulting mixture was directly filtered through a short silica-gel pad eluted with hexane/ethyl acetate. Volatiles were removed under reduced pressure and the residue was purified via flash column chromatography.

1-Ethyl-3-phenyl-2-(prop-1-en-2-yl)cyclobutene (3aa)



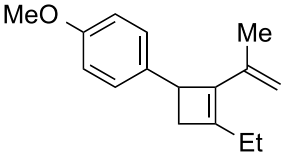
Following the general procedure A, styrene (**1a**, 173.4 mg, 1.66 mmol) and 2-methyl-1-hexen-3-yne (**2a**, 140.1 mg, 1.49 mmol) were used. After purification by flash column chromatography (hexane), **3aa** was obtained (234.3 mg, 79%) as a colorless oil. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.14 (t, J = 7.6 Hz, 3H), 1.99 (s, 3H), 2.15 (d, J = 14.0 Hz, 1H), 2.37–2.48 (m, 2H), 2.86 (dd, J = 14.0, 4.8 Hz, 1H), 3.86 (m, 1H), 4.59 (s, 1H), 4.72 (s, 1H), 7.18–7.36 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 12.2, 20.9, 23.0, 37.7, 43.1, 112.7, 125.9, 126.7, 128.3, 138.5, 140.7, 143.8, 145.3. HRMS Calcd for $C_{15}H_{18}$: 198.1409, Found: 198.1408.

1-Ethyl-3-(4-methylphenyl)-2-(prop-1-en-2-yl)cyclobutene (3ca)



Following the general procedure A, *p*-methylstyrene (**1c**, 208.9 mg, 1.77 mmol) and **2a** (157.7 mg, 1.67 mmol) were used. After purification by flash column chromatography (hexane), **3ca** was obtained (295.9 mg, 83%) as a colorless oil. **Spectral data:** ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.10 (t, J = 7.6 Hz, 3H), 1.95 (s, 3H), 2.09 (d, J = 14.0 Hz, 1H), 2.33 (s, 3H), 2.29–2.50 (m, 2H), 2.81 (dd, J = 14.0, 5.2 Hz, 1H), 3.76–3.83 (m, 1H), 4.56 (s, 1H), 4.68 (s, 1H), 7.07–7.15 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 12.2, 20.9, 21.1, 23.0, 37.8, 42.7, 112.6, 126.6, 129.0, 135.4, 138.5, 140.7, 140.8, 145.2. HRMS Calcd for $C_{16}H_{20}$: 212.1565, Found: 212.1563.

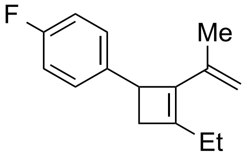
1-Ethyl-3-(4-methoxyphenyl)-2-(prop-1-en-2-yl)cyclobutene (3da)



Following the general procedure A, *p*-methoxystyrene (**1d**, 249.8 mg, 1.86 mmol) and **2a** (150.2 mg, 1.60 mmol) were used. After purification by flash column chromatography (10% ethyl acetate in hexane), **3da** was obtained (287.1 mg, 80%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.10 (t, J = 7.6 Hz, 3H), 1.96 (s, 3H), 2.08 (d, J = 13.6 Hz, 1H), 2.29–2.50 (m, 2H), 2.81 (dd, J = 13.6, 5.2 Hz, 1H), 3.76–3.84 (m, 4H), 4.56 (s, 1H), 4.69 (s, 1H), 6.84 (m, 2H), 7.15 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 12.2, 20.9, 23.0, 37.9, 42.3, 55.2, 112.6, 113.7, 127.6, 135.9, 138.5 (*g*), 140.8, 145.2, 157.9. HRMS Calcd for $C_{16}H_{20}O$: 228.1514, Found: 228.1513.

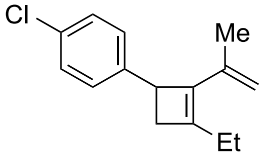
1-Ethyl-3-(4-fluorophenyl)-2-(prop-1-en-2-yl)cyclobutene (3ea)



Following the general procedure A, *p*-fluorostyrene (**1e**, 208.5 mg, 1.71 mmol) and **2a** (138.5 mg, 1.47 mmol) were used. After purification by flash column chromatography (hexane), **3ea** was obtained (256.7mg, 81%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.09 (t, J = 7.6 Hz, 3H), 1.95 (s, 3H), 2.06 (d, J = 14.0 Hz, 1H), 2.29–2.49 (m, 2H), 2.81 (dd, J = 14.0, 5.2 Hz, 1H), 3.80 (m, 1H), 4.52 (s, 1H), 4.68 (s, 1H), 6.92–7.00 (m, 2H), 7.13–7.20 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 12.2, 20.9, 22.9, 37.9, 42.3, 112.7, 115.0 (d, J_{CF} = 21.2 Hz), 128.0 (d, J_{CF} = 8.0 Hz), 138.4, 139.4 (d, J_{CF} = 2.9 Hz), 140.5, 145.4, 161.3 (d, J_{CF} = 242.1 Hz). ^{19}F{^{1}H} NMR (100 MHz, CDCl$_3$): δ –117.6. HRMS Calcd for $C_{15}H_{17}F$: 216.1314, Found: 216.1317.

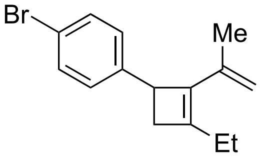
3-(4-Chlorophenyl)-1-ethyl-2-(prop-1-en-2-yl)cyclobutene (3fa)



Following the general procedure A, *p*-chlorostyrene (**1f**, 219.6 mg, 1.58 mmol) and **2a** (140.5 mg, 1.49 mmol) were used. After purification by flash column chromatography (hexane), **3fa** was obtained (264.3 mg, 76%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.09 (t, J = 7.6 Hz, 3H), 1.95 (s, 3H), 2.06 (d, J = 14.0 Hz, 1H), 2.29–2.49 (m, 2H), 2.82 (dd, J = 14.0, 5.2 Hz, 2H*d*), 3.79 (m, 1H), 4.50 (s, 1H), 4.69 (s, 1H), 7.12–7.27 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 12.2, 20.8, 22.9, 37.7, 42.4, 112.8, 128.1, 128.4, 131.4, 138.3, 140.4, 142.4, 145.5. HRMS Calcd for $C_{15}H_{17}Cl$: 232.1019, Found: 232.1020.

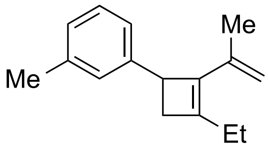
3-(4-Bromophenyl)-1-ethyl-2-(prop-1-en-2-yl)cyclobutene (3ga)



Following the general procedure A, *p*-brorostyrene (**1g**, 307.0 mg, 1.68 mmol) and **2a** (138.5 mg, 1.47 mmol) were used. After purification by flash column chromatography (hexane), **3ga** was obtained (345.8 mg, 85%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.10 (t, J = 7.6 Hz, 3H), 1.95 (s, 3H), 2.06 (d, J = 13.6 Hz, 1H), 2.29–2.50 (m, 2H), 2.82 (dd, J = 13.6, 4.8 Hz, 1H), 3.78 (m, 1H), 4.51 (s, 1H), 4.69 (s, 1H), 7.06 (dt, J = 8.4, 1.6 Hz, 2H), 7.40 (dt, J = 8.4, 1.6 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 12.1, 20.8, 22.9, 37.6, 42.4, 112.8, 119.5, 128.5, 131.3, 138.3, 140.3, 142.9, 145.5. HRMS Calcd for $C_{15}H_{17}Br$: 276.0514, Found: 276.0512.

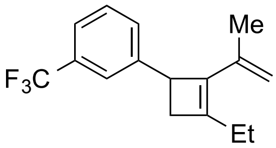
1-Ethyl-3-(3-methylphenyl)-2-(prop-1-en-2-yl)cyclobutene (3ha)



Following the general procedure A, *m*-methylstyrene (**1h**, 216.5 mg, 1.83 mmol) and **2a** (155.2 mg, 1.65 mmol) were used. After purification by flash column chromatography (hexane), **3ha** was obtained (289.3 mg, 83%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.11 (t, *J* = 7.6 Hz, 3H, *f*), 1.96 (s, 3H), 2.11 (d, *J* = 13.6 Hz, 1H), 2.31–2.51 (m, 2H), 2.34 (s, 3H), 2.81 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.79 (d, *J* = 4.8 Hz, 1H), 4.57 (s, 1H), 4.69 (s, 1H), 6.97–7.07 (m, 3H), 7.18 (t, *J* = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 12.2, 20.9, 21.5, 23.0, 37.7, 43.0, 112.6, 123.7, 126.7, 127.5, 128.4, 137.7, 138.5, 140.7, 143.8, 145.21. HRMS Calcd for $C_{16}H_{20}$: 212.1565, Found: 212.1564.

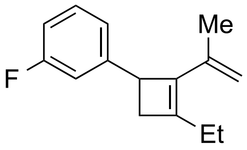
1-Ethyl-2-(prop-1-en-2-yl)-3-(3-trifluoromethylphenyl)cyclobutene (3ia)



Following the general procedure A, *m*-trifluoromethylstyrene (**1i**, 303.6 mg, 1.76 mmol) and **2a** (140.9 mg, 1.50 mmol) were used. After purification by flash column chromatography (hexane), **3ia** was obtained (90.8 mg, 23%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.11 (t, *J* = 7.6 Hz, 3H), 1.96 (s, 3H), 2.09 (d, *J* = 14.0 Hz, 1H), 2.31–2.52 (m, 2H), 2.85 (dd, *J* = 14.0, 5.2 Hz, 1H), 3.88 (m, 1H), 4.50 (s, 1H), 4.69 (s, 1H), 7.37–7.49 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* 12.1, 20.8, 23.0, 37.7, 42.7, 112.9, 122.9 (q, J_{CF} = 3.6 Hz), 123.6 (q, $J_{C\text{-}F}$ = 3.6 Hz), 125.7 (q, J_{CF} = 270.5 Hz), 128.7, 130.0, 130.6 (q, J_{CF} = 31.4 Hz), 138.2, 140.2, 144.9, 145.7. ^{19}F{^{1}H} NMR (100 MHz, $CDCl_3$): *δ* –62.5. HRMS Calcd for $C_{17}H_{16}F_3$: 266.1282, Found: 266.1280.

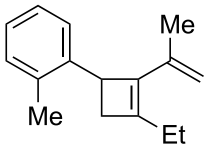
3-(3-Fluorophenyl)-1-ethyl-2-(prop-1-en-2-yl)cyclobutene (3ja)



Following the general procedure A, *m*-fluorostyrene (**1j**, 205.8 mg, 1.68 mmol) and **2a** (141.2 mg, 1.50 mmol) were used. After purification by flash column chromatography (hexane), **3ja** was obtained (135.0 mg, 42%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.10 (t, J = 7.6 Hz, 3H), 1.96 (s, 3H), 2.09 (d, J = 14.0 Hz, 1H), 2.29–2.50 (m, 2H), 2.82 (dd, J = 14.0, 5.2 Hz, 1H), 3.82 (d, J = 5.2 Hz, 1H), 4.54 (s, 1H), 4.70 (s, 1H), 6.83–6.95 (m, 2H), 7.01 (d, J = 7.6 Hz, 1H), 7.23 (dt, J = 7.6 Hz, J_{HF} = 6.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 12.1, 20.8, 22.9, 37.6, 42.7, 112.8 (d, J_{CF} = 21.1 Hz), 112.8, 113.3 (d, J_{CF} = 21.1 Hz), 122.5 (d, J_{CF} = 2.9 Hz), 129.6 (d, J_{CF} = 8.0 Hz), 138.3, 140.3, 145.5, 146.7 (d, J_{CF} = 7.3 Hz), 163.2 (d, J_{CF} = 243.6 Hz). ^{19}F{^{1}H} NMR (100 MHz, CDCl$_3$): δ –114.1. HRMS Calcd for $C_{15}H_{17}F$: 216.1314, Found: 216.1313.

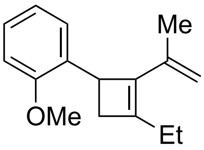
3-(2-Methylphenyl)-1-ethyl-2-(prop-1-en-2-yl)cyclobutene (3ka)



Following the general procedure A, *o*-methylstyrene (**1k**, 199.5 mg, 1.69 mmol) and **2a** (140.9 mg, 1.50 mmol) were used. After purification by flash column chromatography (hexane), **3ka** was obtained (25.7 mg, 8%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.09 (t, J = 7.6 Hz, 3H), 1.96–2.08 (m, 4H), 2.32–2.49 (m, 5H), 2.90 (dd, J = 13.6, 5.2 Hz, 1H), 4.05 (m, 1H), 4.59 (s, 1H), 4.79 (s, 1H), 7.07–7.23 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 12.1, 19.2, 20.9, 23.0, 36.8, 39.5, 112.9, 125.7, 125.8, 125.9, 129.7 135.7, 138.7, 139.8, 141.6, 144.8. HRMS Calcd for $C_{16}H_{20}$: 212.1565, Found: 212.1567.

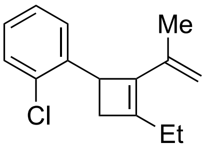
1-Ethyl-3-(2-methoxyphenyl)-2-(prop-1-en-2-yl)cyclobutene (3la)



Following the general procedure A, *o*-methoxystyrene (**1l**, 226.9 mg, 1.69 mmol) and **2a** (140.8 mg, 1.50 mmol) were used. After purification by flash column chromatography (10% ethyl acetate in hexane), **3la** was obtained (311.5 mg, 91%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.08 (t, J = 7.6 Hz, 3H), 1.98 (s, 3H), 2.02 (d, J = 13.6 Hz, 1H), 2.29–2.49 (m, 2H), 2.84 (dd, J = 13.6, 5.2 Hz, 1H), 3.85 (s, 3H), 4.25 (m, 1H), 4.60 (s, 1H), 4.73 (s, 1H), 6.83–6.93 (m, 2H), 7.12–7.21 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 12.2, 20.9, 23.0, 35.8, 37.1, 55.5, 110.2, 112.6, 120.4, 126.7, 126.9, 132.0, 138.6, 140.0, 145.1, 157.2. HRMS Calcd for $C_{16}H_{20}O$: 228.1514, Found: 228.1515.

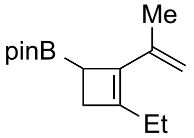
3-(2-Chlorophenyl)-1-ethyl-2-(prop-1-en-2-yl)cyclobutene (3ma)



Following the general procedure A, *o*-chlorostyrene (**1m**, 241.7 mg, 1.74 mmol) and **2a** (141.3 mg, 1.50 mmol) were used. After purification by flash column chromatography (hexane), **3ma** was obtained (311.5 mg, 51%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.08 (t, J = 7.6 Hz, 3H), 1.96–2.07 (m, 4H), 2.32–2.48 (m, 2H), 2.93 (dd, J = 13.6, 4.8 Hz, 1H), 4.29 (m, 1H), 4.58 (s, 1H), 4.77 (s, 1H), 7.07–7.24 (m, 3H), 7.34 (dd, J = 7.6, 1.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 12.1, 20.8, 23.0, 36.9, 39.4, 113.0, 126.6, 127.0, 127.6, 129.0, 133.8, 138.4, 139.3, 140.9, 145.5. HRMS Calcd for $C_{15}H_{17}Cl$: 232.1019, Found: 232.1018.

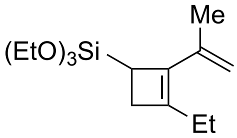
2-(3-ethyl-2-(prop-1-en-2-yl)cyclobut-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3na)



Following the general procedure A, vinylboronic acid pinacol ester (**1n**, 263.1 mg, 1.71 mmol) and **2a** (141.3 mg, 1.50 mmol) were used. The NMR yield of the crude product was determined using nitromethane ($MeNO_2$) as an internal standard. After purification by flash column chromatography (5% ethyl acetate in hexane), **3na** was obtained (146.8 mg, 39%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (t, J = 7.6 Hz, 3H), 1.25 (s, 12H), 1.92 (s, 3H), 2.17–2.52 (m, 5H), 4.70 (s, 1H), 4.76 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ12.2, 20.6, 23.4, 24.7, 24.8, 26.9, 83.0, 110.2, 138.1, 140.2, 145.9. Carbon atom *c* was not detected. HRMS Calcd for $C_{15}H_{25}BO_2$: 248.1948, Found: 248.1949.

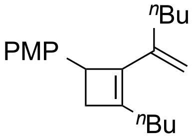
1-Ethyl-2-(prop-1-en-2-yl)-3-(triethoxysilyl)cyclobutene (3oa)



Following the general procedure A, triethoxyvinylsilane (**1o**, 323.0 mg, 1.70 mmol) and **2a** (140.2 mg, 1.49 mmol) were used. After purification by flash column chromatography (5% ethyl acetate in hexane), **3oa** was obtained (91.4 mg, 22%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (t, J = 7.6 Hz, 3H, *f*), 1.22 (t, J = 7.2 Hz, 9H, *k*), 1.92 (s, 3H, *i*), 2.13–2.57 (m, 5H, *c*,*d*,*e*), 3.83 (q, J = 7.2 Hz, 6H, *j*), 4.70 (s, 1H, *h*), 4.76 (s, 1H, *h*). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 12.3 (*f*), 18.3 (*k*), 20.6 (*i*), 23.5 (*e*), 24.9 (*c*), 26.3 (*d*), 58.5 (*j*), 110.1 (*h*), 137.5 (*b*), 140.0 (*g*), 145.5 (*a*). HRMS Calcd for $C_{15}H_{28}O_3Si$: 284.1808, Found: 284.1806.

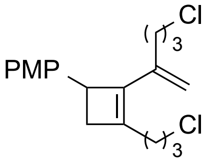
1-Butyl-2-(hex-1-en-2-yl)-3-(4-methoxyphenyl)cyclobutene (3db)



Following the general procedure A, *p*-methoxystyrene (**1d**, 224.7 mg, 1.67 mmol) and **2b** (258.8 mg, 1.58 mmol) were used. After purification by flash column chromatography (0%→3% ethyl acetate in hexane), **3db** was obtained (257.2 mg, 55%) as a yellow oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.93 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H), 1.28–1.56 (m, 8H), 2.05 (d, J = 13.6 Hz, 1H), 2.11–2.43 (m, 4H), 2.78 (dd, J = 13.6, 4.8 Hz, 1H), 3.76–3.81 (m, 1H), 3.79 (s, 3H), 4.59 (s, 1H), 4.70 (s, 1H), 6.80–6.86 (m, 2H), 7.10–7.15 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 14.0, 14.0, 22.5, 22.8, 29.8, 31.0, 33.9, 38.4, 42.5, 55.2, 111.8, 113.7, 127.6, 136.1, 141.0, 143.2, 143.2, 157.8. HRMS Calcd for $C_{21}H_{30}O$: 298.2297, Found: 298.2295.

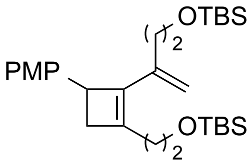
2-(5-Chloropent-1-en-2-yl)-1-(3-chloropropyl)-3-(4-methoxyphenyl)cyclobutene (3dc)



Following the general procedure A, *p*-methoxystyrene (**1d**, 226.1 mg, 1.69 mmol) and **2c** (326.8 mg, 1.59 mmol) were used. After purification by flash column chromatography (3% ethyl acetate in hexane), **3dc** was obtained (425.3 mg, 79%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.87–2.04 (m, 4H), 2.07 (d, J = 14.0 Hz, 1H), 2.29–2.61 (m, 4H), 2.79 (dd, J = 14.0, 5.2 Hz, 1H), 3.49–3.64 (m, 4H), 3.80 (s, 3H), 3.82 (dd, J = 5.2, 2.0 Hz, 1H), 4.70 (s, 1H), 4.79 (s, 1H), 6.81–6.86 (m, 2H), 7.07–7.13 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 27.2, 30.4, 31.0, 31.5, 38.3, 42.6, 44.5, 44.6, 55.2, 113.7, 113.8, 127.5, 135.3, 140.9, 141.2, 142.1, 158.0. HRMS Calcd for $C_{19}H_{24}Cl_2O$: 338.1204, Found: 338.1203.

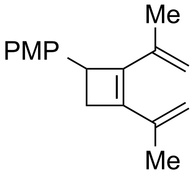
1-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-2-(4-(*tert*-butyldimethylsilyloxy)but-1-en-2-yl)-3-(4-methoxyphenyl)cyclobutene (3dd)



Following the general procedure A, *p*-methoxystyrene (**1d**, 225.5 mg, 1.68 mmol) and **2d** (551.8 mg, 1.50 mmol) were used. The NMR yield of the crude product was determined using nitromethane ($MeNO_2$) as an internal standard. Due to difficulty in separating the product and starting enyne, purification by flash column chromatography (2% ethyl acetate in hexane) was performed three times to afford **3dd** (354.5 mg, 47%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.07 (s, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 2.09 (d, *J* = 13.6 Hz, 1H), 2.44–2.57 (m, 3H), 2.63 (dt, *J* = 14.4, 7.2 Hz, 1H), 2.79 (dd, *J* = 13.6, 4.8 Hz, 1H), 3.68–3.84 (m, 8H), 4.68 (s, 1H), 4.75 (s, 1H), 6.79–6.84 (m, 2H), 7.10–7.16 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ –5.4, –5.4, –5.3, –5.2, 18.2, 18.3, 25.9, 25.9, 33.7, 37.2, 38.8, 43.0, 55.2, 61.2, 62.7, 113.6, 113.9, 127.7, 135.6, 139.3, 140.2, 142.6, 157.8. HRMS Calcd for $C_{29}H_{50}O_3Si_2$: 502.3298, Found: 502.3292.

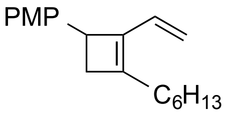
1,2-Di(prop-1-en-2-yl)-3-(4-methoxyphenyl)cyclobutene (3de)



The reaction was performed in 1 mmol scale with 5 mol% catalyst loading. Following the general procedure A, *p*-methoxystyrene (**1d**, 144.4 mg, 1.08 mmol) and **2e** (102.6 mg, 0.97 mmol) were used. After purification by flash column chromatography (5% ethyl acetate in hexane), **3de** was obtained (113.5 mg, 49%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83 (s, 3H), 1.99 (s, 3H), 2.24 (dd, *J* = 13.2, 1.6 Hz, 1H), 2.91 (dd, *J* = 13.2, 5.2 Hz, 1H), 3.79 (s, 3H), 3.82 (m, 1H), 4.87 (s, 1H), 4.90 (s, 1H), 5.00 (s, 1H), 5.03 (s, 1H), 6.81–6.86 (m, 2H), 7.12–7.18 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.2, 21.4, 37.3, 42.8, 55.2, 113.7, 115.0, 115.8, 127.8, 135.5, 138.9, 140.0, 140.5, 143.6 , 158.0. HRMS Calcd for $C_{16}H_{20}O$: 240.1514, Found: 240.1512.

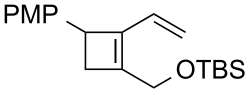
1-Hexyl-3-(4-methoxyphenyl)-2-vinylcyclobutene (3df)



The reaction performed in 1 mmol scale with 5 mol% catalyst loading. Following the general procedure A, *p*-methoxystyrene (**1d**, 140.2 mg, 1.04 mmol) and **2f** (109.6 mg, 0.80 mmol) were used. After purification by flash column chromatography (2% ethyl acetate in hexane), **3df** was obtained (109.2 mg, 50%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.2 Hz, 3H), 1.25–1.43 (m, 6H), 1.45–1.56 (m, 2H), 2.13 (d, *J* = 14.0 Hz, 1H), 2.16–2.34 (m, 2H), 2.84 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.80 (s, 3H), 3.87 (d, *J* = 4.8 Hz, 1H), 4.80 (d, *J* = 17.2 Hz, 1H), 4.91 (d, *J* = 10.8 Hz, 1H), 6.44 (dd, *J* = 17.2, 10.8 Hz, 1H), 6.82–6.88 (m, 2H), 7.14–7.19 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 27.3, 28.7, 29.2, 31.7, 39.3, 42.5, 55.2, 113.7, 113.8, 127.6, 128.1, 135.5, 140.4, 145.3, 157.9. HRMS Calcd for $C_{19}H_{26}O$: 270.1984, Found: 270.1985.

1-((*tert*-Butyldimethylsiloxy)methyl)-3-(4-methoxyphenyl)-2-vinylcyclobutene (3dg)



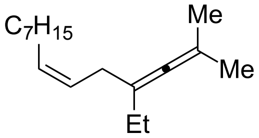
The reaction was performed in 1 mmol scale with 5 mol% catalyst loading. Following the general procedure A, *p*-methoxystyrene (**1d**, 148.3 mg, 1.11 mmol) and **2g** (208.1 mg, 1.06 mmol) were used. After purification by flash column chromatography (10% ethyl acetate in hexane), **3dg** was obtained (119.6 mg, 34%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): *d* 0.12 (s, 6H), 0.94 (s, 9H), 2.16 (d, *J* = 14.0 Hz, 1H), 2.88 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.80 (s, 3H), 3.85–3.90 (m, 1H), 4.36 (s, 2H), 4.84 (d, *J* = 17.6 Hz, 1H), 4.96 (d, *J* = 10.8 Hz, 1H), 6.58 (dd, *J* = 17.6, 10.8 Hz, 1H), 6.81–6.87 (m, 2H), 7.13–7.19 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *d* –5.3, 18.4, 25.9, 37.9, 42.6, 55.2, 60.6, 113.7, 115.4, 127.7, 128.5, 135.0, 140.9, 142.0, 158.0. HRMS Calcd for $C_{20}H_{30}O_2Si$: 330.2015, Found: 330.2010.

Cobalt-catalyzed hydroallylation of alkenes to 1,3-enynes

General procedure B: In a screw-capped vial, Zn dust (6.5 mg, 0.10 mmol, 20 mol%), ZnI_2 (63.8 mg, 0.20 mmol, 40 mol%), $CoBr_2$ (10.9 mg, 0.05 mmol, 10 mol%), dppp (20.6 mg, 0.05 mmol, 10 mol%) and CH_2Cl_2 (2.5 mL) were stirred for 10 min at room temperature. Alkene (1.0 mmol, 2 eq.) and 1,3-enyne (0.5 mmol) were added to the resulting suspension. The vial was sealed and the reaction mixture was stirred at room temperature for 20 hrs. The resulting mixture was directly filtered through a short silica-gel pad eluted with hexane/ethyl acetate. Volatiles were removed and the residue was purified via flash column chromatography.

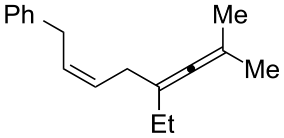
(*Z*)-4-Ethyl-2-methyltetradeca-2,3,6-triene (4ba)



Following the general procedure B, 1-decene (**1b**, 138.4 mg, 0.99 mmol) and **2a** (47.2 mg, 0.50 mmol) were used. After purification by flash column chromatography (hexane), **5** was obtained (102.9 mg, 88%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 6.8 Hz, 3H), 0.97 (t, J = 7.6 Hz, 3H), 1.21–1.41 (m, 10H), 1.67 (s, 6H), 1.92 (q, J = 7.6 Hz, 2H), 2.04 (m, 2H), 2.67 (d, J = 5.2 Hz, 2H), 5.35–5.46 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 12.4, 14.1, 21.0, 22.7, 25.7, 27.3, 29.2, 29.3, 29.7, 31.3, 31.9, 96.2, 102.9, 127.5, 130.5, 198.5. HRMS Calcd for $C_{17}H_{30}$: 234.2348, Found: 234.2350.

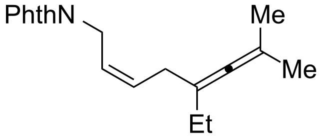
(*Z*)-5-ethyl-7-methyl-1-phenylocta-2,5,6-triene (4pa)



Following the general procedure B, 4-phenyl-1-butene (**1p**, 131.8 mg, 1.00 mmol) and **2a** (46.5 mg, 0.49 mmol) were used. After purification by flash column chromatography (hexane), **4pa** was obtained (77.9 mg, 70%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.2 Hz, 3H), 1.69 (s, 6H), 1.96 (q, J = 7.2 Hz, 2H), 2.80 (d, J = 5.6 Hz, 2H), 3.43 (d, J = 5.6 Hz, 2H), 5.45–5.65 (m, 2H), 7.15–7.33 (m, 5H$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 12.4, 21.0, 25.9, 31.3, 33.5, 96.6, 102.7, 125.8, 128.4, 128.4, 128.5, 128.7, 141.1, 198.6. HRMS Calcd for $C_{17}H_{22}$: 226.1722, Found: 226.1719.

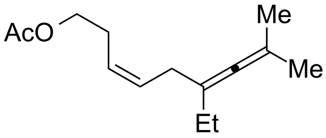
(*Z*)-2-(5-Ethyl-7-methylocta-2,5,6-trien-1-yl)isoindoline-1,3-dione (4qa)



Following the general procedure B, *N*-(3-buten-1-yl)phthalimide (**1q**, 200.6 mg, 1.00 mmol) and **2a** (45.7 mg, 0.49 mmol) were used. After purification by flash column chromatography (30% ethyl acetate in hexane), **4qa** was obtained (96.9 mg, 68%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, *J* = 7.2 Hz, 3H), 1.66 (s, 6H), 1.97 (q, *J* = 7.2 Hz, 2H), 2.90 (d, *J* = 7.2 Hz, 2H), 4.32 (d, *J* = 7.2 Hz, 2H), 5.52 (dtt, *J* = 10.4, 7.2, 1.6 Hz, 1H), 5.66 (dtt, *J* = 10.4, 7.2, 1.6 Hz, 1H), 7.71 (dd, *J* = 5.6, 3.2 Hz, 2H), 7.84 (dd, *J* = 5.6, 3.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 12.3, 20.9, 25.9, 31.2, 34.9, 97.0, 102.4, 123.2, 123.4, 132.3, 132.3, 133.8, 167.9, 198.5. HRMS Calcd for $C_{19}H_{21}NO_2$: 295.1572, Found: 295.1571.

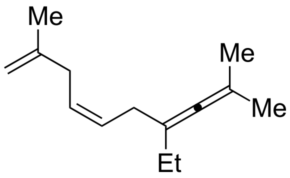
(*Z*)-6-Ethyl-8-methylnona-3,6,7-trien-1-yl acetate (4ra)



Following the general procedure B, 4-penten-1-yl acetate (**1r**, 126.4 mg, 0.99 mmol) and **2a** (46.5 mg, 0.49 mmol) were used. After purification by flash column chromatography (10% ethyl acetate in hexane), **4ra** was obtained (71.3 mg, 65%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, *J* = 7.2 Hz, 3H, *k*), 1.66 (s, 6H), 1.91 (q, *J* = 7.2 Hz, 2H), 2.05 (s, 3H), 2.39 (q, *J* = 7.2 Hz, 2H), 2.68 (d, *J* = 7.2 Hz, 2H), 4.07 (t, *J* = 7.2 Hz, 2H), 5.39 (dtt, *J* = 10.8, 7.2, 1.6 Hz, 1H), 5.57 (dtt, *J* = 10.8, 7.2, 1.6 Hz, 1H, *f*). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 12.3, 20.9, 21.0, 25.8, 26.8, 31.3, 63.9, 96.6, 102.5, 124.8 130.6, 171.1, 198.5. HRMS Calcd for $C_{14}H_{22}O_2$: 222.1620, Found: 222.1616.

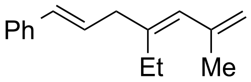
(*Z*)-7-Ethyl-2,9-dimethyldeca-1,4,7,8-tetraene (4sa)



Following the general procedure B, 2-methyl-1,5-hexadiene (**1s**, 95.1 mg, 0.99 mmol) and **2a** (42.7 mg, 0.45 mmol) were used. After purification by flash column chromatography (pentane), **4sa** was obtained (74.2 mg, 86%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.97 (t, J = 7.2 Hz, 3H, *l*), 1.67 (s, 6H), 1.74 (s, 3H), 1.92 (q, J = 7.2 Hz, 2H), 2.69 (d, J = 7.2 Hz, 2H), 2.76 (d, J = 7.2 Hz, 2H), 4.71–4.75 (m, 2H), 5.40–5.45 (m, J = 18.0 Hz, 1H), 5.45–5.49 (m, J = 18.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 12.4, 21.0, 22.6, 25.8, 31.1, 35.7, 96.4, 102.7, 110.1, 127.4, 129.1, 144.8, 198.5. HRMS Calcd for $C_{14}H_{22}$: 190.1722, Found: 190.1728.

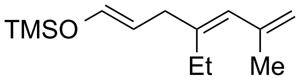
(3*E*,6*E*)-4-Ethyl-7-phenyl-2-methylhepta-1,3,6-triene (5ta)



Following the general procedure B, allylbenzene (**1t**, 116.7 mg, 0.99 mmol) and **2a** (47.1 mg, 0.50 mmol) were used. After purification by flash column chromatography (hexane), **5ta** was obtained (48.7 mg, 46%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.70 (t, J = 7.6 Hz, 3H, *m*), 1.87 (s, 3H), 2.30 (q, J = 7.6 Hz, 2H), 2.97 (d, J = 7.2 Hz, 2H), 4.82 (s, 1H), 4.94 (m, 1H), 5,72 (s, 1H), 6.23 (dt, J = 16.0, 7.2 Hz, 1H), 6.44 (d, J = 16.0 Hz, 1H, *a*), 7.19-7.42 (m, 5H) . ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ 13.5, 23.7, 24.2, 40.5, 113.6, 126.0, 127.0, 127.6, 128.5, 128.7, 131.3, 137.6, 141.9, 142.1. HRMS Calcd for $C_{16}H_{20}$: 212.1565, Found: 212.1565.

(3*E*,6*E*)-7-(trimethylsiloxy)-4-ethyl-2-methylhepta-1,3,6-triene (5ua)



Following the general procedure B, allyloxytrimethylsilane (**1u**, 129.3 mg, 0.99 mmol) and **2a** (46.5 mg, 0.49 mmol) were used. After purification by flash column chromatography (pentane), **5ua** was obtained (60.8 mg, 55%) as a colorless oil.

Spectral data: ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.21 (s, 9H), 1.01 (t, J = 7.6 Hz, 3H), 1.84 (s, 3H), 2.23 (q, J = 7.6 Hz, 2H), 2.64 (dt, J = 7.6, 1.2 Hz, 2H), 4.77 (s, 1H), 4.90 (dq, J = 2.4, 1.2 Hz, 1H), 4.99 (dt, J = 12.0, 7.6 Hz, 1H), 5.64 (s, 1H), 6.22 (dt, J = 12.0, 1.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): δ –0.4, 13.4, 23.7, 24.0, 34.7, 109.8, 113.2, 126.6, 140.7, 142.3, 142.9. HRMS Calcd for $C_{13}H_{24}OSi$: 224.1596, Found: 224.1588

4.5 References and Notes

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Conclusion

Included in this thesis are the studies on transformation of conjugated unsaturated substrates via metallacycle intermediates. The formation of the η^3-coordinated metallacycle is the key for selective transformation, such as [2 + 2 + 2] cycloaddition, acyclic co-trimerization, [2 + 2] cycloaddition and hydrovallylations. Nickel complexes accomplished the assembly of electron-deficient alkenes with alkynes, ethylene and 1,3-enynes while cobalt catalysts allowed the dimerization of simple alkenes with 1,3-enynes.

Chapter 1 and 2 described the nickel-catalyzed transformations of conjugated enones with alkyne or ethyenes via an η^3-oxaallyl nickelacycle, which is in equilibrium with an η^1-*O*-enolate nickelacycle through η^1-η^3 isomerization. In chapter 1, the nickel-catalyzed [2 + 2 + 2] cycloaddition of two enones with an alkyne was developed. This reaction provided cyclohexene derivatives possessing four stereogenic centers as a single diastereomer. According to the mechanistic study, the insertion the second enone would proceed via 1,4-addition of an η^1-*O*-enolate nickel complex to the enone. In addition, the asymmetric version of [2 + 2 + 2] cycloaddition was successfully established by utilizing the chiral NHC ligand. In chapter 2, the smallest alkene, ethylene, would be incorporated into the corresponding nickelacycle at high temperature. Thus, ethylene was utilized as a C4 building block as butenyl and butyl groups.

In chapter 3 and 4, the [2 + 2] cycloaddition of alkenes with 1,3-enynes was demonstrated. The formation of η^3-butadienyl metallacycles which avoid the undesired pathways is the key for the chemo- and regioselective reaction. In nickel-catalyzed reaction, a wide range of electron-deficient alkenes was applicable to afford a variety of cyclobutene derivatives. Under cobalt catalysis, the [2 + 2] cycloaddition occurred with simple alkenes bearing no allylic hydrogen, such as styrene derivatives vinyl boronte and vinylsilane, in which the possible *endo*-cyclic β-H elimination of the metallacycle intermediate might be avoided by the η^3-butadienyl coordination. The cobalt-catalyzed hydroallylation of alkyl alkenes with 1,3-enynes proceeded via *exo*-cyclic β-H elimination of metallacycle intermediate.

The studies in this thesis would provide new strategies for utilizing conjugated unsaturated compounds in organic synthesis and also lend insight into the transition-metal-catalyzed transformations via metallacycle intermediates.

List of Publications

(1) Nickel-Catalyzed Reactions between Enone and Two Ethylenes
Sensuke Ogoshi, Akira Nishimura, Toshifumi Haba, and Masato Ohashi
Chem. Lett. **2009**, *38*, 1166–1167.

(2) Nickel-Catalyzed [2 + 2 + 2] Cycloaddition of Two Enones and an Alkyne
Sensuke Ogoshi, Akira Nishimura, and Masato Ohashi
Org. Lett. **2010**, *12*, 3450–3452.

(3) Nickel-Catalyzed Intermolecular [2 + 2] Cycloaddition of Conjugated Enynes with Alkenes
Akira Nishimura, Masato Ohashi, and Sensuke Ogoshi
J. Am. Chem. Soc. **2012**, *134*, 15692–15695.

(4) Synthesis of Cyclobutenes and Allenes via Cobalt-Catalyzed Cross-Dimerization of Simple Alkenes with 1,3-Enynes
Akira Nishimura, Eri Tamai, Masato Ohashi, and Sensuke Ogoshi
Manuscript in preparation

(5) Enantioselective Synthesis of Cyclohexenes with Four Stereocenters via Ni(0)/Chiral NHC-Catalyzed Intermolecular [2 + 2 + 2] Cycloaddition
Akira Nishimura, Hiromu Tokura, Eri Tamai, Masato Ohashi, and Sensuke Ogoshi
Manuscript in preparation

Supplementary Publication

(1) Nickel-Catalyzed [2 + 2] Cycloaddition Reaction of Bulky Enones with Simple Alkynes. The Effect of Bulkiness of Substituent Attached at β-Carbon
Abudoukadeer Abulimiti, Akira Nishimura, Masato Ohashi, and Sensuke Ogoshi
Chem. Lett. **2012**, *42*, 904–905.