Studies on Nickel-Catalyzed C–C Bond Formation with α,β-Unsaturated Carbonyl Compounds and Alkynes

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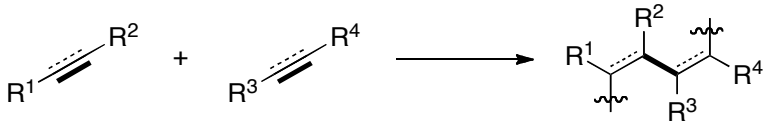
Abbreviations

APCI	atomospheric pressure chemical ionization
aq.	aqueous
br	broad (spectral)
Bu	butyl
°C	degrees Celsius
calcd	calculated
cat.	catalytic
Co.	company
cod	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
Cyp	cyclopentyl
δ	chemical shift in perts per million
d	doublet (spectral)
DBU	1,8-diazabicyclo[5.4.0]-7-undecene
E	*entgegen* (means "opposite")
Ed(s)	editor(s)
EI	electron ionization
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
h	hour(s)
HRMS	high-resolution mass spectrum
Hz	hertz (s^{-1})
i	iso
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	infrared (spectral)
J	coupling constant (spectral)
m	multiplet (spectral)
M	molar (1 M = 1 mol dm^{-3})
Me	methyl
mg	milligram(s)
MHz	megahertz
mL	milliliter(s)
mm	millimeter(s)
mmol	millimole(s)
mp.	melting point
nm	nanometer(s)
pp.	page(s)
Ph	phenyl
ppm	parts per million (spectral)
Pr	propyl
q	quartet (spectral)
rt	room temperature (*ca*. 25 °C)
s	singlet
sept	septet
SIMes	1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene
t	triplet
t (*tert*)	tertiary
TLC	thin-layer chromatography
Z	*zusammen* (means "together")

General Introduction

1. Transition-metal-catalyzed C–C bond formation *via* σ-π isomerization

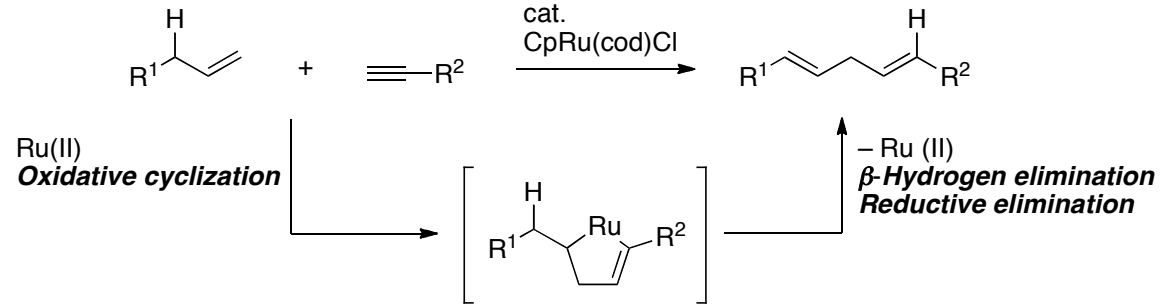
Since a carbon–carbon σ-bond is more energetically stable than a π-bond, π-components such as alkenes and alkynes can construct new carbon–carbon σ-bonds *via* σ-π bond isomerization (Scheme 1). Development of reactions involving such isomerization is an attractive project not only from synthetic chemical point of view, but also from atom economical point of view.[1] Among the classical reactions, Alder–ene reaction[2] and Diels–Alder reaction[3] are the most noteworthy reactions through σ-π isomerization. However, the process is not always easy in spite of the energetic advantage. To address the problem, transition-metal catalyzed reactions have been investigated.



Scheme 1. σ-π Isomerization.

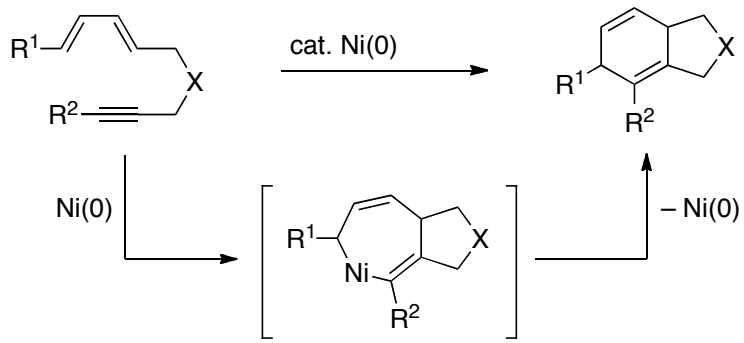
Alder–ene reaction is a reaction between an alkene bearing allylic hydrogens and an enophile, which is typically another unsaturated compound. The reaction usually requires harsh reaction conditions and suffers lack of selectivity. By adding Lewis acids, the reaction can be highly stereoselective, and less reactive enophiles can also be used.[2b] However, simple alkenes and alkynes, which are absence of Lewis basic site, preclude such an approach.

Transition-metal complexes have successfully catalyzed the formal Alder–ene reaction employing unactivated alkynes.[4,5] For instance, Trost reported ruthenium-catalyzed codimerization of alkenes with alkynes to afford 1,4-dienes (Scheme 2).[4] Ruthenacyclopentene arising from oxidative cyclization of an alkene and an alkyne with ruthenium(II) is proposed as an intermediate of the reaction, which is followed by β-hydrogen elimination and reductive elimination to give the 1,4-diene.



Scheme 2. Ruthenium-catalyzed codimerization of alkenes with alkynes to afford 1,4-dienes.

Alkynes as dienophiles do not work efficiently in a Diels–Alder reaction. In order to circumvent extreme reaction conditions, transition-metal-catalyzed [4+2] cycloaddition of dienes with unactivated alkynes has been investigated.[6–9] For instance, Wender reported nickel-catalyzed intramolecular [4+2] cycloaddition of dienynes to provide 1,4-cyclohexadine-containing bicycles (Scheme 3).[8] In the reaction, formation of a seven-membered nickelacycle followed by reductive elimination gives the 1,4-cyclohexadiene.



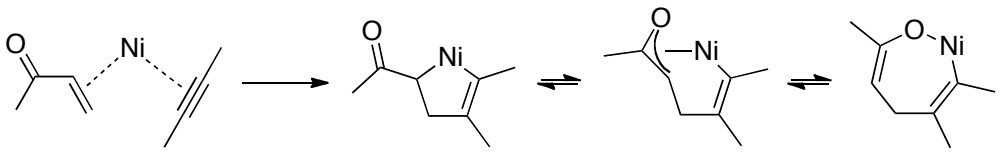
Scheme 3. Nickel-catalyzed intramolecular [4+2] cycloaddition.

As overviewed above, transition-metal-catalyzed reactions, involving σ-π isomerization, are very important synthetic methods for the atom-economical construction of structurally diverse molecular frameworks.[10] The development of efficient catalysts for novel reactions using various compounds containing unsaturated carbon–carbon bonds is a challenging task. Since metallacycles have been proposed as intermediates of most preceding reactions, design of catalytic systems to form a metallacycle could be a hopeful approach.

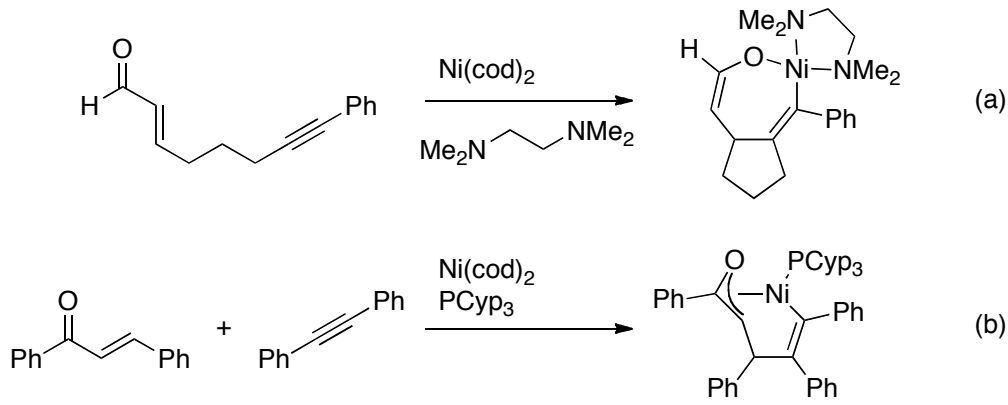
2. Nickel-catalyzed reactions of α,β-unsaturated carbonyl compounds with alkynes

To develop novel transition-metal-catalyzed σ-π isomerization, the author focused on the nickel-catalyzed reaction of α,β-unsaturated carbonyl compounds, such as enones, enals, and enoates, with alkynes.[11] The mechanistic proposals for the reactions have largely focused on the involvement of nickelacycles derived from the oxidative cyclization of an α,β-unsaturated carbonyl compound and an alkyne with nickel(0).

Three types of nickelacycles are presumable: a five-membered C-enolate type, a seven-membered O-enolate type, and an intermediary η^3-oxaally type (Scheme 4). They would be in equilibrium under the reaction conditions. In some cases, the nickelacycles have been isolated and characterized. Montgomery reported that treatment of an alkynylenal with stoichiometric amount of nickel(0) complex gave a seven-membered η^1-oxanickelacycle (Scheme 5a).[12] Ogoshi reported intermolecular reaction of nickel(0) with an enone and an alkyne to afford a η^3-oxaally nickel complex (Scheme 5b).[13]

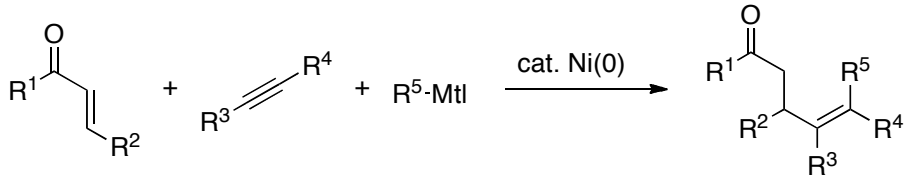


Scheme 4. Formation and equilibrium of nickelacycle.



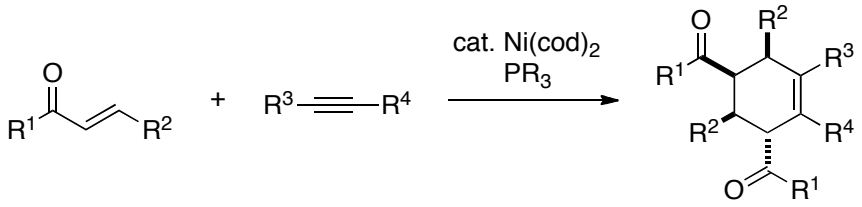
Scheme 5. Examples of characterized nickelacycles.

Catalytic reactions *via* formation of nickelacycles have been widely studied, especially using stoichiometric amount of organometallic reagents or reducing reagents (Scheme 6).[11,14,15] The reactions efficiently afford new σ-bonds from π-components.



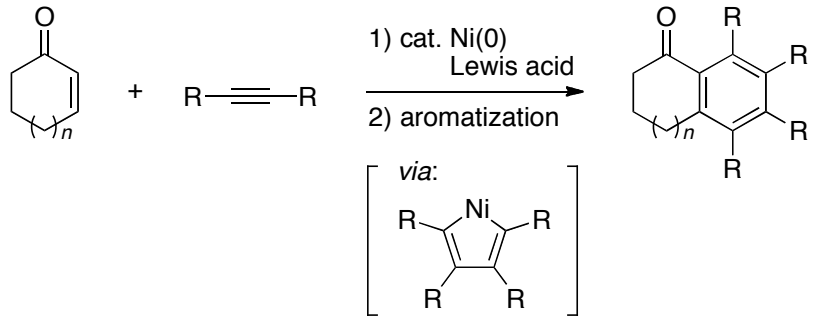
Scheme 6. Nickel-catalyzed three-component coupling.

In contrast to the reactions employing stoichiometric amount of metal reagents, there are not so many examples of reactions without metal reagents. In the absence of metal reagents, the reaction with another α,β-unsaturated carbonyl compound or alkyne is most likely. Montgomery and Ogoshi reported cycloaddition of two molecules of acyclic enones with one molecule of alkynes (Scheme 7).[13,16]



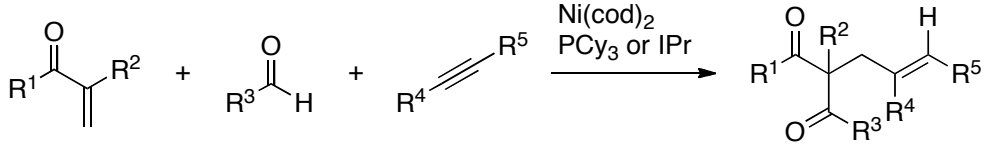
Scheme 7. Nickel-catalyzed [2+2+2] cycloaddition of two acyclic enones with an alkyne.

When cyclic enones are employed without metal reagent, a nickelacyclopentadiene arising from oxidative cyclization of two alkynes with nickel(0) is preferentially formed, which reacts with the remaining enone. Ikeda and Cheng reported nickel-catalyzed [2+2+2] cycloaddition of one molecule of enones with two molecules of alkynes in the presence of catalytic amount of Lewis acid to activate the enones (Scheme 8).[17]



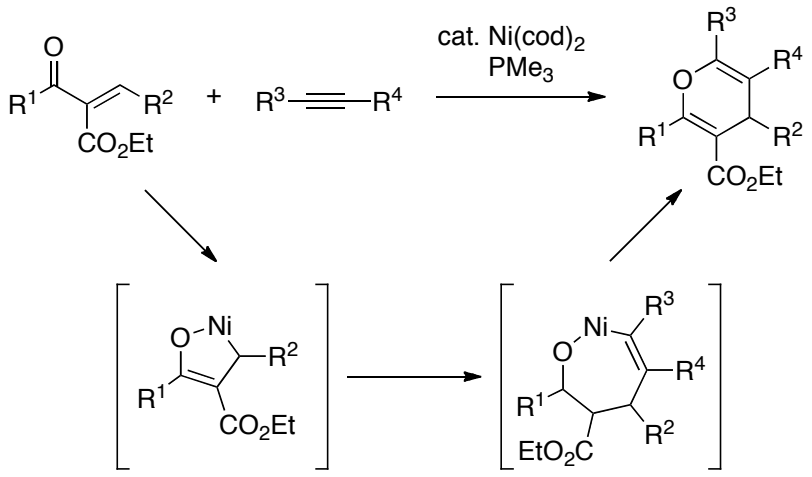
Scheme 8. Nickel-catalyzed [2+2+2] cycloaddition of a cyclic enone with two alkynes.

To tune reaction systems, the reaction of the nickelacycle with the third component can be attained. For example, Montgomery reported nickel-catalyzed three-component reaction between an enone, an aldehyde, and an alkyne (Scheme 9).[18]



Scheme 9. Nickel-catalyzed three-component coupling of enones, aldehydes, and alkynes.

Reductive elimination of seven-membered η^1-oxanickelacycles can furnish six-membered oxacyclic compounds. Matsubara and Kurahashi reported [4+2] cycloaddition of enones bearing an ester group with alkynes to give 4*H*-pyrans (Scheme 10).[19] They proposed that the enone activated by the ester group initially formed a five-membered oxanickelacyle and following insertion of the alkyne gave the nickelacycle.



Scheme 10. Nickel-catalyzed [4+2] cycloaddition of enones with alkynes.

As reviewed above, the nickel-catalyzed reactions of α,β-unsaturated carbonyl compounds with alkynes have also been efficient tools for construction of highly functionalized carbon frameworks or heterocyclic compounds. It might be difficult to control reactions without a metal reagent, but suitable design of substrates and proper choice of ligands would provide new methodologies to approach molecular complexity.

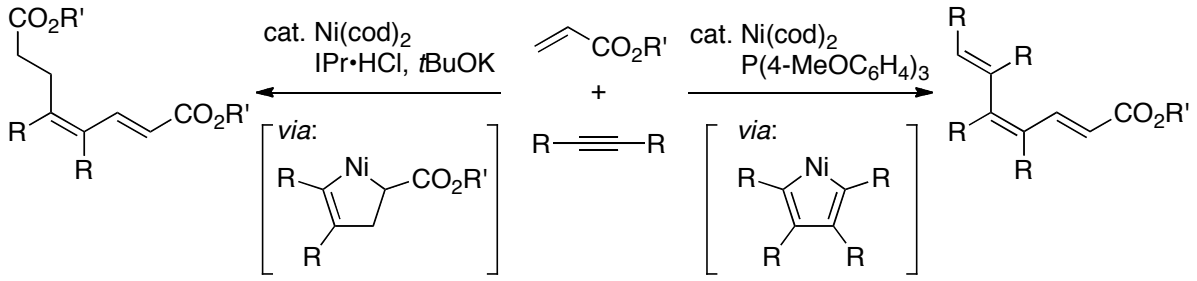
3. Overview of this Thesis

The author investigated nickel-catalyzed reactions of α,β- or α,β,γ,δ-unsaturated carbonyl compounds with alkynes to develop new methods for a selective construction of carbon frameworks by utilizing σ-π isomerization. The reactions were attained without using other metal reagents owing to ligands or design of the unsaturated carbonyl compounds.

3.1. Nickel-catalyzed reactions of acrylates with alkynes (Chapters 1–3)

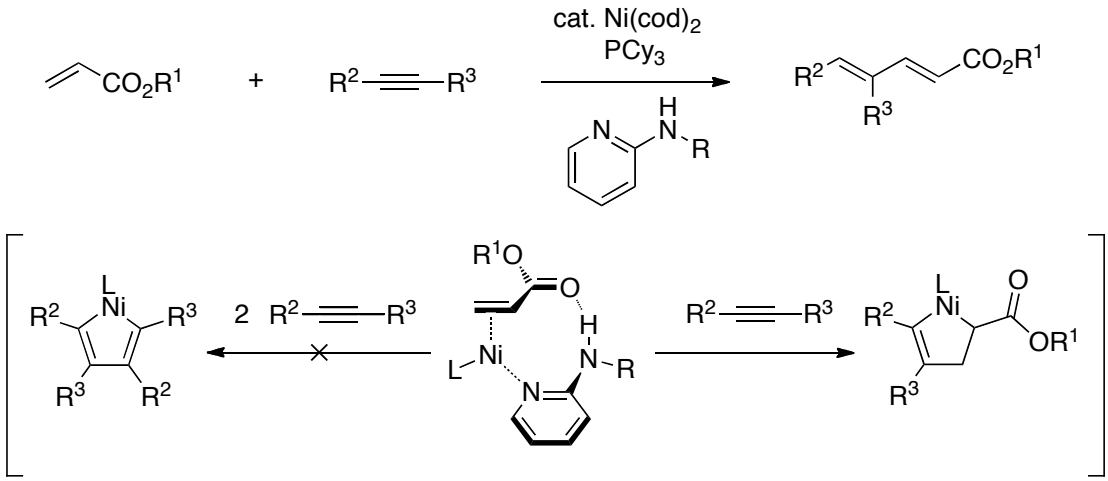
In contrast to enones, enoates have not drawn much attention as a reactant of nickel-catalyzed reactions. A few examples have shown that nickel catalyzes cotrimerization of acrylates with alkynes to afford 1,3,5-trienes.[13,17c] However, nickel-catalyzed reaction of acrylates with alkynes has been limited to the cotrimerization except for using relatively reactive phenyl enoates,[15b,c] strained cyclopropylideneacetates,[20] and the reaction with arynes.[21] The author shows that choice of ligands and additives has expanded the capability of the reactions of acrylates.

In Chapter 1, the author describes two types of cotrimerization of acrylates with alkynes. The reactions proceed selectively depending on the ligand. Cotrimerization of two molecules of acrylates with one molecule of alkynes took place to afford 1,3-dienes with *N*-heterocyclic carbene (NHC) ligand, whereas acrylates reacted with two molecules of alkynes to afford 1,3,5-trienes when phosphine ligand was employed (Scheme 11). As is the reaction with cyclic ketones (Scheme 8),[17] preferential formation of nickelacyclopentadiene from two alkynes might give the 1,3,5-triene. On the other hand, strongly σ-donating and sterically bulky NHC ligand would stimulate the oxidative addition of an acrylate and an alkyne with nickel(0), which reacted another acrylate to give the 1,3-diene.



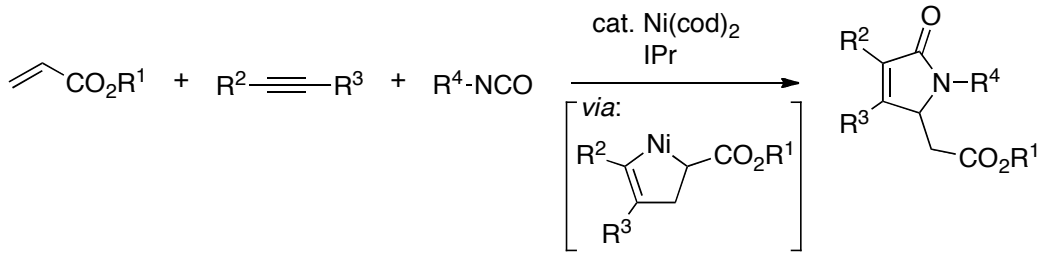
Scheme 11. Two types of cotrimerization of acrylates with alkynes.

In Chapter 2, the author describes codimerization of an acrylate with an alkyne to afford a 1,3-diene (Scheme 12). The reaction was performed by addition of 2-aminopyridine. Hydrogen bonding between a carbonyl group of the acrylate and a proton on the nitrogen atom of the additive would construct bidentate-like ligand, which discouraged the coordination of two alkynes to nickel(0) to form nickelacyclopentadiene.



Scheme 12. Nickel-catalyzed codimerization of an acrylate with an alkyne.

In Chapter 3, the author describes [2+2+1] cycloaddition of an acrylate, an alkyne, and an isocyanate. The mixture of the compounds could give various products, but, as mentioned above, NHC ligand would promote the selective formation of nickelacyclopentene from an acrylate and an alkyne, which reacted with the third component, isocyanate, to afford a γ-butyrolactam (Scheme 13).



Scheme 13. Nickel-catalyzed [2+2+1] cycloaddition of acrylates, alkynes, and isocyanates.

3.2. Nickel-catalyzed cycloadditions of α,β,γ,δ-unsaturated carbonyl compounds with alkynes (Chapters 4 and 5)

In the course of his study, the author became intrigued by the use of different compounds containing unsaturated carbon–carbon bonds, as reaction partners in place of α,β-unsaturated carbonyl compounds. In view of the potentially unique reactivity of α,β,γ,δ-unsaturated carbonyl compounds, which contain a 1,3-diene fragment,[22] the author explored the nickel-catalyzed cycloaddition of α,β,γ,δ-unsaturated carbonyl compounds with alkynes. He employed a γ-ester substituted α,β,γ,δ-unsaturated ester and a simple α,β,γ,δ-unsaturated ketone. The former has a structure combining two enoates, which would construct a C–Ni bond at the α-position of one of the enoate moieties and a C–C bond at the β-position of the other enoate moiety (Figure 1b) as simple enoate forms the bonds at α- and β-positions (Figure 1a). The latter has a structure combining an enone with an electron-rich olefin, which would construct nickelacycle from the enone part and sequentially react with the remaining olefin (Figure 1c). The author shows nickel-catalyzed cycloaddition reactions utilizing the route (b) in Chapter 4 and the route (c) in Chapter 5.

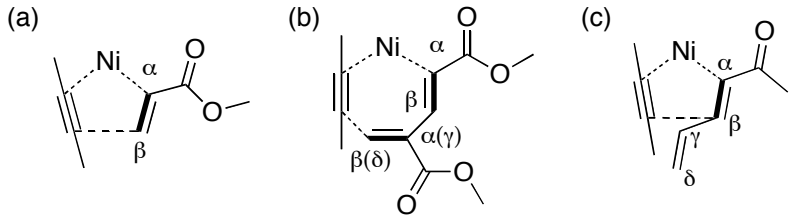
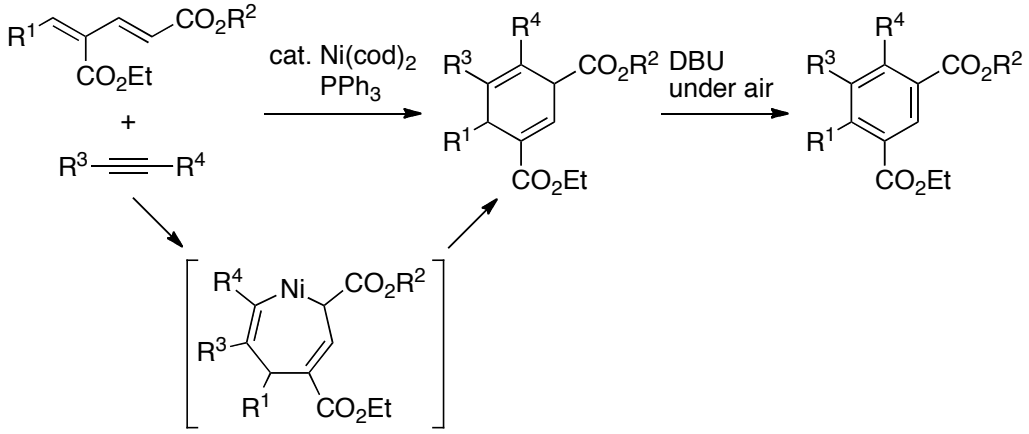


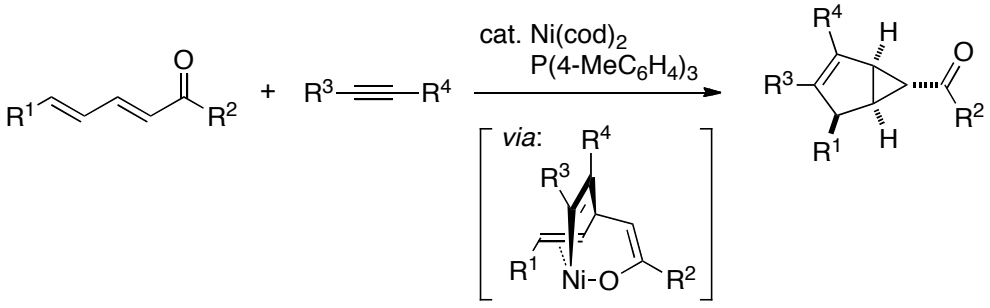
Figure 1. Formation of C–C and C–Ni bonds of unsaturated carbonyl compounds.

In Chapter 4, the author describes [4+2] cycloaddition of dienoates with alkynes, which corresponds to inverse electron-demand Diels–Alder reaction. Formation of seven-membered nickelacycle followed by reductive elimination might furnish a cyclohexadiene, and subsequent aromatization gave a highly substituted arene (Scheme 14).



Scheme 14. Nickel-catalyzed [4+2] cycloaddition of dienoates with alkynes.

In Chapter 5, the author describes cycloaddition of dienones with alkynes to construct bicyclo[3.1.0]hexenes (Scheme 15). Nickelacycle derived from oxidative cyclization of an enone moiety and an alkyne with nickel(0) is a plausible intermediate, and sequential intramolecular insertion of the remaining double bond would give the bicyclic product.



Scheme 15. Nickel-catalyzed cycloaddition of dienones with alkynes.

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19. I. Koyama, T. Kurahashi, S. Matsubara, *J. Am. Chem. Soc.* **2009**, *131*, 1350.
20. (a) S. Saito, M. Masuda, S. Komagawa, *J. Am. Chem. Soc.* **2004**, *126*, 10540; (b) S. Komagawa, S. Saito, *Angew. Chem. Int. Ed.* **2006**, *45*, 2446; (c) S. Saito, S. Komagawa, I. Azumaya, M. Masuda, *J. Org. Chem.* **2007**, *72*, 9114.
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22. Due to the ambident electrophilic character of α,β,γ,δ-unsaturated carbonyl compounds toward nucleophilic addition (e.g. 1,2-, 1,4-, and 1,6-addition), the development of regio- and stereoselective transformations that control such unique properties has been a research topic of great interest. For reviews, see: (a) N. Krause, S. Thorand, *Inorg. Chim. Acta* **1999**, *296*, 1; (b) A. G. Csákÿ, G. de La Herrán, C. Murcia, *Chem. Soc. Rev.* **2010**, *39*, 4080; (c) N. Krause, A. Gerold, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186.

Chapter 1

Selective Synthesis of Trienes and Dienes *via* Nickel-Catalyzed Intermolecular Cotrimerization of Acrylates with Alkynes

Nickel-catalyzed cotrimerization of two molecules of acrylates with one molecule of alkynes took place to afford 1,3-dienes when IPr was employed as a ligand. Although oxidative cyclization of two alkynes with nickel(0) could preferentially proceed, steric and electronic property of IPr would promote the oxidative cyclization of an acrylate and an alkyne with nickel(0), which provided the 1,3-diene. On the other hand, using phosphine ligand gave 1,3,5-trienes *via* cotrimerization of one molecule of acrylates with two molecules of alkynes. Nickelacyclopentadiene from two alkynes would be an intermediate of the cotrimerization.

Introduction

Transition-metal-catalyzed intermolecular cooligomerization reactions of alkenes and alkynes are important tools to form C–C bonds in organic synthesis. The reactions atom-economically provide acyclic carbon frameworks from readily available starting materials. A representative example of codimerization is ruthenium-catalyzed formal Alder–ene reaction to produce 1,4-dienes.[1] Cobalt-catalyzed Alder–ene type reaction have also been reported.[2] Another example of codimerization is construction of 1,3-dienes. The reaction is straightforward method to synthesize highly substituted conjugated dienes, and various catalytic systems have been developed.[3–6]

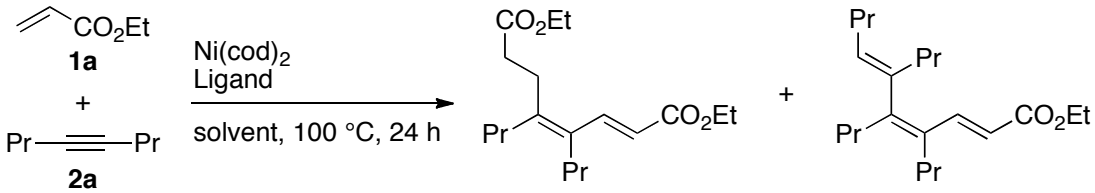
In contrast, cotrimerization of alkenes and alkynes has not received much attention, although the reaction would construct more complex skeletons.[7,8] Among precedents, the reaction of acrylates with alkynes catalyzed by nickel(0) likely has prospects,[8a] because α,β-unsaturated carbonyl compounds can react with alkynes in the presence of nickel catalyst to produce various functionalized molecules.[9] However, another nickel-catalyzed reactions of enoates have been limited to using activated phenyl enoates,[10] strained cyclopropylideneacetate,[11] and the reaction with arynes.[12] In this Chapter, the author shows that *N*-heterocyclic carbene (NHC) ligand educes novel reactivity of acrylates. When NHC ligand was used, nickel(0) catalyzed cotrimerization of two acrylates and an alkyne to produce a 1,3-diene. On the other hand, the same acrylates and alkynes reacted in different manner to produce 1,3,5-trienes when phosphine was used as a ligand.

Results and Discussion

First, the author investigated nickel-catalyzed cotrimerization of ethyl acrylate (**1a**) with 4-octyne (**2a**) using NHC ligand (Table 1). The reaction employing IPr as a ligand gave 1,3-diene **3aa** in moderate yield, along with trace amount of triene **4aa** when toluene or

1,4-dioxane was used as solvent (Table 1, entries 1 and 2). Acetonitrile was poor solvent for the reaction to afford 1,3-diene **3aa**, and 1,3,5-triene **4aa** was formed in 11% yield (entry 3). Increasing the equivalent of **1a** improved the yield of **3aa** (entry 4). Using 5 mol% of $Ni(cod)_2$ and 10 mol% of IPr afforded **3aa** in good yield (entry 6), and a hydrochloride salt of NHC can be employed without decreasing the yield (entry 7). When less sterically hindered IMes was used, the reaction afforded **3aa** in 51% yield, along with **4aa** in 21% yield (entry 8).

Table 1. Nickel-catalyzed cotrimerization of ethyl acrylate (**1a**) with 4-octyne (**2a**) using NHC ligand[a]

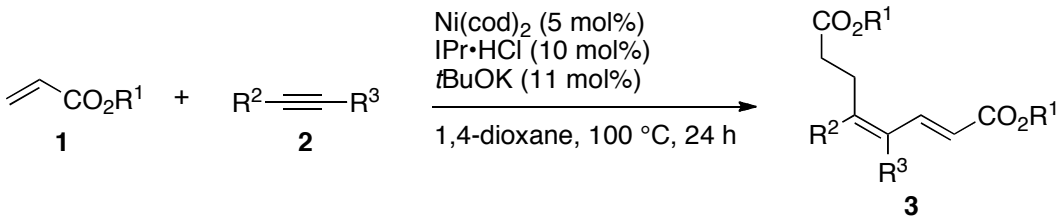


					Yield [%]	
Entry	$Ni(cod)_2$ [mol%]	Ligand	[mol%]	Solvent	**3aa**[b]	**4aa**[c]
1[d]	10	IPr	10	toluene	53	<10
2[d]	10	IPr	10	1,4-dioxane	56	<10
3[d]	10	IPr	10	CH_3CN	28	11
4[e]	10	IPr	10	1,4-dioxane	69	<10
5[e]	5	IPr	5	1,4-dioxane	37	<10
6[e]	5	IPr	10	1,4-dioxane	89 (78)	<10
7[e]	5	IPr[f]	10	1,4-dioxane	87 (82)	<10
8[e]	5	IMes[f]	10	1,4-dioxane	51	21

[a] Reactions were carried out using $Ni(cod)_2$, ligand, ethyl acrylate (**1a**) and 4-octyne (**2a**; 0.50 mmol) in 2 mL of solvent at 100 °C for 24 h. [b] Yield as determined by NMR spectroscopy based on **2a** (0.50 mmol). Yield of the isolated product is given in parentheses. [c] Yield as determined by NMR spectroscopy based on **2a** (0.25 mmol). [d] **1a** (1.2 mmol). [e] **1a** (2.0 mmol). [f] Hydrochloride salt of NHC (10 mol%) and *t*BuOK (11 mol%) were used.

Then, the substrate scope of the reaction to form 1,3-diene **3** was examined using IPr as a ligand (Table 2). Methyl acrylate (**1b**) and *tert*-butyl acrylate (**1c**) produced the diene **3** in 71% and 49% yield, along with the triene **4** in 5% and 23% yield, respectively (Table 2, entries 1 and 2). Unsymmetrical alkynes, such as **2b** and **2c**, gave the 1,3-diene in moderate yields consisting of regioisomeres in 1/1 ratios (entries 3 and 4), whereas bulky *tert*-butyl substituted alkyne **2d** also reacted with **1a** to produce the diene **3ad** in lower yield, but with better regioselectivity

Table 2. Cotrimerization of two acrylates with an alkyne to afford a 1,3-diene[a]



Entry	**1**	R^1	**2**	R^2	R^3	**3**	Yield [%][b]
1	**1b**	Me	**2a**	Pr	Pr	**3ba**	71
2[d,e]	**1c**	*t*Bu	**2a**	Pr	Pr	**3ca**	49
3	**1a**	Et	**2b**	Me	C_5H_{11}	**3ab**	50 (1/1)[c]
4	**1a**	Et	**2c**	Me	*i*Pr	**3ac**	60 (1/1)[c]
5	**1a**	Et	**2d**	Me	*t*Bu	**3ad**	24 (3/1)[c]
6[d,f]	**1a**	Et	**2e**	Ph	Ph	**3ae**	68
7[d,f]	**1a**	Et	**2f**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**3af**	82
8[d,f]	**1a**	Et	**2g**	4-FC_6H_4	4-FC_6H_4	**3ag**	30
9[g]	**1a**	Et	**2h**	Ph	Me	**3ah**	53 (1/1)[c]

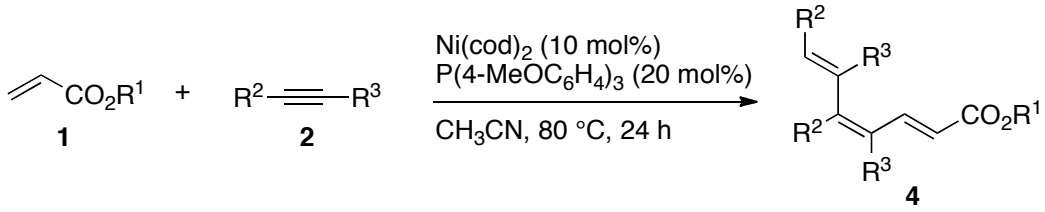
[a] Reactions were carried out using $Ni(cod)_2$ (5 mol%), IPr•HCl (10 mol%), *t*BuOK (11 mol%), **1** (2.0 mmol, 2 equiv) and **2** (0.50 mmol) in 2 mL of 1,4-dioxane at 100 °C for 24 h. [b] Yield of the isolated product. [c] Ratio of regioisomers. [d] $Ni(cod)_2$ (10 mol%), IPr•HCl (20 mol%) and *t*BuOK (22 mol%). [e] **1c** (3.0 mmol, 3 equiv). [f] Slow addition of **2** over a period of 20 h. [g] The reaction was carried out for 44 h with slow addition of **2h** over 40 h.

(entry 5). The reactions of **1a** with aryl-substituted acetylenes also gave the dienes **3** upon slow addition of alkynes (entries 6–9). Without slow addition, the formation of **2ae** resulted in lower yield (49%), and 1-phenyl-1-propyne (**2h**) gave no cotrimer because of rapid [2+2+2] cyclotrimerization of **2h**.

When phosphine was used as a ligand, same acrylates and alkynes afforded 1,3,5-trienes *via* another type of cotrimerization (Table 3).[8] The reaction of **1a** with **2a** in the presence of $Ni(cod)_2$ (10 mol%) and $P(4\text{-}MeOC_6H_4)_3$ (20 mol%) in acetonitrile at 80 °C for 24 h produced triene **4aa** in 92% yield (Table 3, entry 1). Methyl acrylate (**1b**) and *tert*-butyl acrylate (**1c**) also gave triene **4** in 94% and 75% yield, respectively (entries 2 and 3). In this condition, the reaction of ethyl acrylate (**1a**) with diphenylacetylene (**2e**) afforded 1,3,5-triene **4ae** as mixture of two stereoisomers derived from isomerization of terminal substituent R^2. Alternatively, the reaction using PCy_3 as a ligand in toluene at 40 °C for 48 h gave the cotrimer **4ae** in 77% yield without isomerization (entry 4). Functionalized diarylacetylenes **2f** and **2g** also gave the corresponding trienes using PCy_3 in toluene (entries 5 and 6). Although unsymmetrical alkynes **2b** and **2c** gave the trienes, products were obtained as mixtures of four regioisomers. On the other hand, aryl-substituted unsymmetrical alkyne **2h** afforded triene **4ah** in high regioselectivity (entry 7).

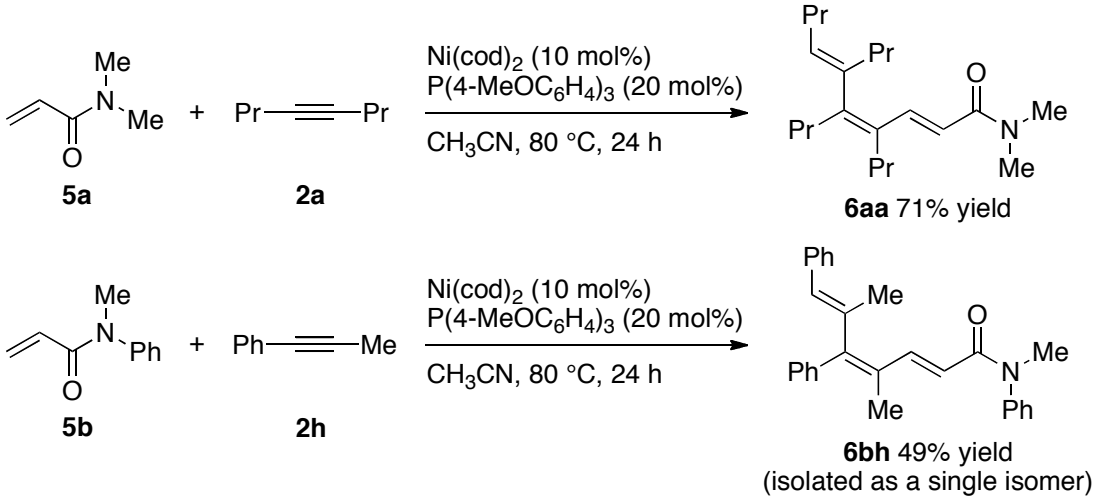
Acrylamides also reacted with two molecules of alkynes (Scheme 1). The reaction of *N*,*N*-dimethylacrylamide (**5a**) with 4-octyne (**2a**) provided cotrimer **6aa** in 71% yield. *N*-Methyl-*N*-phenylacrylamide (**5b**) reacted with alkyne **2h** to provide 1,3,5-triene **6bh**, which was isolated as a single isomer in 49% yield. Figure 1 shows the result of the single-crystal X-ray analysis of triene **6bh**.

Table 3. Cotrimerization of an acrylate with two alkynes to afford a 1,3,5-triene **4**[a]



Entry	**1**	R^1	**2**	R^2	R^3	**4**	Yield [%][b]
1	**1a**	Et	**2a**	Pr	Pr	**4aa**	92
2	**1b**	Me	**2a**	Pr	Pr	**4ba**	94
3	**1c**	*t*Bu	**2a**	Pr	Pr	**4ca**	75
4[c]	**1a**	Et	**2e**	Ph	Ph	**4ae**	77
5[c]	**1a**	Et	**2f**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**4af**	64
6[c]	**1a**	Et	**2g**	4-FC_6H_4	4-FC_6H_4	**4ag**	69
7	**1a**	Et	**2h**	Ph	Me	**4ah**	86 (9/1)[d]

[a] Reactions were carried out using $Ni(cod)_2$ (10 mol%), P(4-$MeOC_6H_4)_3$ (20 mol%), **1** (0.75 mmol, 1.5 equiv) and **2** (1.0 mmol) in 2 mL of acetonitrile at 80 °C for 24 h. [b] Yield of the isolated product. [c] Reactions were carried out using PCy_3 (20 mol%) in place of P(4-$MeOC_6H_4)_3$ in 2 mL of toluene at 40 °C for 48 h. [d] Ratio of regioisomers.



Scheme 1. Nickel-catalyzed cotrimerization of acrylamide with alkyne.

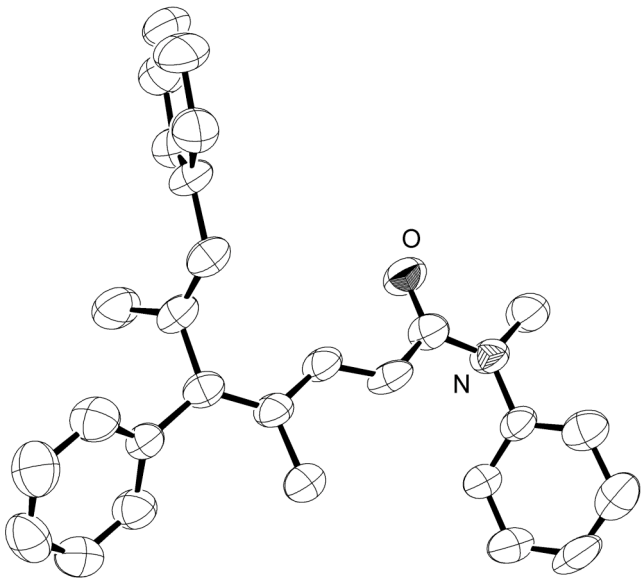
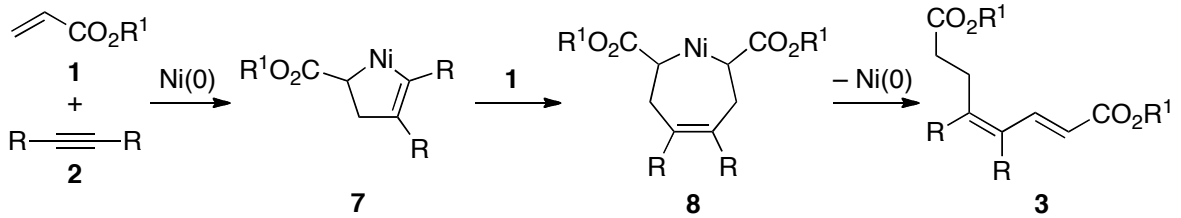


Figure 1. ORTEP drawing of triene **6bh**.

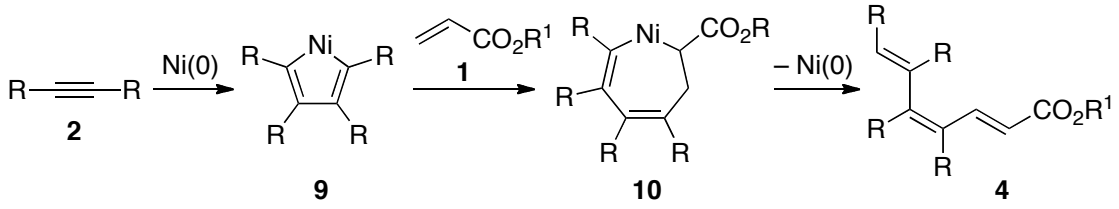
A plausible mechanism of the reaction to afford 1,3-diene **3** is shown in Scheme 2. An acrylate and an alkyne coordinate to nickel(0) complex to form nickelacyclopentene **7**. This intermediate reacts with the second acrylate **1** to generate a nickelacycle **8**. Subsequent β-hydrogen elimination followed by reductive elimination furnishes conjugated diene **3** and regenerates nickel(0) complex.



Scheme 2. Plausible reaction mechanism to construct 1,3-diene **3**.

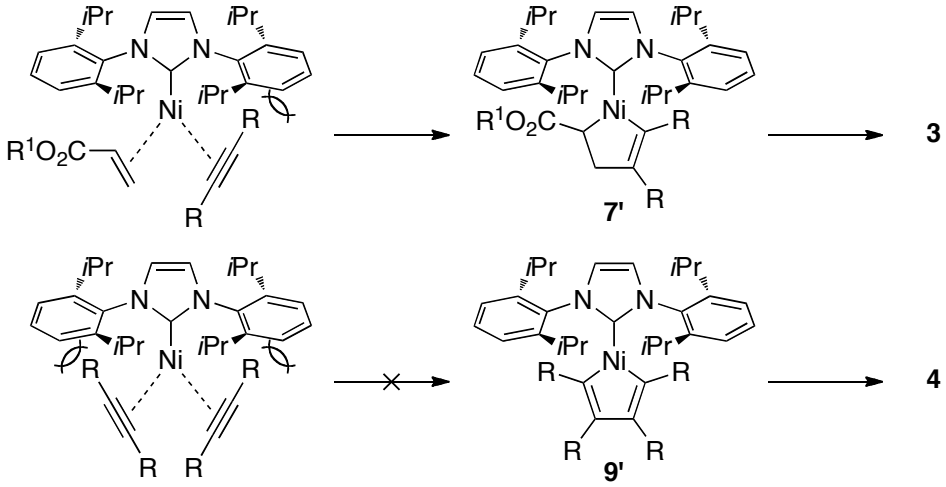
Considering the mechanical studies on nickel-catalyzed reactions of α,β-unsaturated carbonyl compounds with two molecules of alkynes,[11c,13] the formation of 1,3,5-triene **4** is rationalized as arising from oxidative cyclization of two alkynes with nickel(0) (Scheme 3). Insertion of an acrylate to the complex **9** leads to a seven-membered nickelacycle **10** and

following β-hydrogen elimination and reductive elimination afford triene **4**. However, it may not be ruled out that insertion of alkyne to nickel complex **7** gives the intermediate **10**.



Scheme 3. Plausible reaction mechanism to construct 1,3,5-triene **4**.

When NHC was employed as a ligand, strong σ-donating and week π-accepting property of NHC ligand caused the reaction of nickel complexes with electron-deficient π-bond of acrylates.[14] In addition, the result, more sterically hindered IPr was effective ligand for construction of diene **3**, indicates that steric repulsive interaction between ligand and alkynes prevents the formation of nickelacycle from two alkynes (Scheme 4).



Scheme 4. Effect of IPr ligand on cotrimerization of acrylates with alkynes.

Conclusion

The author demonstrated novel nickel-catalyzed cotrimerization of acrylates with alkynes. The steric and electronic property of IPr ligand would promote the formation of

nickelacyclopentene **7** from an acrylate and an alkyne, which reacted another acrylate to give a 1,3-diene. He also showed that same acrylates and alkynes reacted in inverse ratio to afford 1,3,5-trienes when phosphine was employed as a ligand. Nickelacyclopentadiene **9** from two alkynes is a plausible intermediate of the latter cotrimerization.

Experimental Section

General remarks compatible to all the experimental part in the present Thesis

All manipulations of oxygen- and moisture-sensitive materials were conducted in a dry box or with a standard Schlenk technique under a purified argon atmosphere. ^{1}H NMR (500 MHz) and ^{13}C NMR (125.7 MHz) spectra were taken on Varian UNITY INOVA 500 spectrometer and were recorded in $CDCl_3$. Chemical shifts (δ) are in parts per million relative to $CHCl_3$ at 7.26 ppm for ^{1}H and relative to $CDCl_3$ at 77.0 ppm for ^{13}C unless otherwise noted. Elemental analyses were performed by Elemental Analysis Center of Kyoto University. High-resolution mass spectra were obtained with a JEOL JMS-MS700 (EI), a JEOL JMS-HX110A (FAB) or a Thermo Fisher SCIENTIFIC EXACTIVE (ESI, APCI) spectrometer. Infrared spectra (IR) spectra were determined on a SHIMADZU IR Affinity-1 spectrometer. Melting points were determined using a YANAKO MP-500D. TLC analyses were performed by means of Merck Kieselgel 60 F_{254} (0.25 mm) Plates. Visualization was accomplished with ultraviolet light (254 nm) and/or an aqueous alkaline $KMnO_4$ solution followed by heating. Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–50 mm). Unless otherwise noted, commercially available reagents were used without purification. 1,4-Dioxane, acetonitrile, and toluene were purchased from Wako Pure Chemical Co. and stored in a dry box under a purified argon atmosphere.

Chemicals. 1,2-Bis(4-methoxyphenyl)ethyne (**2f**) and 1,2-bis(4-fluorophenyl)ethyne (**2g**) were prepared by Sonogashira cross-coupling of corresponding acetylenes with aryliodides. *N*-Methyl-*N*-phenylacrylamide (**5b**) was prepared by Schotten–Baumann reaction of acryloyl chloride with *N*-methylaniline. Pottasium *tert*-butoxide was purchased from Wako Pure Chemical Co. and purified by sublimation.

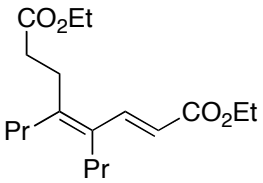
Experimental procedure for the nickel-catalyzed cotrimerization of two acrylates with an alkyne to afford a 1,3-diene

General Procedure. The reaction was performed in a 5 mL sealed vessel equipped with a Teflon-coated magnetic stirrer tip. An acrylate (2.0 mmol) and an alkyne (0.50 mmol) were added to a solution of bis(1,5-cyclooctadiene)nickel (6.8 mg, 0.025 mmol), IPr•HCl (21 mg, 0.050 mmol) and pottasium *tert*-butoxide (6.2 mg, 0.055 mmol) in 1,4-dioxane (2 mL) in a dry box. The VIAL was taken outside the dry box and heated at 100 ºC for 24 h. The resulting reaction mixture was cooled to ambient temperature and filtered through a silica gel pad, concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 10:1) to give the corresponding conjugated diene.

Slow addition procedure. The reaction was performed in a 15 mL sealed tube equipped with a Teflon-coated magnetic stirrer. An acrylate (2.0 mmol) was added to a solution of bis(1,5-cyclooctadiene)nickel (14 mg, 0.050 mmol), IPr•HCl (43 mg, 0.10 mmol) and pottasium *tert*-butoxide (12 mg, 0.11 mmol) in 1,4-dioxane (0.5 mL) in a dry box and the VIAL was taken outside the dry box. To the mixture was added dropwise a solution of alkyne (0.50 mmol) in 1,4-dioxane (1.5 mL) at 100 ºC over 20 h. The resulting mixture was stirred for 4 h and cooled to ambient temperature and filtered through a silica gel pad, concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 10:1) to give the corresponding conjugated diene.

Characterization data

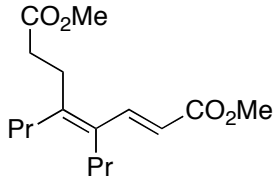
Diethyl (2*E*,4*Z*)-4,5-dipropyl-2,4-octadienedioate (3aa).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 15.5 Hz, 1H), 5.85 (d, *J* = 15.5 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 2.62 (t, *J* = 8.0 Hz, 2H), 2.38 (t, *J* = 8.0 Hz, 2H), 2.21 (t, *J* = 8.0 Hz, 2H), 2.15 (t, *J* = 8.0 Hz, 2H), 1.44 (m, 2H), 1.38 (m, 2H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.0

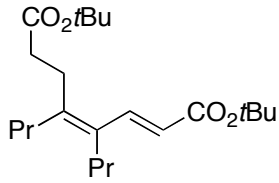
Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.70, 167.88, 147.45, 142.00, 132.30, 116.71, 60.51, 60.18, 35.55, 34.31, 30.26, 27.28, 22.49, 21.97, 14.39, 14.35, 14.30, 14.18. IR (neat): 2961, 2907, 1732, 1712, 1614, 1466, 1300, 1261, 1177, 1040, 980, 860, 739 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{30}O_4$ ([M]$^+$): 310.2144. Found: 310.2140.

Dimethyl (2*E*,4*Z*)-4,5-dipropyl-2,4-octadienedioate (3ba).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 15.5 Hz, 1H), 5.84 (d, *J* = 15.5 Hz, 1H), 3.74 (s, 3H), 3.65 (s, 3H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.38 (t, *J* = 8.0 Hz, 2H), 2.18 (t, *J* = 8.0 Hz, 2H), 2.12 (t, *J* = 8.0 Hz, 2H), 1.42 (m, 2H), 1.35 (m, 2H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.03, 168.21, 147.50, 142.07, 132.30, 116.27, 51.60, 51.42, 35.50, 33.98, 30.17, 27.23, 22.42, 21.92, 14.35, 14.24. IR (neat): 2959, 2872, 1741, 1715, 1614, 1435, 1304, 1265, 1171, 1022, 860, 739 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{26}O_4$ ([M]$^+$): 282.1831. Found: 282.1842. Anal calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.26; H, 9.27.

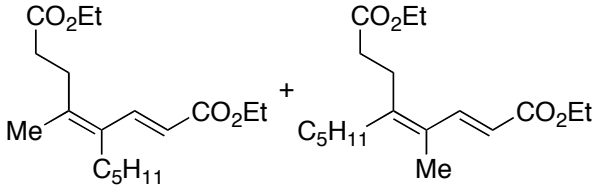
Di*tert*-Butyl (2*E*,4*Z*)-4,5-dipropyl-2,4-octadienedioate (3ca).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 15.5 Hz, 1H), 5.76 (d, *J* = 15.5 Hz, 1H), 2.56 (t, *J* = 8.0 Hz, 2H), 2.30 (t, *J* = 8.0 Hz, 2H), 2.19 (t, *J* = 8.0 Hz, 2H), 2.13 (t, *J* = 8.0 Hz, 2H), 1.50 (s, 9H), 1.43 (s, 9H), 1.50–1.38 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.08, 167.34, 147.22, 141.23, 132.05, 118.33, 80.42, 79.93, 35.48, 35.44, 30.24, 28.22, 28.07, 27.26, 22.48, 21.96, 14.37, 14.31. IR (neat): 2965, 1730, 1709, 1614, 1456, 1368, 1308, 1258, 1150, 982, 849, 754 cm^{-1}. HRMS (FAB) calcd for $C_{22}H_{38}O_4$ ([M]$^+$): 366.2770. Found: 366.2764.

Diethyl (2*E*,4*Z*)-5-methyl-4-pentyl-2,4-octadienedioate and

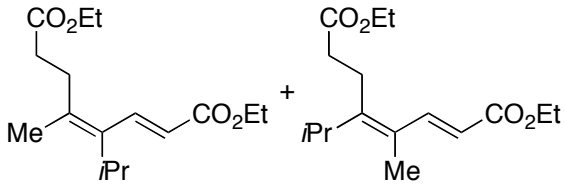
diethyl (2*E*,4*Z*)-4-methyl-5-pentyl-2,4-octadienedioate (1:1 mixture) (3ab).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 15.5 Hz, 0.5H), 7.75 (d, *J* = 15.5 Hz, 0.5H), 5.84 (d, *J* = 15.5 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 1H), 2.64 (m, 2H), 2.40 (m, 2H), 2.22 (t, *J* = 7.5 Hz, 1H), 2.17 (t, *J* = 8.0 Hz, 1H), 1.87 (s, 1.5H), 1.79 (s, 1.5H), 1.31 (m, 6H), 1.25 (m, 6H), 0.89 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.69, 172.62, 167.93, 167.77, 147.68, 142.80, 141.68, 132.54, 127.26, 116.95, 116.35, 60.51, 60.13, 34.13, 33.95, 33.64, 32.07, 32.05, 29.73, 28.56, 28.32, 28.14, 27.81, 22.54, 22.52, 19.87, 14.34, 14.17, 14.08, 14.03, 13.97. IR (neat): 2959, 2872, 1738, 1713, 1614, 1466, 1368, 1301, 1267, 1177, 1037, 978, 856, 731 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{32}O_4$ ($[M]^+$): 310.2144. Found: 310.2148. Anal calcd for $C_{18}H_{32}O_4$: C, 69.64; H, 9.74. Found: C, 69.77; H, 9.53.

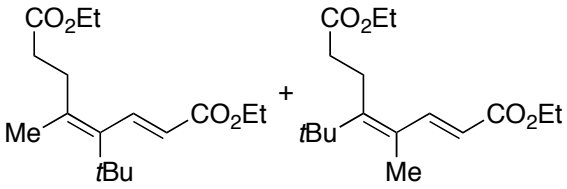
Diethyl (2*E*,4*Z*)-4-isopropyl-5-methyl-2,4-octadienedioate and

diethyl (2*E*,4*E*)-5-isopropyl-4-methyl-2,4-octadienedioate (1:1 mixture) (3ac).



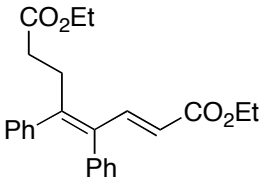
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 16.0 Hz, 0.5H), 7.75 (d, *J* = 16.0 Hz, 0.5H), 5.86 (d, *J* = 16.0 Hz, 0.5H), 5.85 (d, *J* = 16.0 Hz, 0.5H), 4.21 (q, 7.0 Hz, 2H), 4.14 (q, *J* = 7.0 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 1H), 3.03 (sept, *J* = 7.0 Hz, 0.5H), 2.92 (sept, *J* = 7.0 Hz, 0.5H), 2.59 (t, *J* = 8.0 Hz, 1H), 2.51 (t, *J* = 8.0 Hz, 1H), 2.37 (m, 2H). 1.29 (m, 6H), 1.04 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.86, 172.60, 167.66, 167.16, 151.90, 143.48, 142.56, 137.57, 135.97, 126.30, 120.42, 117.29, 60.48, 60.41, 60.21, 60.13, 35.85, 33.50, 31.71, 30.95, 29.48, 22.65, 20.91, 20.66, 18.65, 14.31, 14.19, 14.17, 13.63. IR (neat): 2976, 1738, 1712, 1614, 1460, 1368, 1290, 1177, 1038, 982, 858 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{26}O_4$ ($[M]^+$): 282.1831. Found: 282.1837. Anal calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.29; H, 9.34.

Diethyl (2*E*,4*E*)-4-*tert*-butyl-5-methyl-2,4-octadienedioate and diethyl (2*E*,4*E*)-5-*tert*-butyl-4-methyl-2,4-octadienedioate (3:1 mixture) (3ad).



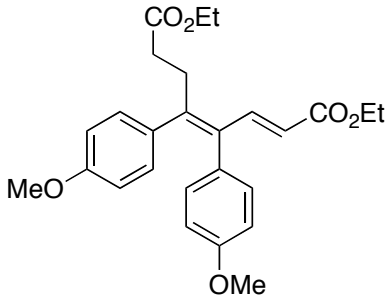
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 16.0 Hz, 0.25H), 7.34 (d, *J* = 16.0 Hz, 0.75H), 5.88 (d, *J* = 16.0 Hz, 0.25H), 5.59 (d, *J* = 16.0 Hz, 0.75H), 4.21 (q, *J* = 7.0 Hz, 0.5H), 4.20 (q, *J* = 7.0 Hz, 1.5 H), 4.13 (q, *J* = 7.0 Hz, 0.5H), 4.10 (q, *J* = 7.0 Hz, 1.5H), 2.73 (t, *J* = 8.5 Hz, 0.5H), 2.32 (m, 3.5H), 1.98 (s, 0.75H), 1.85 (s, 2.25H), 1.30 (t, *J* = 7.0 Hz, 3H), 1.26 (s, 2.25H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.14 (s, 6.75H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.12, 172.43, 167.71, 166.53, 153.94, 148.53, 145.48, 140.19, 131.30, 128.43, 121.59, 117.17, 60.47, 60.29, 60.22, 60.13, 36.95, 35.80, 35.66, 33.54, 33.44, 31.04, 30.70, 26.06, 19.84, 17.45, 14.31, 14.26, 14.17. IR (neat): 2978, 1736, 1721, 1638, 1613, 1466, 1368, 1304, 1261, 1175, 1098, 1036, 988, 864 cm^{-1}. HRMS (FAB) calcd for $C_{17}H_{28}O_4$ ($[M]^+$): 296.1988. Found: 296.1978. Anal calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.93; H, 9.56.

Diethyl (2*E*,4*Z*)-4,5-diphenyl-2,4-octadienedioate (3ae).



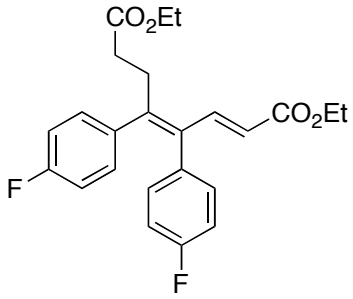
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, *J* = 15.5 Hz, 1H), 7.13-7.30 (m, 6H), 6.94–6.89 (m, 4H), 5.53 (d, *J* = 15.5 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.15 (t, *J* = 8.0 Hz, 2H), 2.39 (t, *J* = 8.0 Hz, 2H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.43, 167.47, 147.48, 142.51, 140.95, 138.62, 136.82, 130.63, 129.00, 127.80, 127.67, 126.83, 126.60, 122.47, 60.55, 60.33, 33.16, 29.49, 14.27, 14.17. IR (neat): 2982, 1732, 1713, 1614, 1443, 1368, 1292, 1175, 1034, 978, 868, 770, 700, 598 cm^{-1}. HRMS calcd for $C_{24}H_{26}O_4$ ($[M]^+$): 378.1831. Found: 378.1828.

Diethyl (2*E*,4*Z*)-4,5-bis(4-methoxyphenyl)-2,4-octadienedioate (3af).



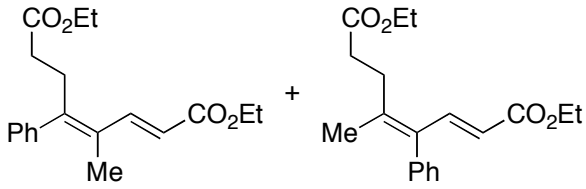
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, J = 15.5 Hz, 1H), 6.87 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 6.68 (d, J = 9.0 Hz, 2H), 6.62 (d, J = 9.0 Hz, 2H), 5.55 (d, J = 15.5 Hz, 1H), 4.19 (q, J = 7.0 Hz, 2H), 4.09 (q, J = 7.0 Hz, 2H), 3.73 (s, 3H), 3.71 (s, 3H), 3.11 (t, J = 8.0 Hz, 2H), 2.37 (t, J = 8.0 Hz, 2H), 1.27 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.52, 167.60, 158.26, 158.07, 146.94, 143.21, 135.90, 133.31, 131.81, 131.23, 130.37, 121.88, 113.38, 113.16, 60.50, 60.24, 55.06, 33.34, 29.55, 14.29, 14.18. IR (neat): 2980, 1732, 1712, 1607, 1508, 1292, 1248, 1175, 1034, 978, 868, 835, 600 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{30}O_6$ ([M]$^+$): 438.2042. Found: 438.2032. Anal calcd for $C_{26}H_{30}O_6$: C, 71.21; H, 6.90. Found: C, 71.10; H, 6.99.

Diethyl (2*E*,4*Z*)-4,5-bis(4-fluorophenyl)-2,4-octadienedioate (3ag).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 15.5 Hz, 1H), 6.91–6.78 (m, 8H), 5.50 (d, J = 15.5 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 4.09 (q, J = 7.0 Hz, 2H), 3.12 (t, J = 8.0 Hz, 2H), 2.37 (t, J = 8.0 Hz, 2H), 1.27 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H).). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.21, 167.22, 161.54 (d, J_{CF} = 245 Hz), 146.77, 142.20, 136.65, 136.25, 134.38, 132.17 (d, J_{CF} = 8.1 Hz), 130.67 (d, J_{CF} = 8.0 Hz), 122.83, 115.03 (d, J_{CF} = 21.0 Hz), 114.90 (d, J_{CF} = 21.0 Hz), 60.63, 60.44, 33.03, 29.55, 14.26, 14.16. IR (neat): 2983, 1733, 1713, 1615, 1602, 1506, 1292, 1223, 1178, 1159, 1046, 978, 838, 736 cm^{-1}. HRMS (EI) calcd for $C_{24}H_{24}F_2O_4$ ([M]$^+$): 414.1643. Found: 414.1650.

Diethyl (2*E*,4*E*)-4-methyl-5-phenyl-2,4-octadienedioate and diethyl (2*E*,4*E*)-5-methyl-4-phenyl-2,4-octadienedioate (1:1 mixture) (3ah).



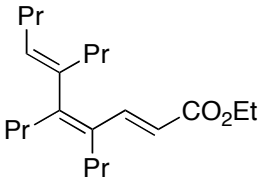
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 16.0 Hz, 0.5H), 7.96 (d, *J* = 15.5 Hz, 0.5H), 7.36 (m, 2H), 7.30 (m, 1H), 7.10 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.01 (dd, *J* = 8.0, 1.5 Hz, 1H), 5.99 (d, *J* = 16.0 Hz, 0.5H), 5.23 (d, *J* = 15.5 Hz, 0.5H), 4.25 (q, *J* = 7.0 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 1H), 4.15 (q, *J* = 7.0 Hz, 1H), 4.05 (q, *J* = 7.0 Hz, 1H), 2.97 (t, *J* = 8.0 Hz, 1H), 2.80 (t, *J* = 8.0 Hz, 1H), 2.54 (t, *J* = 8.0 Hz, 1H), 2.28 (t, *J* = 8.0 Hz, 1H), 1.68 (s, 1.5H), 1.63 (s, 1.5H), 1.34–1.19 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.52, 172.44, 167.61, 167.54, 146.95, 144.10, 142.29, 142.13, 141.74, 139.16, 135.85, 129.49, 128.89, 128.50, 128.32, 128.28, 127.24, 126.99, 120.39, 119.05, 60.63, 60.43, 60.31, 60.14, 33.49, 33.21, 29.54, 29.24, 21.36, 16.31, 14.34, 14.27, 14.20, 14.12. IR (neat): 2981, 1732, 1712, 1617, 1443, 1368, 1293, 1177, 1036, 976, 861, 772, 704 cm^{-1}. HRMS (EI) calcd for $C_{19}H_{24}O_4$ ($[M]^+$): 316.1675. Found: 316.1683.

Experimental procedure for the nickel-catalyzed cotrimerization of an acrylate with two alkynes to afford a 1,3,5-triene

General procedure. The reaction was performed in a 5 mL sealed vessel equipped with a Teflon-coated magnetic stirrer tip. An acrylate (0.75 mmol) and an alkyne (1.0 mmol) were added to a solution of bis(1,5-cyclooctadiene)nickel (14 mg, 0.050 mmol) and tris(4-methoxyphenyl)phosphine (35 mg, 0.10 mmol) in acetonitrile (2 mL) in a dry box. The VIAL was taken outside the dry box and heated at 80 ºC for 24 h. The resulting reaction mixture was cooled to ambient temperature and filtered through a silica gel pad, concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 40:1) to give the corresponding conjugated triene.

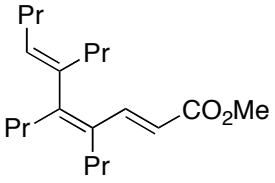
Characterization Data

Ethyl (2*E*,4*Z*,6*E*)-4,5,6-tripropyl-2,4,6-decatrienoate (4aa).



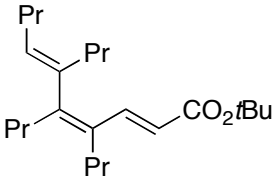
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 16.0 Hz, 1H), 5.76 (d, *J* = 16.0 Hz, 1H), 5.00 (t, *J* = 7.0 Hz, 1H), 4.17 (q, *J* = 7.5 Hz, 2H), 2.25 (m, 2H), 2.20 (t, *J* = 8.0 Hz, 2H), 2.12 (m, 4H), 1.48–1.26 (m, 8H), 1.28 (t, *J* = 7.5 Hz, 3H), 0.96–0.88 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.15, 154.13, 146.16, 138.65, 132.58, 132.26, 114.71, 59.87, 33.13, 31.58, 30.09, 30.01, 22.99, 22.37, 21.83, 21.30, 14.41, 14.33, 14.17, 13.95. IR (neat): 2959, 2872, 1711, 1613, 1458, 1266, 1165, 1045, 991, 899, 853, 746 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{36}O_2$ ([M]$^+$): 320.2715. Found: 320.2708.

Methyl (2*E*,4*Z*,6*E*)-4,5,6-tripropyl-2,4,6-decatrienoate (4ba).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 16.0 Hz, 1H), 5.77 (d, *J* = 16.0 Hz, 1H), 5.04 (t, *J* = 7.5 Hz, 1H), 3.71 (s, 3H), 2.25 (m, 2H), 2.20 (t, *J* = 7.5 Hz, 2H), 2.11 (m, 4H), 0.96–0.87 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.56, 154.34, 146.44, 138.72, 132.55, 132.31, 114.29, 51.19, 33.18, 31.65, 30.08, 30.02, 22.94, 22.36, 21.83, 21.33, 14.42, 14.30, 14.16, 13.86. IR (neat): 2957, 2872, 1722, 1614, 1456, 1433, 1267, 1165, 1045, 991, 898, 858, 748 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{34}O_2$ ([M]$^+$): 306.2559. Found: 306.2558.

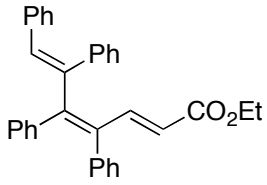
***tert*-Butyl (2*E*,4*Z*,6*E*)-4,5,6-tripropyl-2,4,6-decatrienoate (4ca).**



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 16.0 Hz, 1H), 5.67 (d, *J* = 16.0 Hz, 1H), 5.04 (t, *J* = 7.5 Hz, 1H), 2.23 (m, 2H), 2.18 (t, *J* = 7.0 Hz, 2H), 2.11 (m, 4H), 1.47 (s, 9H), 1.45–1.24 (m, 8H), 0.95–0.87 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.48, 153.24, 145.06, 138.72, 132.60, 132.08, 116.77, 79.44, 33.14, 31.61, 30.05, 28.23, 23.05, 22.39, 21.83, 21.29, 14.45, 14.35, 14.16, 13.98. IR (neat): 2956, 2872, 1703, 1613, 1456, 1366, 1287, 1150, 988, 897, 856, 746 cm^{-1}. HRMS (EI)

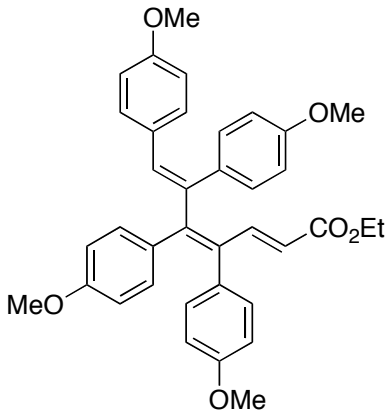
calcd for $C_{23}H_{40}O_2$ ($[M]^+$): 348.3028. Found: 348.3024.

Ethyl (2*E*,4*Z*,6*E*)-4,5,6,7-tetraphenyl-2,4,6-heptatrienoate (4ae).



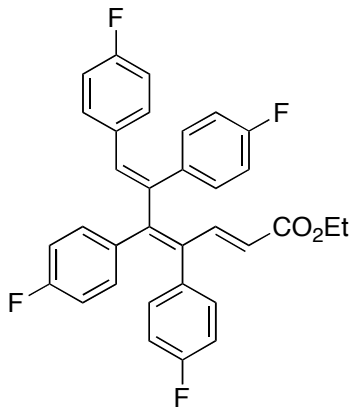
Pale yellow powder, mp. 159–161 °C (CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (d, *J* = 15.5 Hz, 1H), 7.19 (m, 8H), 7.13 (m, 7H), 7.00–6.94 (m, 5H), 6.89 (s, 1H), 6.82 (m, 1H), 5.69 (d, *J* = 15.5 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.45, 151.69, 146.21, 141.32, 138.90, 138.75, 138.33, 136.44, 134.52, 131.10, 130.47, 129.68, 129.56, 128.19, 128.06, 128.03, 127.35, 127.32, 127.03, 127.00, 121.75, 60.11, 14.12. IR (KBr): 1709, 1608, 1280, 1178, 698 cm^{-1}. HRMS (EI) calcd for $C_{33}H_{28}O_2$ ($[M]^+$): 456.2089. Found: 456.2099.

Ethyl (2*E*,4*Z*,6*E*)-4,5,6,7-tetrakis(4-methoxyphenyl)-2,4,6-heptatrienoate (4af).



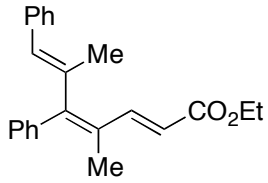
Pale red powder, mp. 56–60 °C (hexane-AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, *J* = 15.0 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.76 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 6.67 (s, 1H), 6.66 (d, *J* = 9.0 Hz, 2H), 6.49 (d, *J* = 9.0 Hz, 2H), 5.64 (d, *J* = 15.0 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.78 (s, 6H), 3.72 (s, 3H), 3.65 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.75, 158.82, 158.59, 158.49, 158.32, 151.61, 147.35, 139.57, 137.01, 133.57, 132.34, 132.05, 131.64, 131.56, 131.22, 130.97, 130.87, 129.54, 120.44, 113.67, 113.58, 112.86, 59.98, 55.21, 55.17, 55.03, 54.94, 14.18. IR (KBr): 1705, 1604, 1507, 1290, 1248, 1174, 1033, 833 cm^{-1}. HRMS (EI) calcd for $C_{37}H_{36}O_6$ ($[M]^+$): 576.2512. Found: 576.2523.

Ethyl (2*E*,4*Z*,6*E*)-4,5,6,7-tetrakis(4-fluorophenyl)-2,4,6-heptatrienoate (4ag).



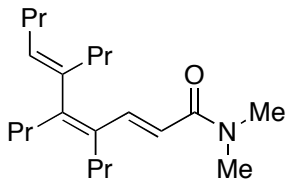
White powder, mp. 156–158 °C (hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, J = 15.5 Hz, 1H), 7.15 (m, 2H), 7.05 (m, 4H), 6.92 (m, 6H), 6.83 (m, 2H), 6.80 (s, 1H), 6.67 (m, 2H), 5.66 (d, J = 15.5 Hz, 1H), 4.13 (q, J = 7.0 Hz, 2H), 1.19 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.24, 162.17 (d, J_{CF} = 247 Hz), 162.04 (d, J_{CF} = 246 Hz), 161.95 (d, J_{CF} = 246 Hz), 161.16 (d, J_{CF} = 247 Hz), 150.41, 145.60, 139.90, 137.86, 134.54 (d, J_{CF} = 3.3 Hz), 134.38 (d, J_{CF} = 3.3 Hz), 133.99, 133.85 (d, J_{CF} = 3.4 Hz), 132.70 (d, J_{CF} = 8.1 Hz), 132.11 (d, J_{CF} = 8.5 Hz), 131.38 (d, J_{CF} = 7.8 Hz), 131.26 (d, J_{CF} = 8.1 Hz), 122.31, 115.58 (d, J_{CF} = 21.5 Hz), 115.36 (d, J_{CF} = 21.4 Hz), 115.30 (d, J_{CF} = 21.5 Hz), 114.76 (d, J_{CF} = 21.5 Hz), 60.31, 14.13. IR (KBr): 1714, 1600, 1502, 1285, 1225, 831 cm^{-1}. HRMS (EI) calcd for $C_{33}H_{24}F_4O_2$ ([M]$^+$): 528.1712. Found: 528.1711.

Ethyl (2*E*,4*E*,6*E*)-4,6-dimethyl-5,7-diphenyl-2,4,6-heptatrienoate (4ah, major).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 15.5 Hz, 1H), 7.37 (m, 6H), 7.27 (m, 4H), 6.49 (s, 1H), 6.00 (d, J = 15.5 Hz, 1H), 4.21 (q, J = 7.5 Hz, 2H), 1.88 (s, 3H), 1.78 (s, 3H), 1.29 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.71, 153.74, 145.80, 139.67, 137.79, 137.38, 132.65, 129.38, 129.11, 128.87, 128.19, 128.14, 127.65, 126.81, 117.71, 60.14, 18.16, 16.32, 14.30. IR (neat): 2980, 1717, 1615, 1288, 1179, 1037, 857, 753, 701 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{24}O_2$ ([M]$^+$): 332.1776. Found: 332.1771.

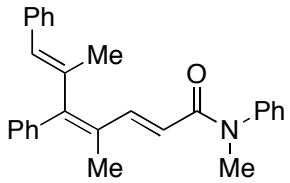
(2*E*,4*Z*,6*E*)-*N*,*N*-Dimethyl-4,5,6-tripropyl-2,4,6-decatrienamide (6aa).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 15.0 Hz, 1H), 6.17 (d, J = 15.0 Hz, 1H), 5.04 (t, J = 7.5 Hz, 1H), 3.08 (s, 3H), 3.00 (s, 3H), 2.27 (m, 2H), 2.18 (t, J = 8.0 Hz, 2H), 2.10 (m, 4H), 1.46–1.28 (m,

8H), 0.96–0.87 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.01, 152.33, 143.52, 138.64, 132.40, 131.76, 113.97, 37.34, 35.72, 33.24, 31.83, 30.20, 30.08, 22.99, 22.40, 21.80, 21.35, 14.52, 14.40, 14.18, 13.96. IR (neat): 2957, 2872, 1643, 1595, 1458, 1389, 1265, 1130, 990, 899, 844, 735 cm^{-1}. HRMS (EI) calcd for $C_{21}H_{37}NO$ ([M]$^+$): 319.2875. Found: 319.2873.

(2*E*,4*E*,6*E*)-*N*,4,6-trimethyl-*N*,5,7-triphenyl-2,4,6-heptatrienamide (6bh).



White powder, mp. 142–144 ºC (hexane-CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, *J* = 15.5 Hz, 1H), 7.42-7.21 (m, 15H), 6.48 (s, 1H), 5.93 (d, *J* = 15.5 Hz, 1H), 3.37 (s, 3H), 1.78 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.99, 152.37, 144.03, 142.84, 140.13, 137.94, 137.56, 132.26, 129.44, 129.39, 129.26, 129.02, 128.15, 128.04, 127.37, 127.29, 126.67, 118.58, 37.43, 18.23, 16.24. IR (KBr): 1642, 1597, 1495, 1417, 1374, 1283, 1125, 773, 750, 698 cm^{-1}. HRMS (EI) calcd for $C_{28}H_{27}NO$ ([M]$^+$): 393.2093. Found: 393.2088.

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Chapter 2

Nickel-Catalyzed Codimerization of Acrylic Acid Derivatives with Alkynes

By using hydrogen bonding, nickel-catalyzed codimerization of an acrylic acid derivative with an alkyne to produce a 1,3-diene proceeded over cotrimerization. Codimerization of a secondary acrylamide with an alkyne proceeded in the presence of nickel catalyst. Isolated nickel complex indicated that hydrogen bonding between two acrylamides was essential for the reaction. Adding 2-aminopyridine, nickel(0) complex catalyzed codimerization of an acrylate with an alkyne to afford a corresponding 1,3-diene, which would be promoted by hydrogen bonding between the acrylate and the 2-aminopyridine.

Introduction

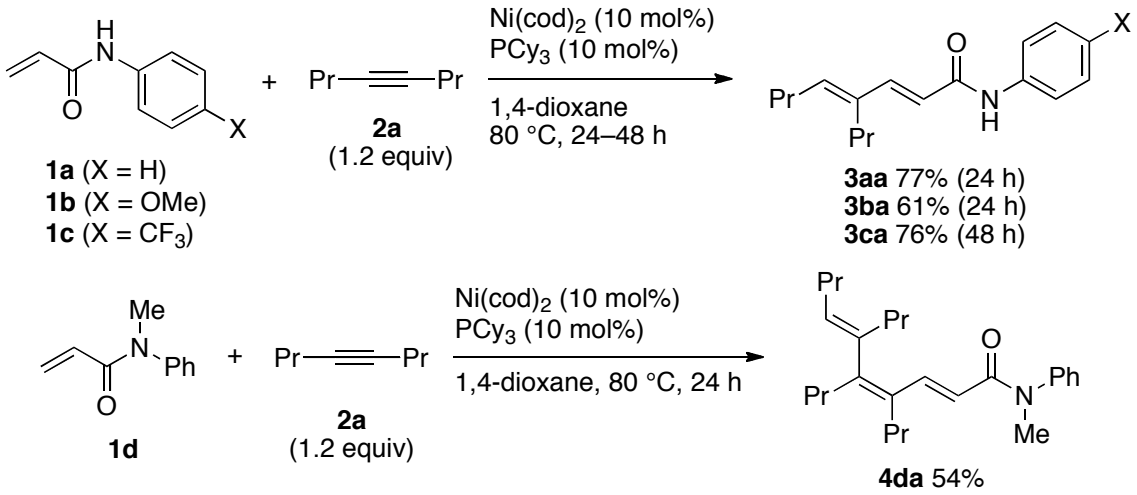
Transition-metal-catalyzed codimerization of alkenes and alkynes to afford 1,3-dienes is a straightforward method for construction of highly substituted conjugated dienes. Various catalytic systems have been reported, using ruthenium,[1] palladium,[2] rhodium[3] or cobalt complexes.[4] They have shown different chemo-, regio- and stereoselectivity depending on catalyst. In addition to them, in this Chapter, the author describes nickel-catalyzed reaction system. The reaction provides 1,3-dienes stereo- and regioselectively from internal alkyl-substituted alkynes, which have been difficult to react selectively.

In Chapter 1, the author described two types of cotrimerization of acrylates with alkynes catalyzed by nickel(0) complex. Acrylates reacted with two molecules of alkynes to provide 1,3,5-trienes when phosphine was used as a ligand.[5] In addition, the reaction of tertiary acrylamides with alkynes also proceeded under the same reaction condition. In the course of his study, he found that codimerization of a secondary acrylamide with an alkyne took place to afford a 1,3-diene, and that the proton on the nitrogen atom was essential for this reaction. Following the result, he anticipated that an additive bearing NH group would promote codimerization of an acrylate with an alkyne. Then, he examined the nickel-catalyzed reaction with addition of 2-aminopyridine, which afforded 1,3-dienes *via* codimerization.

Results and Discussion

First, the author examined the reaction of *N*-phenylacrylamide (**1a**) with 4-octyne (**2a**). As shown in Scheme 1, treatment of **1a** and **2a** in the presence of $Ni(cod)_2$ (10 mol%) and PCy_3 (10 mol%) in 1,4-dioxane at 80 °C for 24 h afforded conjugated diene **3aa** in 77% yield. Both electron-donating and -withdrawing group substituted derivatives **1b** and **1c** also gave corresponding dienes. It is noteworthy that formation of 1,3,5-triene *via* cotrimerization was not observed in those attempts.[5] On the other hand, *N*-methyl-*N*-phenylacrylamide (**1d**) reacted

with two molecules of **2a** under the same reaction condition to produce 1,3,5-triene **4da** without forming 1,3-diene.



Scheme 1. Nickel-catalyzed cooligomerization of *N*-arylacrylamide **1** with 4-octyne **2a**.

Treatment of *N*-phenylacrylamide (**1a**) with stoichiometric quantity of $Ni(cod)_2$ and PCy_3 gave nickel complex **5**.[6] Single-crystal X-ray analysis of **5** showed that two amides and one phosphine ligand are coordinated to the nickel in a trigonal planar arrangement (Figure 1). A short intermolecular N···O distance (2.816 Å) may indicate that two amides are intermolecular NH···O=C hydrogen-bonded.[7]

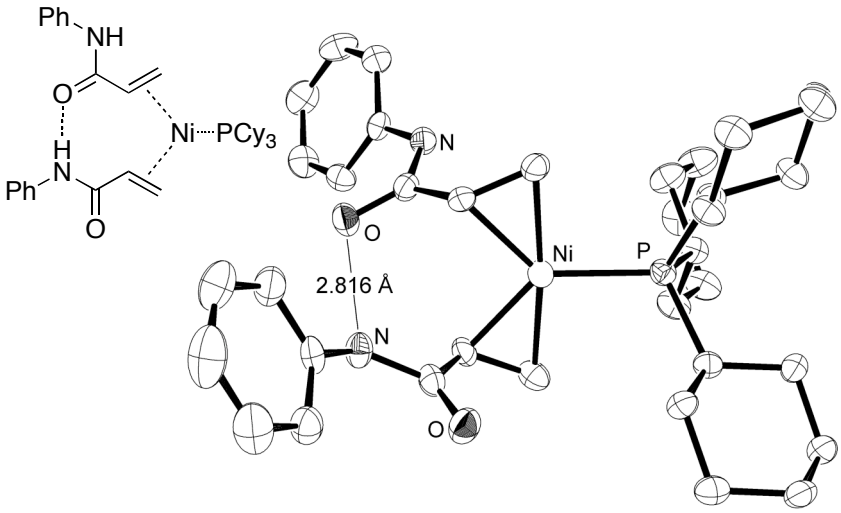
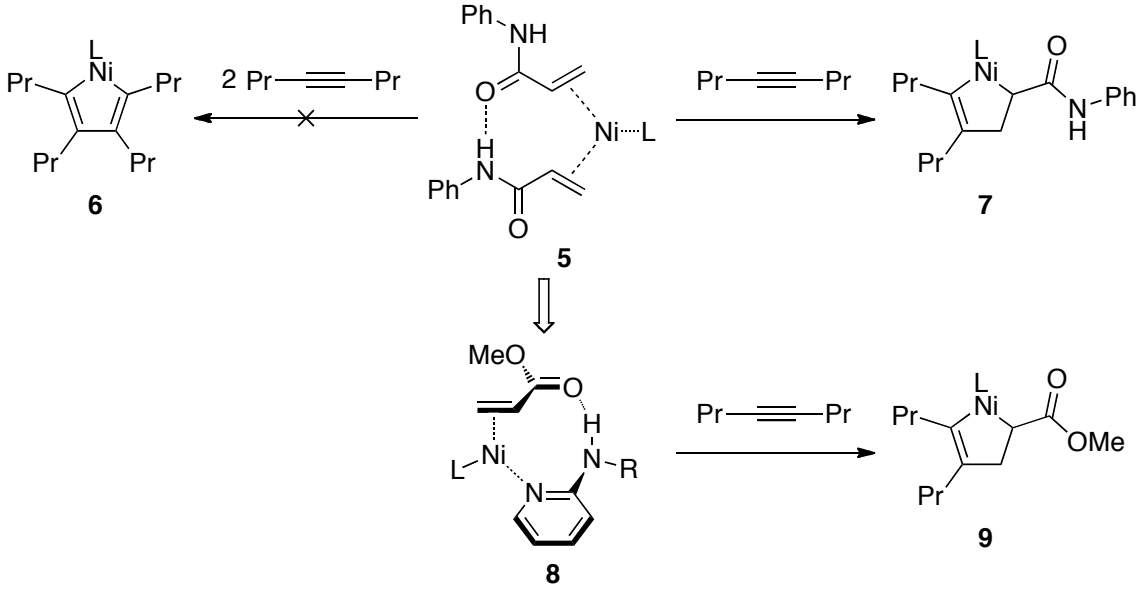


Figure 1. Structure and ORTEP drawing of nickel-amide complex **5**.

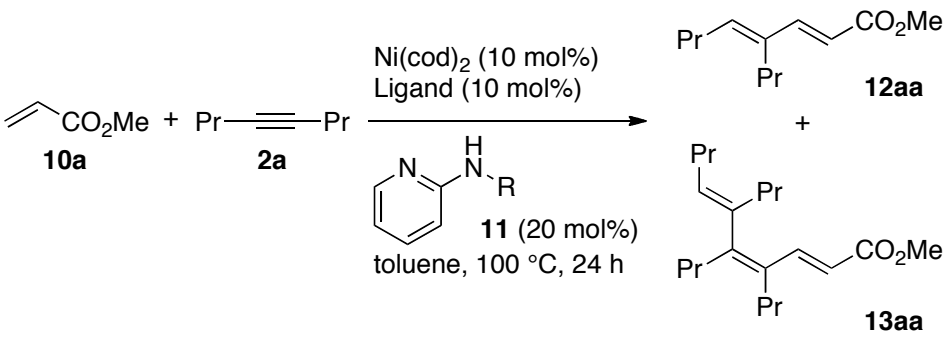
While the reaction to form conjugated trienes such as **4da** would be initiated by formation of nickelacyclopentadiene **6**, the codimerization probably proceeds *via* nickelacycle **7**. The author proposed that two acrylamides connected through a hydrogen bonding coordinated to nickel(0) as a diene-like ligand,[8] which inhibited forming nickelacycle **6** (Scheme 2). Furthermore, he expected that 2-aminopyridine would promote codimerization of an acrylate with an alkyne by constructing complex **8** as an analog of complex **5**.



Scheme 2. Effect of hydrogen bonding.

Indeed, the reaction of methyl acrylate (**10a**) with 4-octyne (**2a**) in the presence of $Ni(cod)_2$ (10 mol%), PCy_3 (10 mol%), and *N*-methyl-2-aminopyridine (**11a**; 20 mol%) in toluene at 100 °C for 24 h afforded codimer **12aa** in 56% yield, along with cotrimer **13aa** in 25% yield (Table 1, entry 1). In the absence of 2-aminopyridine, the reaction afforded **13aa** in 39% yield as a sole product (entry 2).[5] Encouraged by this result, he further examined ligands and additives to improve the selectivity of the reaction. Among phosphine ligands examined, PCy_3 gave the best yield of **12aa** (entries 1, 3 and 4). It was found that *N*-phenyl-2-aminopyridine (**11b**) was effective for the codimerization (entry 5). Almost same results were obtained when trifluoromethyl-, methoxy-, or methyl-substituted derivative was employed as an additive (entries

Table 1. Optimization of reaction conditions[a]



Entry	R (**11**)	Ligand	Yield of **12aa**[b]/**13aa**[c] [%]
1	Me (**11a**)	PCy_3	56/25
2	—[d]	PCy_3	<5/39
3	Me (**11a**)	PBu_3	42/36
4	Me (**11a**)	PPh_3	52/27
5	Ph (**11b**)	PCy_3	95/<5
6	3-$CF_3C_6H_4$ (**11c**)	PCy_3	95/<5
7	4-$MeOC_6H_4$ (**11d**)	PCy_3	91/<5
8	2-MeC_6H_4 (**11e**)	PCy_3	91/<5

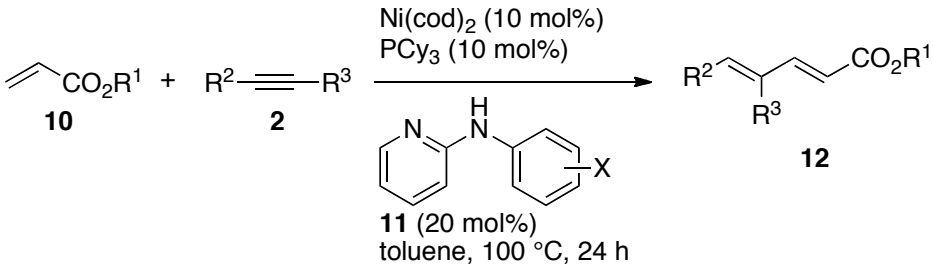
[a] Reactions were carried out using $Ni(cod)_2$ (10 mol%), ligand (10 mol%), 2-aminopyridine **11** (20 mol%), methyl acrylate (**10a**; 0.60 mmol, 1.2 equiv) and 4-octyne (**2a**; 0.50 mmol) in 5 mL of toluene at 100 °C for 24 h. [b] NMR yields based on **2a** (0.50 mmol). [c] NMR yields based on **2a** (0.25 mmol). [d] The reaction was carried out without adding 2-aminopyridine.

6–8).

The scope of the reaction of various acrylates with alkynes is summarized in Table 2. In the presence of nickel catalyst and 2-aminopyridine, *tert*-butyl acrylate (**10b**) also provided 1,3-diene **12ba** in 92% yield (entry 2). The reaction with unsymmetrical alkynes, such as 2-octyne (**2c**) and 4-methyl-2-pentyne (**2d**), gave the corresponding codimer **12ac** and **12ad** consisting of regioisomers in 5/1 and 10/1 ratio, respectively (entries 4 and 5). The

codimerization reaction is also compatible with aryl-substituted alkynes and afforded corresponding 1,3-dienes in good yield with excellent regioselectivities (entries 6–8). Cyclopropyl-substituted alkyne **2h** also reacted with **10a** to furnish 1,3-diene **12ah** in 53% yield regioselectively (entry 9). However, terminal alkynes, such as 1-octyne and phenylacetylene, failed to participate in the reaction.

Table 2. Codimerization of acrylate **10** with alkyne **2**[a]

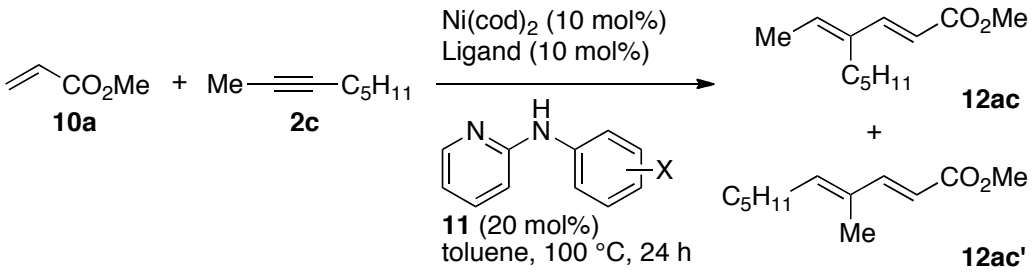


Entry	**10**	R^1 (equiv.)	**2**	R^2	R^3	**11**	X	**12**	Yield [%][b]
1	**10a**	Me (1.2)	**2a**	Pr	Pr	**11b**	H	**12aa**	95
2	**10b**	*t*Bu (1.2)	**2a**	Pr	Pr	**11b**	H	**12ba**	92
3	**10a**	Me (1.2)	**2b**	C_5H_{11}	C_5H_{11}	**11b**	H	**12ab**	90
4	**10a**	Me (1.2)	**2c**	Me	C_5H_{11}	**11e**	2-Me	**12ac**	79 (5/1)[c]
5	**10a**	Me (1.2)	**2d**	Me	*i*Pr	**11e**	2-Me	**12ad**	69 (10/1)[c]
6	**10a**	Me (2.0)	**2e**	Ph	Pr	**11c**	3-CF_3	**12ae**	62
7	**10a**	Me (2.0)	**2f**	4-$MeOC_6H_4$	C_5H_{11}	**11c**	3-CF_3	**12af**	87
8	**10a**	Me (2.0)	**2g**	4-FC_6H_4	C_5H_{11}	**11c**	3-CF_3	**12ag**	67
9	**10a**	Me (2.0)	**2h**	Ph	Cyclopropyl	**11c**	3-CF_3	**12ah**	53

[a] Reactions were carried out using $Ni(cod)_2$ (10 mol%), PCy_3 (10 mol%), **11** (20 mol%), **10** (0.60–1.0 mmol, 1.2–2.0 equiv) and **2** (0.50 mmol) in 5 mL of toluene at 100 °C for 24 h. [b] Yield of the isolated product. [c] Ratio of regioisomers.

It should be noted that 2-aminopyrideines have less effects on the regioselectivity of the reaction. The reaction of **10a** with **2c** in the presence of various derivatives of aminopyridine was examined, and it was found that the reaction afforded 1,3-diene **12ac** consisting of regioisomers in 5/1 ratio independent of aminopyridines (Table 3, entries 1–4). The phosphine ligands have more influence on the regioselectivity of the reaction (entry 5). The result might indicate that 2-aminopyridine has effect not on forming intermediate **9** but on forming **8** to discourage construction of **6** (Scheme 2). The regioselectivity is derived from steric repulsion between a bulkier substituent of the alkyne and the phosphine ligand when both substituents of the unsymmetrical alkyne are alkyl group.

Table 3. Regioselectivity of the codimerization of **10a** with **2c**[a]



Entry	Ligand	X (**11**)	Yield [%][b]	Ratio of **12ac**/**12ac'**
1	PCy_3	H (**11b**)	76	5/1
2	PCy_3	3-CF_3 (**11c**)	76	5/1
3	PCy_3	4-OMe (**11d**)	73	5/1
4	PCy_3	2-Me (**11e**)	79	5/1
5	PPh_3	H (**11b**)	40	3/2

[a] Reactions were carried out using $Ni(cod)_2$ (10 mol%), ligand (10 mol%), 2-aminopyridine **11** (20 mol%), methyl acrylate (**10a**; 0.60 mmol, 1.2 equiv) and 2-octyne (**2c**; 0.50 mmol) in 5 mL of toluene at 100 °C for 24 h. [b] Yield of the isolated product.

Conclusion

The author developed a new nickel-catalyzed codimerization of an acrylic acid derivative with an alkyne to provide a 1,3-diene. Although tertiary acrylamides gave 1,3,5-trienes *via* cotrimerization with alkynes, secondary acrylamides gave 1,3-dienes *via* codimerization. Codimerization between an acrylate with an alkyne proceeded with addition of 2-aminopyridine. In the absence of 2-aminopyridine, 1,3,5-trienes arising from cotrimerization were solely obtained. Hydrogen bonding between the hydrogen atom on the nitrogen and the oxygen atom of the carbonyl group would promote the oxidative addition of an acrylic acid derivative and an alkyne with nickel(0) over formation of nickelacyclopentadiene **6** from two alkynes.

Experimental Section

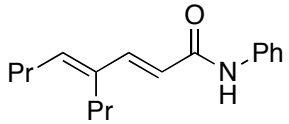
Chemicals. Acrylamide **1a–d** were prepared by Schotten–Baumann reaction of acryloyl chloride with corresponding aniline derivatives. Alkyne **2f–h** were prepared by Sonogashira cross-coupling reaction of 1-heptyne or ethynylcyclopropane with corresponding aryliodides. 2-Aminopyridine derivatives **11b–e** were prepared according to the literature.[9]

Experimental procedure for the nickel-catalyzed codimerization or cotrimerization of acrylamides with alkynes

General procedure. The reaction was performed in a 5 mL sealed vessel equipped with a Teflon-coated magnetic stirrer tip. An acrylamide (0.50 mmol) and an alkyne (0.60 mmol) were added to a solution of bis(1,5-cyclooctadiene)nickel (14 mg, 0.050 mmol) and tricyclohexyl-phosphine (14 mg, 0.050 mmol) in 1,4-dioxane (5 mL) in a dry box. The VIAL was taken outside the dry box and heated at 80 ºC for 24 h. The resulting reaction mixture was cooled to ambient temperature and filtered through a silica gel pad, concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 10:1) to give the corresponding conjugated diene or triene.

Characterization data

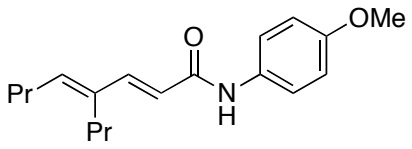
(2*E*,4*E*)-*N*-Phenyl-4-propyl-2,4-octadienamide (3aa).



White powder, mp. 107–108 ºC (CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.5 Hz, 2H), 7.46 (br, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 15.5 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 1H), 5.92 (d, *J* = 15.5 Hz, 1H), 5.87 (t, *J* = 7.5 Hz, 1H), 2.23 (t, *J* = 8.0 Hz, 2H), 2.16 (td, *J* = 7.5, 7.5 Hz, 2H), 1.44 (m, 4H), 0.93 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.89, 146.64, 142.09, 138.29, 137.04, 128.96, 124.07, 119.82, 117.57, 30.79, 28.80, 22.44, 21.96, 14.20, 13.87. IR (KBr): 3254, 2959, 2870, 1655, 1599, 1541,

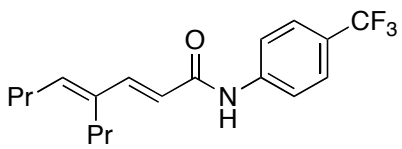
1499, 1441, 1339, 1246, 1182, 1087, 901, 866, 754, 690 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{23}NO$ ($[M]^+$): 257.1780. Found: 257.1786. Anal calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.42; H, 9.13; N, 5.43.

(2*E*,4*E*)-*N*-(4-Methoxyphenyl)-4-propyl-2,4-octadienamide (3ba).



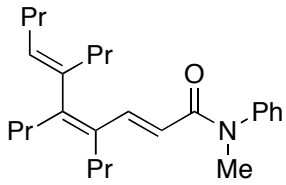
Pale yellow powder, mp. 69–70 ºC (CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, *J* = 9.0 Hz, 2H), 7.31 (br, 1H), 7.27 (d, *J* = 15.5 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.89 (d, *J* = 15.5 Hz, 1H), 5.87 (t, *J* = 7.5 Hz, 1H), 3.79 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 2.16 (td, *J* = 7.5, 7.5 Hz, 2H), 1.44 (m, 4H), 0.93 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.66, 156.25, 146.19, 141.80, 137.04, 131.45, 121.52, 117.64, 114.14, 55.46, 30.77, 28.80, 22.46, 21.97, 14.22, 13.88. IR (KBr): 3287, 2957, 2870, 1651, 1616, 1537, 1514, 1466, 1408, 1348, 1302, 1252, 1180, 1171, 1040, 976, 824, 750 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{25}NO_2$ ($[M]^+$): 287.1885. Found: 287.1882. Anal calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.08; H, 8.91; N, 4.87.

(2*E*,4*E*)-4-Propyl-*N*-(4-(trifluoromethyl)phenyl)-2,4-octadienamide (3ca).



White powder, mp. 70–72 ºC (CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.43 (br, 1H), 7.33 (d, *J* = 15.5 Hz, 1H), 5.92 (t, *J* = 7.5 Hz, 1H), 5.90 (d, *J* = 15.5 Hz, 1H), 2.24 (t, *J* = 8.0 Hz, 2H), 2.18 (td, *J* = 7.5, 7.5 Hz, 2H), 1.45 (m, 4H), 0.94 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.48, 147.62, 143.07, 141.46, 136.99, 126.16 (q, J_{CF} = 3.38 Hz), 125.74 (q, J_{CF} = 33.0 Hz), 124.10 (q, J_{CF} = 270 Hz), 119.46, 117.08, 30.81, 28.71, 22.36, 21.90, 14.10, 13.81. IR (KBr): 3339, 2961, 2872, 1665, 1620, 1533, 1406, 1343, 1157, 1115, 1067, 968, 831, 648 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{22}F_3NO$ ($[M]^+$): 325.1653. Found: 325.1655. Anal calcd for $C_{18}H_{22}F_3NO$: C, 66.45; H, 6.82; N, 4.30. Found: C, 66.70; H, 7.05; N, 4.22.

(2*E*,4*Z*,6*E*)-*N*-Methyl-*N*-phenyl-4,5,6-tripropyldeca-2,4,6-trienamide (4da).



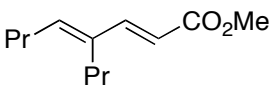
Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 15.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 2H), 5.66 (d, *J* = 15.5 Hz, 1H), 5.03 (t, *J* = 7.5 Hz, 1H), 3.35 (s, 3H), 2.12 (m, 6H), 1.94 (t, *J* = 7.5 Hz, 2H), 1.46 (m, 2H), 1.38 (m, 4H), 1.18 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.85 (t, *J* = 7.5 Hz, 3H), 0.67 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.37, 152.32, 144.30, 142.75, 138.69, 132.63, 131.78, 129.29, 127.39, 127.07, 115.86, 37.12, 33.26, 31.87, 30.16, 30.14, 23.03, 22.20, 21.81, 21.37, 14.52, 14.13, 14.06, 13.99. IR (neat): 2958, 2871, 1657, 1596, 1496, 1362, 1289, 1122, 990, 898, 857, 772, 700 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{39}NO$ ($[M]^+$): 381.3032. Found: 381.3031.

Experimental procedure for the nickel-catalyzed codimerization of acrylates with alkynes

General procedure. The reaction was performed in a 5 mL sealed vessel equipped with a Teflon-coated magnetic stirrer tip. An acrylates (0.60 mmol) and an alkyne (0.50 mmol) were added to a solution of bis(1,5-cyclooctadiene)nickel (14 mg, 0.050 mmol), tricyclohexyl-phosphine (14 mg, 0.050 mmol) and *N*-phenyl-2-aminopyridine (17 mg, 0.10 mmol) in toluene (5 mL) in a dry box. The VIAL was taken outside the dry box and heated at 100 ºC for 24 h. The reaction mixture was poured into 0.5 M HCl aq. (30 mL) and the mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (eluted by hexane/ethyl acetate = 40:1) to give the corresponding conjugated diene.

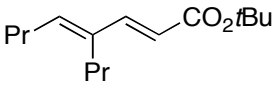
Characterization data

Methyl (2*E*,4*E*)-4-propyl-2,4-octadienoate (12aa).



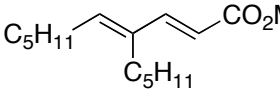
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 15.5 Hz, 1H), 5.88 (t, *J* = 7.5 Hz, 1H), 5.80 (d, *J* = 15.5 Hz, 1H), 3.75 (s, 3H), 2.21 (t, *J* = 9.5 Hz, 2H), 2.16 (td, *J* = 7.5, 7.5 Hz, 2H), 1.43 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.15, 149.28, 142.78, 137.35, 114.58, 51.42, 30.79, 28.57, 22.41, 21.90, 14.19, 13.88. IR (neat): 2960, 2873, 1722, 1625, 1464, 1434, 1378, 1307, 1265, 1191, 1168, 1043, 985, 858 cm^{-1}. HRMS (EI) calcd for $C_{12}H_{20}O_2$ ([M]$^+$): 196.1463. Found: 196.1462. Anal calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.18; H, 10.51.

***tert*-Butyl (2*E*,4*E*)-4-propyl-2,4-octadienoate (12ba).**



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, *J* = 15.5 Hz, 1H), 5.83 (t, *J* = 7.0 Hz, 1H), 5.72 (d, *J* = 15.5 Hz, 1H), 2.20 (t, *J* = 8.0 Hz, 2H), 2.15 (td, *J* = 7.0, 7.0 Hz, 2H), 1.49 (s, 9H), 1.43 (m, 4H), 0.92 (t, *J* = 7.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.13, 147.96, 141.77, 137.38, 116.94, 79.93, 30.74, 28.65, 28.21, 22.47, 21.94, 14.20, 13.87. IR (neat): 2961, 2872, 1709, 1624, 1456, 1368, 1308, 1285, 1256, 1152, 1086, 984, 858 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{26}O_2$ ([M]$^+$): 238.1933. Found: 238.1935.

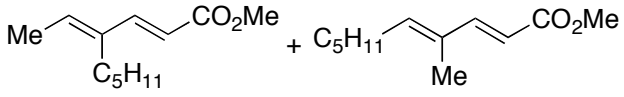
Methyl (2*E*,4*E*)-4-pentyl-2,4-decadienoate (12ab).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 16.0 Hz, 1H), 5.86 (t, *J* = 7.5 Hz, 1H), 5.80 (d, *J* = 16.0 Hz, 1H), 3.75 (s, 3H), 2.21 (t, *J* = 7.5 Hz, 2H), 2.17 (q, *J* = 7.5 Hz, 2H), 1.46–1.25 (m, 12H), 0.89 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.14, 149.27, 142.74, 137.52, 114.58, 51.37, 32.02, 31.57, 28.86, 28.71, 28.44, 26.62, 22.52, 22.50, 13.99, 13.96. IR (neat): 2956, 2860, 1722, 1622, 1467, 1435, 1379, 1308, 1268, 1166, 1096, 1044, 985, 851 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{28}O_2$ ([M]$^+$): 252. 2089. Found: 252.2084.

Methyl (2*E*,4*E*)-4-ethylidene-2-nonenoate (12ac) and

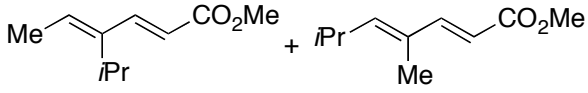
methyl (2*E*,4*E*)-4-methyl-2,4-decadienoate (12ac') (5:1 mixture).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, *J* = 15.5 Hz, 0.17H), 7.24 (d, *J* = 16.0 Hz, 0.83H), 5.96 (q, *J* = 7.0 Hz, 0.83H), 5.91 (t, *J* = 7.0 Hz, 0.17H), 5.80 (d, *J* = 16.0 Hz, 0.83H), 5.78 (d, *J* = 15.5 Hz, 0.17H), 3.75 (s, 3H), 2.23 (t, *J* = 8.0 Hz, 1.67H), 2.19 (td, *J* = 7.0 Hz, 7.0 Hz, 0.33H), 1.80 (d, *J* = 7.0 Hz, 2.5H), 1.76 (s, 0.50H), 1.45–1.27 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.17, 149.04, 138.63, 136.58, 114.43, 51.42, 31.95, 28.10, 26.21, 22.54, 14.48, 14.02. IR (neat): 2959, 2873, 1721, 1624, 1435, 1308, 1269, 1192, 1167, 984, 818 cm^{-1}. HRMS (EI) calcd for $C_{12}H_{20}O_2$ ([M]$^+$): 196.1463. Found: 196.1454.

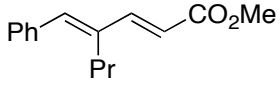
Methyl (2*E*,4*E*)-4-isopropyl-2,4-hexadienoate (12ad) and

methyl (2*E*,4*E*)-4,6-dimethyl-2,4-heptadienoate (12ad') (10:1 mixture).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 15.5 Hz, 0.09H), 7.24 (d, *J* = 16.0 Hz, 0.91H), 5.96 (d, *J* = 16.0 Hz, 0.91H), 5.89 (q, *J* = 7.0 Hz, 0.91H), 5.78 (d, *J* = 15.5 Hz, 0.09H), 5.71 (d, *J* = 9.0 Hz, 0.09H), 3.74 (s, 3H), 2.92 (sept, *J* = 7.0 Hz, 0.91H), 2.68 (dsept, *J* = 9.0, 7.0 Hz, 0.09H), 1.78 (d, *J* = 7.0 Hz, 0.91H), 1.77 (s, 0.09H), 1.11 (d, *J* = 7.0 Hz, 5.45H), 1.01 (d, *J* = 7.0 Hz, 0.55H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.91, 146.99, 143.05, 130.93, 115.98, 51.39, 27.23, 20.76, 14.10. IR (neat): 2963, 2874, 1722, 1621, 1435, 1300, 1270, 1173, 1045, 985, 865, 821 cm^{-1}. HRMS (EI) calcd for $C_{10}H_{16}O_2$ ([M]$^+$): 168.1150. Found: 168.1158.

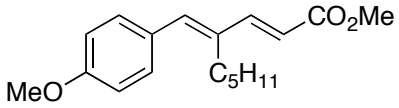
Methyl (2*E*,4*E*)-4-benzylidene-2-heptenoate (12ae).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 16.0 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.31 (m, 3H), 6.81 (s, 1H), 5.99 (d, *J* = 16.0 Hz, 1H), 3.79 (s, 3H), 2.45 (t, *J* = 8.0 Hz, 2H), 1.56 (m, 2H), 0.99 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.82, 149.44, 138.99, 138.83, 136.63, 129.04, 128.45, 127.78, 116.74, 51.54,

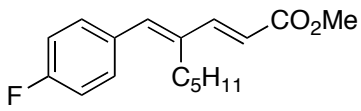
29.36, 22.18, 14.28. IR (neat): 2957, 2873, 1717, 1619, 1435, 1309, 1266, 1168, 1084, 1031, 983, 851, 696 cm^{-1}. HRMS (EI) calcd for $C_{15}H_{18}O_2$ ($[M]^+$): 230.1307. Found: 230.1301.

Methyl (2*E*,4*E*)-4-(4-methoxybenzylidene)-2-nonenoate (12af).



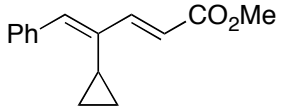
White solid, mp. 35–37 ºC (hexane-AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 15.5 Hz, 1H), 7.29 (d, J = 9.0 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 6.73 (s, 1H), 5.94 (d, J = 15.5 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 2.46 (t, J = 7.5 Hz, 2H), 1.56 (m, 2H), 1.37 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.98, 159.34, 149.98, 138.60, 137.44, 130.65, 129.24, 115.67, 113.98, 55.29, 51.47, 32.17, 28.38, 27.31, 22.44, 14.04. IR (neat): 2954, 2871, 1717, 1618, 1601, 1509, 1435, 1306, 1255, 1165, 1035, 982, 851, 824, 730 cm^{-1}. HRMS (EI) calcd for $C_{18}H_{24}O_3$ ($[M]^+$): 288.1725. Found: 288.1728. Anal calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.98; H, 8.68.

Methyl (2*E*,4*E*)-4-(4-fluorobenzylidene)-2-nonenoate (12ag).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 16.0 Hz, 1H), 7.29 (dd, J_{HH} = 9.0 Hz, J_{HF} = 5.0 Hz, 2H), 7.07 (dd, J_{HH} = 9.0 Hz, J_{HF} = 9.0 Hz, 2H), 6.75 (s, 1H), 5.98 (d, J = 16.0 Hz, 1H), 3.79 (s, 3H), 2.43 (t, J = 8.0 Hz, 2H), 1.53 (m, 2H), 1.34 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.76, 162.20 (d, J_{CF} = 247 Hz), 149.18, 139.04, 137.36, 132.75 (d, J_{CF} = 3.4 Hz), 130.75 (d, J_{CF} = 7.8 Hz), 116.89, 115.49 (d, J_{CF} = 21.5 Hz), 51.55, 32.08, 28.48, 27.23, 22.37, 13.98. IR(neat): 2954, 2872, 1706, 1622, 1598, 1506, 1435, 1312, 1269, 1235, 1167, 1091, 981, 855, 826, 728 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{21}FO_2$ ($[M]^+$): 276.1526. Found: 276.1521. Anal calcd for $C_{17}H_{21}FO_2$: C, 73.89; H, 7.66. Found: C, 73.63; H, 7.66.

Methyl (2*E*,4*E*)-4-cyclopropyl-5-phenyl-2,4-pentadienoate (12ah).



White powder, mp. 62–65 ºC (Et_2O). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, J = 7.5 Hz, 2H), 7.41 (d, J = 15.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H),

7.28 (t, J = 7.5 Hz, 1H), 6.84 (s, 1H), 6.36 (d, J = 15.5 Hz, 1H), 3.79 (s, 3H), 1.61 (m, 1H), 0.89 (m, 2H), 0.25 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.92, 149.56, 140.07, 138.53, 136.11, 130.06, 127.94, 127.89, 117.99, 51.47, 9.71, 8.89. IR (KBr): 3026, 2988, 2949, 1709, 1615, 1447, 1429, 1309, 1292, 1195, 1162, 1006, 857, 694 cm^{-1}. HRMS calcd for $C_{15}H_{16}O_2$ ($[M]^+$): 228.1150. Found: 228.1156. Anal calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.85; H, 7.20.

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Chapter 3

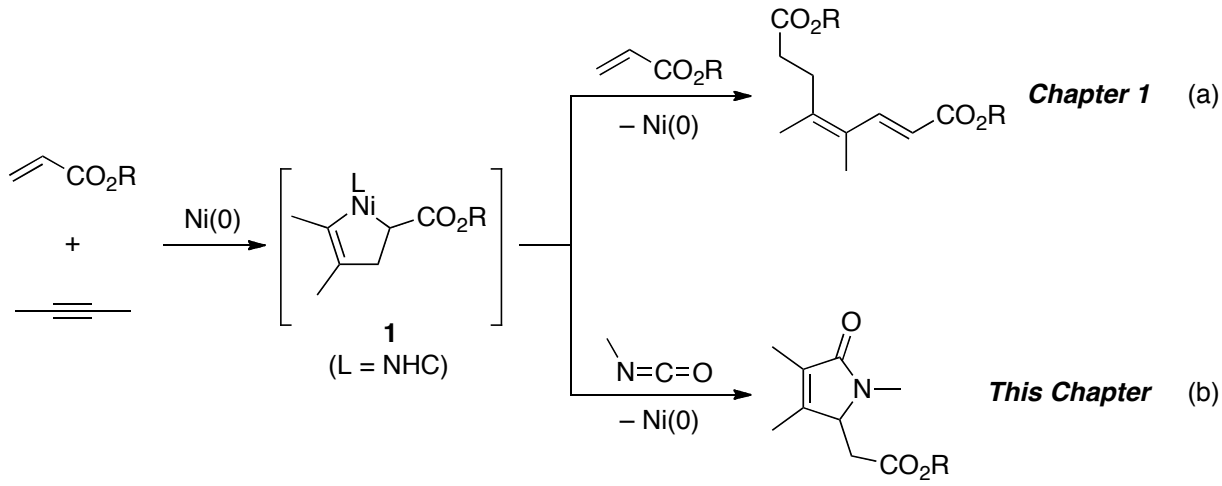
Nickel-Catalyzed [2+2+1] Cycloaddition of Acrylates, Alkynes and Isocyanates

[2+2+1] Cycloaddition of acrylates with alkynes and isocyanates proceeded in the presence of nickel catalyst to afford γ-butyrolactams. Nicklacyclopentene arising from oxidative cyclization of an acrylate and an alkyne with nickel(0) would be an intermediate of the reaction. Although the mixture of such compounds could give various products, *N*-heterocyclic carbene ligand promoted the selective formation of the nickelacycle, which sequentially reacted with isocyanate.

Introduction

Transition-metal-catalyzed cycloaddition reactions are the most powerful methodologies for the construction of structurally diverse carbo- or heterocyclic compounds from readily accessible starting materials.[1,2] Hetero-Pauson-Khand reaction, which is formal [2+2+1] cycloaddition promoted by transition-metal complex, represents a facile synthetic access to γ-butyrolactams[3] or -lactones,[4] and has been a research subject of great interest. On the other hand, another route to access such heterocycles would be needed to circumvent using stoichiometric amount of metal carbonyl complexes or poisonous carbon monoxide.[5]

In Chapter 1, the author described nickel-catalyzed cotrimerization of acrylates with alkynes. When *N*-heterocyclic carbene (NHC) was used as a ligand, a 1,3-diene was furnished *via* intermediate **1** (Scheme 1a). On the basis of the result, he anticipated that nickelacycle **1** would react with isocyanate to afford a heterocyclic compound.[6,7] According to this working hypothesis, he attempted the reaction of acrylates and alkynes with isocyanates in the presence of nickel catalyst, and found that the reaction afforded γ-butyrolactams through [2+2+1] cycloaddition (Scheme 1b).

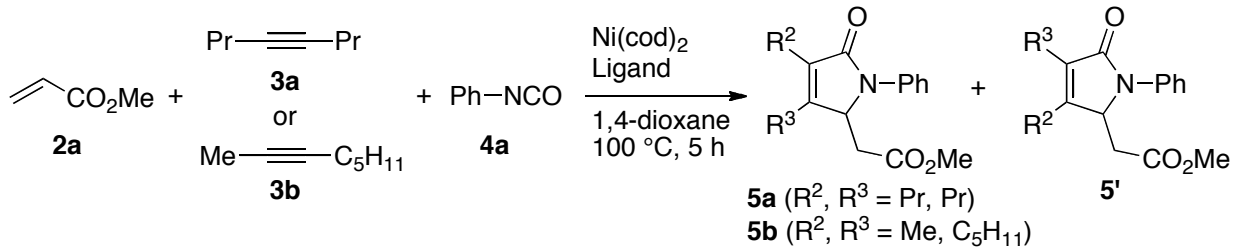


Scheme 1. Formation of nickelacycle **1** and reaction with acrylate or isocyanate.

Results and Discussion

First, the author examined the reaction of methyl acrylate (**2a**), 4-octyne (**3a**; 2 equiv), and phenyl isocyanate (**4a**) in the presence of $Ni(cod)_2$ (5 mol%) and IPr (10 mol%) in 1,4-dioxane at 100 °C for 5 h. The reaction afforded γ-butyrolactam **5a** in 37% yield, along with hydantoin produced by cycloaddition of an acrylate with two isocyanates in 42% yield (Table 1, entry 1).[6i]

Table 1. Screening of reaction conditions



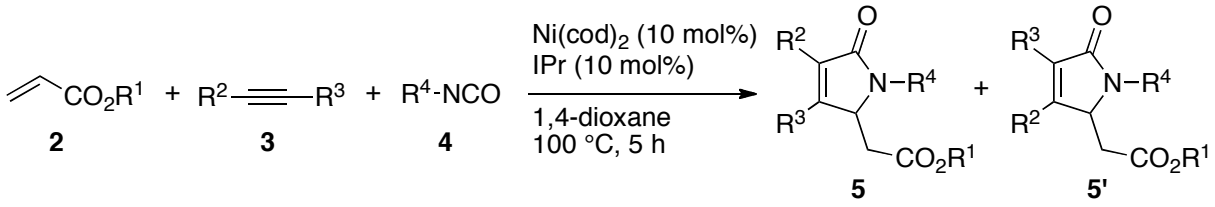
Entry	Ni [mol%]	Ligand	[mol%]	Alkyne	Equiv of **2a**:**3**:**4a**	Yield [%][a]	Ratio of **5**/**5'**
1	5	IPr	10	**3a**	1:2:1	37	—
2	5	IMes	10	**3a**	1:2:1	47	—
3	5	IMes	10	**3a**	2:1:1	29[b]	—
4	5	IMes	10	**3a**	1:1:2	27	—
5	5	IMes	10	**3a**	1:4:1	48	—
6	5	IPr	10	**3a**	1:4:1	44	—
7	5	SIMes	10	**3a**	1:4:1	33	—
8	5	PPh_3	10	**3a**	1:4:1	<1	—
9	5	PCy_3	10	**3a**	1:4:1	<1	—
10	5	IMes	5	**3a**	1:4:1	48	—
11	10	IMes	10	**3a**	1:4:1	66	—
12	10	IMes	10	**3b**	1:4:1	48	1/1
13	10	IPr	10	**3b**	1:4:1	76	5/1

[a] NMR yield based on acrylate **2a** (0.50 mmol). [b] NMR yield based on alkyne **3a** (0.50 mmol).

IMes gave cycloadduct **5a** in better yield (entry 2), and it was found that the ratio of **2a**/**3a**/**4a** with 1:4:1 gave the highest yield of **5a** without formation of hydantoin (entries 3–5). Phosphine ligands did not afford **5a** but gave 2-pyridone as a major product *via* cycloaddition of two alkynes with an isocyanate (entries 8 and 9).[6a–e] The ratio of ligand to nickel did not affect the yield of **5a** (entry 10), and increasing the amount of catalyst improved the yield to 66% (entry 11). Then, the reaction employing 2-octyne (**3b**) was examined, but two regioisomers **5b** and **5b'** were obtained in low selectivity (entry 12). In this case, employing IPr instead of IMes improved both the yield and the selectivity of **5b** (entry 13).

The author next investigated the scope of the reaction (Table 2). The reaction using 4-methyl-2-pentyne (**3c**) afforded corresponding γ-butyrolactam **5c** in 72% yield with a regioselectivity ratio of 7/1 (entry 1). Unsymmetrical alkynes possessing ether group **3d** and **3e** gave the products consisting of regioisomers in 1/1 and 2/1 ratio, respectively (entries 2 and 3). The cycloaddition was also compatible with aryl-substituted alkyne **3f** and provided cycloadduct **5f** in 56% yield with a regioselectivity ratio of 2/1 (entry 4). Terminal alkynes, such as 1-octyne and phenylacetylene, failed to participate in the reaction. The scope of the [2+2+1] cycloaddition was also explored by using various isocyanates. Either electron-donating or -withdrawing substituents on phenyl isocyanate tolerated the reaction conditions to afford corresponding cycloadducts in moderate yield (entries 5–9). However, alkyl isocyanates, such as propyl isocyanate (**4e**) and cyclohexyl isocyanate (**4f**), reacted with **2a** and **3a** to provide γ-butyrolactam in poor yield (entries 10 and 11). It should be noted that isocyanates have no effect on the regioselectivity of the reaction. The reaction using ethyl acrylate (**2b**) or *tert*-butyl acrylate (**2c**) afforded γ-butyrolactam in lower yield but with better regioselectivity (entries 12 and 13). Therefore, the steric environment of the acrylate **2** and alkyne **3** dictated the regioselectivity of the reaction.

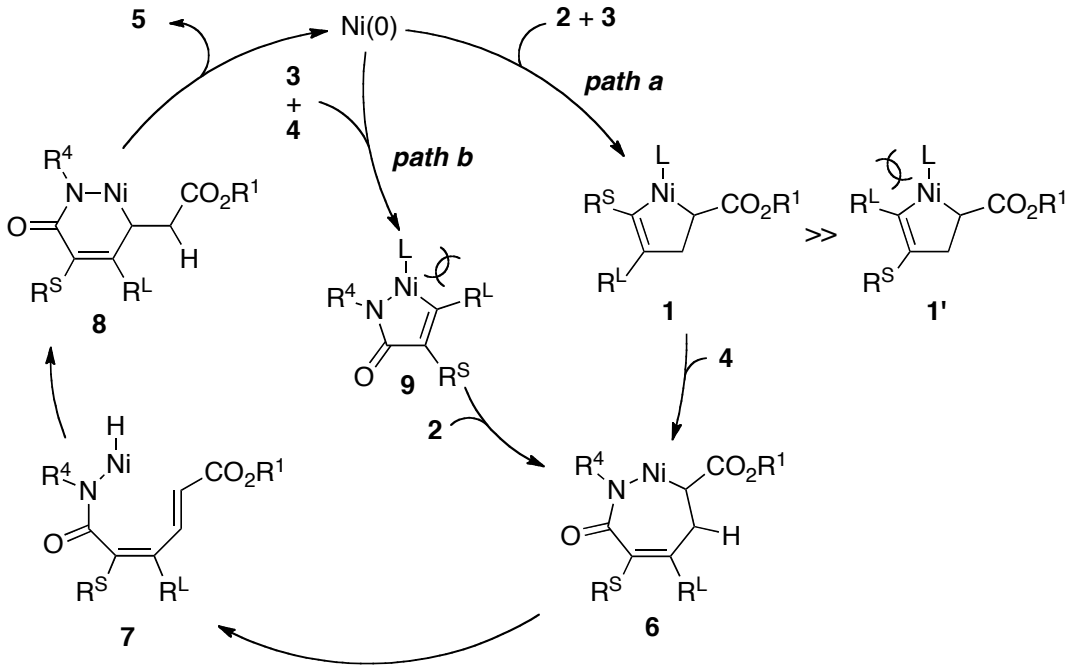
Table 2. Scope of nickel-catalyzed [2+2+1] cycloaddition[a]



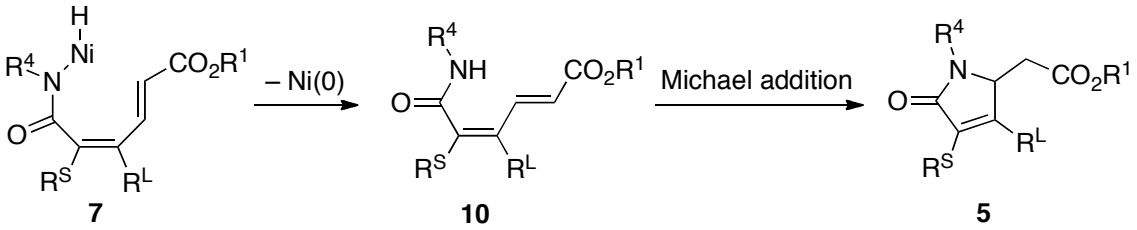
Entry	**2**	R^1	**3**	R^2	R^3	**4**	R^4	**5**	Yield [%][b]	Ratio of **5**/**5'**
1	**2a**	Me	**3c**	Me	*i*Pr	**4a**	Ph	**5c**	72	7/1
2	**2a**	Me	**3d**	CH_2OMe	Pr	**4a**	Ph	**5d**	45	1/1
3	**2a**	Me	**3e**	$(CH_2)_2OMe$	Pr	**4a**	Ph	**5e**	69	2/1
4	**2a**	Me	**3f**	Me	Ph	**4a**	Ph	**5f**	56	2/1
5	**2a**	Me	**3b**	Me	C_5H_{11}	**4b**	4-$MeOC_6H_4$	**5g**	56	5/1
6	**2a**	Me	**3b**	Me	C_5H_{11}	**4c**	4-$CF_3C_6H_4$	**5h**	61	5/1
7	**2a**	Me	**3b**	Me	C_5H_{11}	**4d**	4-FC_6H_4	**5i**	66	5/1
8	**2a**	Me	**3c**	Me	*i*Pr	**4b**	4-$MeOC_6H_4$	**5j**	54	7/1
9	**2a**	Me	**3c**	Me	*i*Pr	**4d**	4-FC_6H_4	**5k**	60	7/1
10	**2a**	Me	**3b**	Me	C_5H_{11}	**4e**	Pr	**5m**	29	5/1
11	**2a**	Me	**3b**	Me	C_5H_{11}	**4f**	Cy	**5n**	24	5/1
12	**2b**	Et	**3b**	Me	C_5H_{11}	**4a**	Ph	**5o**	63	6/1
13	**2c**	*t*Bu	**3b**	Me	C_5H_{11}	**4a**	Ph	**5p**	28	10/1

[a] Reactions were carried out using $Ni(cod)_2$ (10 mol%), IPr (10 mol%), acrylate **2** (0.50 mmol), alkyne **3** (2.0 mmol, 4 equiv) and isocyanate **4** (0.50 mmol) in 2 mL of 1,4-dioxane at 100 °C for 5 h. [b] NMR yield.

A plausible reaction pathway to account for the formation of γ-butyrolactam **5** is outlined in Scheme 2. The catalytic cycle of the present reaction may consist of oxidative cyclization of an acrylate **2** and alkyne **3** with nickel(0) to provide nickelacyclopenetene **1** (Scheme 2, path a), in which the steric repulsive interaction is minimal between the bulkier R^L and the IPr ligand on the nickel. Then, subsequent insertion of isocyanate **4** takes place, to give intermediate **6**. β-Hydrogen elimination would give **7**, in which a C–C double bond inserts into the Ni–H bond to provide **8**. Following reductive elimination would give **5** and regenerate the nickel(0). Alternatively, reductive elimination from intermediate **7** followed by intramolecular Michael addition could give γ-butyrolactam **5** (Scheme 3),[6i,8] although corresponding intermediate **10** was not detected. Another mechanism involving the oxidative cyclization of alkyne **3** and isocyanate **4** with nickel(0) may not be ruled out (Scheme 2, path b).[6a–f] However, since isocyanates did not affect the regioselectivity in contrast to acrylates (Table 2, entries 7–13 versus entries 14 and 15), the mechanism *via* intermediate **1** (path a) may be more plausible. In addition, the reaction pathway through nickelacycle **9** would afford inverse regioisomer **5'** as a major isomer because of steric repulsion between R^L and the ligand on the nickel.[6f]



Scheme 2. Plausible reaction pathway.



7 10 5

Scheme 3. Alternative reaction pathway.

Conclusion

An unprecedented type of [2+2+1] cycloaddition of acrylates and alkynes with isocyanates was successfully demonstrated using a nickel catalyst. The key intermediate is a nickelacycle **1**, which would be formed *via* oxidative cyclization of an acrylate and an alkyne with nickel(0) when NHC was used as a ligand.

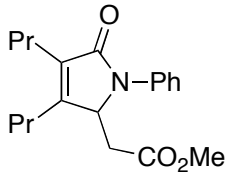
Experimental Section

Experimental procedure for nickel-catalyzed [2+2+1] cycloaddition of acrylates, alkynes, and isocyanates.

General procedure. The reaction was performed in a 15 mL sealed tube equipped with a Teflon-coated magnetic stirrer bar. An isocyanate (0.50 mmol), an alkyne (2.0 mmol) and an acrylate (0.50 mmol) were added to a solution of bis(1,5-cyclooctadiene)nickel (14 mg, 0.050 mmol) and IPr (19 mg, 0.050 mmol) in 1,4-dioxane (2 mL) in a dry box. The flask was taken outside the dry box and heated at 100 °C for 5 h under argon atmosphere. The resulting reaction mixture was cooled to ambient temperature and filtered through a silica gel pad, concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 3:1) to give the corresponding product.

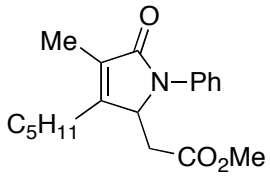
Characterization data

Methyl 2-(5-oxo-1-phenyl-3,4-dipropyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5a).



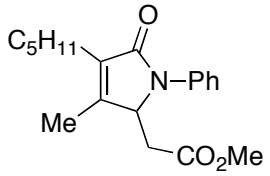
Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (m, 2H), 7.38 (m, 2H), 7.15 (m, 1H), 4.95 (dd, *J* = 4.5, 2.0 Hz, 1H), 3.55 (s, 3H), 2.64 (dd, *J* = 15.0, 8.0 Hz, 1H), 2.47 (m, 1H), 2.53 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.33–2.25 (m, 2H), 2.22 (m, 1H), 1.64 (m, 1H), 1.56–1.52 (m, 2H), 1.47 (m, 1H), 0.98 (t, *J* = 7.5 Hz, 3H), 0.94 (t, *J* = 7.5Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.0, 153.1, 136.7, 133.7, 128.9, 124.7, 122.4, 58.2, 51.7, 35.7, 28.4, 25.6, 22.0, 21.8, 14.1, 14.0. IR (neat): 2959, 2872, 1738, 1694, 1599, 1501, 1381, 757 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{26}NO_3$ ($[M+H]^+$): 316.1913. Found: 316.1908.

Methyl 2-(4-methyl-5-oxo-3-pentyl-1-phenyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5b).



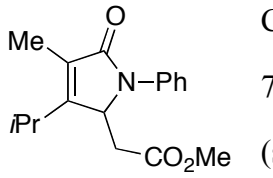
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (m, 2H), 7.39 (m, 2H), 7.17 (m, 1H), 4.97 (m, 1H), 3.56 (s, 3H), 2.63 (dd, *J* = 15.5, 4.5 Hz, 1H), 2.51 (m, 1H), 2.50 (dd, *J* = 16.0, 7.5 Hz, 1H), 2.24–2.18 (m, 1H), 1.87 (s, 3H), 1.62–1.43 (m, 2H), 1.38–1,27 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.5, 153.3, 136.7, 129.4, 129.0, 124.9, 122.6, 58.6, 51.9, 35.7, 31.7, 28.1, 26.5, 22.3, 13.9, 8.8. IR (neat): 2954, 2871, 1737, 1694, 1599, 1501, 1381, 760 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{26}NO_3$ ($[M+H]^+$): 316.1913. Found: 316.1909.

Methyl 2-(3-methyl-5-oxo-4-pentyl-1-phenyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5b').



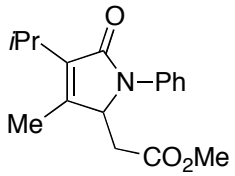
Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (m, 2H), 7.39 (m, 2H), 7.16 (m, 1H), 4.88 (m, 1H), 2.71 (dd, *J* = 15.5, 4.0 Hz, 1H), 2.50 (dd, *J* = 16.0, 7.5 Hz, 1H), 2.31 (t, *J* = 7.0 Hz, 2H), 2.00 (s, 3H), 1.50 (m, 2H), 1.36–1.28 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): d 170.6, 170.0, 148.9, 136.7, 133.9, 129.0, 124.8, 122.4, 60.0, 51.8, 35.6, 31.6, 28.0, 23.5, 22.4, 14.0, 12.1. IR (neat): 2954, 2858, 1738, 1687, 1598, 1394, 1121, 757 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{26}NO_3$ ($[M+H]^+$): 316.1913. Found: 316.1910.

Methyl 2-(3-isopropyl-4-methyl-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5c).



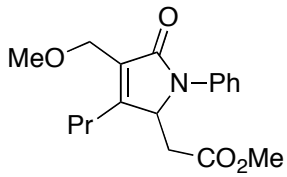
Colorless crystal, mp. 68–70 °C (CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (m, 2H), 7.38 (m, 2H), 7.16 (m, 1H), 4.95 (m, 1H), 3.50 (s, 3H), 2.76 (sept, *J* = 7.0 Hz, 1H), 2.65 (dd, *J* = 16.0, 5.5 Hz, 1H), 2.58 (dd, *J* = 16.0, 5.0 Hz, 1H), 1.94 (d, *J* = 1.0 Hz, 3H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.26 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.6, 157.3, 136.5, 128.9, 128.5, 125.0, 123.0, 59.0, 51.8, 35.7, 27.7, 21.3, 20.5, 9.4. IR (KBr): 2964, 2919, 2871, 1733, 1662, 1502, 1434, 1265, 760, 699 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{22}NO_3$ ($[M+H]^+$): 288.1600. Found: 288.1593.

Methyl 2-(4-isopropyl-3-methyl-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5c').



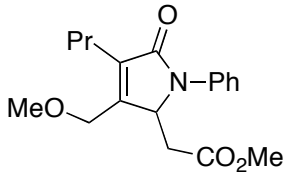
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (m, 2H), 7.38 (m, 2H), 7.16 (m, 1H), 4.81 (dd, *J* = 7.0, 4.0 Hz, 1H), 3.57 (s, 3H), 2.89 (sept, *J* = 7.0 Hz, 1H), 2.66 (dd, *J* = 15.0, 4.0 Hz, 1H), 2.51 (dd, *J* = 15.0, 7.0 Hz, 1H), 2.02 (d, *J* = 0.5 Hz, 3H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 169.4, 147.5, 137.9, 136.6, 128.9, 124.8, 122.5, 59.9, 51.8, 35.6, 25.1, 20.5, 20.3, 12.1. IR (neat): 2962, 2932, 1736, 1688, 1501, 1392, 757, 694 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{22}NO_3$ ($[M+H]^+$): 288.1600. Found: 288.1596.

Methyl 2-(4-(methoxymethyl)-5-oxo-1-phenyl-3-propyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5d).



Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (m, 2H), 7.38 (m, 2H), 7.18 (m, 1H), 5.03 (dd, *J* = 7.0, 4.5 Hz, 1H), 4.23 (d, *J* = 12.0 Hz, 1H), 4.20 (d, *J* = 12.0 Hz, 1H), 3.57 (s, 3H), 3.39 (s, 3H), 2.71 (m, 1H), 2.66 (dd, *J* = 15.5, 4.5 Hz, 1H), 2.56 (dd, *J* = 16.0, 7.0 Hz, 1H), 2.27 (m, 1H), 1.66 (m, 1H), 1.54 (m, 1H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 169.1, 159.0, 136.4, 130.0, 129.0, 125.1, 122.7, 63.5, 58.8, 58.5, 35.5, 28.6, 22.1, 14.1. IR (neat): 2960, 2874, 1738, 1687, 1598, 1386, 1096, 695 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{24}NO_4$ ($[M+H]^+$): 318.1705. Found: 318.1701.

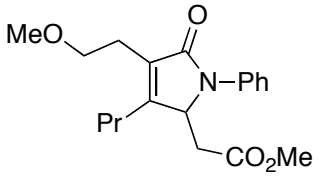
Methyl 2-(3-(methoxymethyl)-5-oxo-1-phenyl-4-propyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5d').



Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (m, 2H), 7.49 (m, 2H), 7.18 (m, 1H), 5.07 (dd, *J* = 3.5, 3.5 Hz, 1H), 4.33 (dd, *J* = 14.5, 13.0 Hz, 2H), 3.56 (s, 3H), 3.37 (s, 3H), 2.72 (dd, *J* = 15.0, 4.0 Hz, 1H), 2.62 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.40–2.26 (m, 2H), 1.59–1.52 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.2, 169.4, 148.6, 136.5, 135.7, 129.0, 125.1, 122.7, 66.5, 58.7, 58.3,

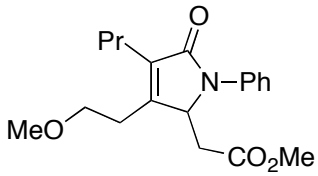
51.6, 35.4, 25.7, 21.9, 13.8. IR (neat): 2958, 2873, 1728, 1678, 1598, 1500, 1172, 759, 694 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{24}NO_4$ ($[M+H]^+$): 318.1705. Found: 318.1700.

Methyl 2-(4-(2-methoxyethyl)-5-oxo-1-phenyl-3-propyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5e).



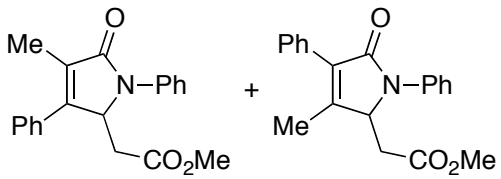
Yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.48 (m, 2H), 7.38 (m, 2H), 7.17 (m, 1H), 4.99 (dd, *J* = 6.5, 4.0 Hz, 1H), 3.56 (s, 3H), 3.52 (t, *J* = 6.5 Hz, 2H), 3.33 (s, 3H), 2.67–2.50 (m, 5H), 2.22 (m, 1H), 1.64 (m, 1H), 1.49 (m, 1H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 169.8, 155.3, 136.6, 130.3, 129.0, 124.9, 122.5, 70.5, 58.5, 58.5, 51.8, 35.6, 28.5, 24.5, 22.1, 14.2. IR (neat): 2959, 2875, 1737, 1661, 1599, 1494, 1367, 758, 694 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{26}NO_4$ ($[M+H]^+$): 332.1862. Found: 332.1857.

Methyl 2-(3-(2-methoxyethyl)-5-oxo-1-phenyl-4-propyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5e').



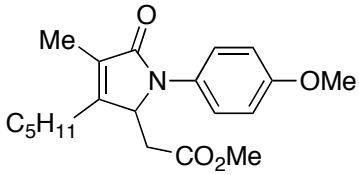
Yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.48 (m, 2H), 7.39 (m, 2H), 7.17 (m, 1H), 4.99 (dd, *J* = 5.0, 5.0 Hz, 1H), 3.57 (m, 1H), 3.53 (s, 3H), 3.50 (m, 1H), 3.36 (s, 3H), 2.85 (td, *J* = 14.5, 6.0 Hz, 1H), 2.68 (dd, *J* = 15.0, 4.0 Hz, 1H), 2.64 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.54 (m, 1H), 2.29 (m, 1H), 1.54 (m, 2H), 0.95 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 169.8, 150.4, 136.7, 135.0, 128.9, 124.9, 122.7, 71.0, 59.2, 58.7, 51.7, 35.3, 27.0, 25.8, 21.9, 14.0. IR (neat): 2957, 2873, 1737, 1694, 1598, 1500, 1112, 759, 694 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{26}NO_4$ ($[M+H]^+$): 332.1862. Found: 332.1857.

Methyl 2-(4-methyl-5-oxo-1,3-diphenyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5f) and methyl 2-(3-methyl-5-oxo-1,4-diphenyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5f') (2:1 mixture).



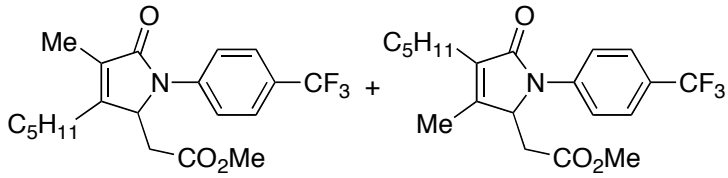
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56–7.39 (m, 8.33H), 7.35 (m, 0.67H), 7.22-7.18 (m, 1H), 5.50 (m, 0.67H), 5.04 (m, 0.33H), 3.61 (s, 1H), 3.29 (s, 2H), 2.80 (dd, *J* = 16.0, 4.5 Hz, 0.33H), 2.65 (dd, *J* = 15.5, 7.0 Hz, 0.33H), 2.51 (dd, *J* = 15.0, 5.0 Hz, 0.67H), 2.46 (dd, *J* = 15.5, 6.0 Hz, 0.67H), 2.19 (s, 1H), 2.07 (d, *J* = 1.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 170.4, 170.4, 170.1, 168.6, 150.9, 150.6, 136.6, 132.9, 132.2, 131.0, 130.3, 129.3, 129.1,129.1, 129.0, 128.7, 128.4, 128.2, 128.0, 125.3, 125.2, 123.1, 122.8, 60.3, 59.2, 52.0, 51.6, 36.7, 35.6, 13.3, 10.0. IR (neat): 3060, 2952, 1738, 1729, 1694, 1674, 1597, 1494, 1385, 1176, 759, 696 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{20}NO_3$ ($[M+H]^+$): 322.1443. Found: 322.1438.

Methyl 2-(1-(4-methoxyphenyl)-4-methyl-5-oxo-3-pentyl-2,5-dihydro-1H-pyrrol-2-yl)-acetate (5g).



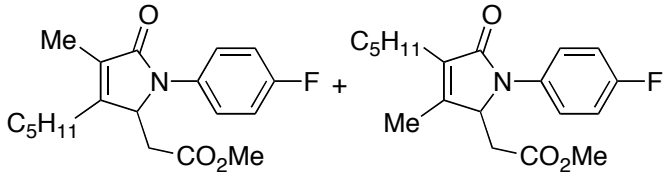
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (m, 2H), 6.91 (m, 2H), 4.86 (m, 1H), 3.79 (s, 3H), 3.53 (s, 3H), 2.60–2.47 (m, 3H), 2.20 (m, 1H), 1.85 (s, 3H), 1.56 (m, 1H), 1.45 (m, 1H), 1.37–1.29 (m, 4H), 0.91 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170,5, 157.2, 152.9, 129.3, 128.9, 125.0, 114.2, 59.3, 55.4, 51.7, 36.7, 31.7, 28.1, 26.4, 22.3,13.8, 8.7. IR (neat): 2955, 2870, 1737, 1682, 1514, 1248, 1170, 830 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{28}NO_4$ ($[M+H]^+$): 346.2018. Found: 346.2013.

Methyl 2-(4-methyl-5-oxo-3-pentyl-1-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1H-pyrrol-2-yl)acetate (5h) and methyl 2-(3-methyl-5-oxo-4-pentyl-1-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1H-pyrrol-2-yl)acetate (5h') (1:1 mixture).



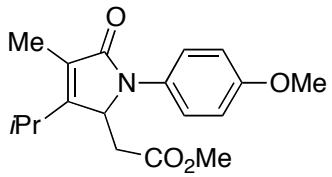
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68–7.63 (m, 4H), 5.01 (m, 0.5H), 4.91 (m, 0.5H), 2.74 (dd, J = 15.5, 3.5 Hz, 0.5H), 2.67 (dd, J = 16.0, 4.0 Hz, 0.5H), 2.55–2.50 (m, 1.5H), 2.31 (m, 1H), 2.22 (m, 0.5H), 2.02 (s, 1.5H), 1.88 (s, 1.5H), 1.60–1.45 (m, 2H), 1.39–1.28 (m, 4H), 0.93–0.88 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.4, 170.3, 170.1, 154.1, 149.7, 139.9, 133.9, 129.3, 126.2, 126.2, 125.1 (q, J_{CF} = 188 Hz), 123.0, 121.3, 121.2, 59.6, 58.2, 52.0, 52.0, 50.9, 35.4, 35.3, 33.5, 31.7, 31.6, 31.0, 29.7, 28.0, 26.7, 26.5, 23.5, 22.4, 22.4, 22.3, 13.9, 13.9, 12.1, 8.7. IR (neat): 2956, 2929, 1731, 1701, 1692, 1681, 1614, 1378, 1325, 1164, 1120, 1067 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{25}F_3NO_3$ ([M+H]$^+$): 384.1787. Found: 384.1777.

Methyl 2-(1-(4-fluorophenyl)-4-methyl-5-oxo-3-pentyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5i) and methyl 2-(1-(4-fluorophenyl)-3-methyl-5-oxo-4-pentyl-2,5-dihydro-1H-pyrrol-2-yl)-acetate (5i') (5:1 mixture).



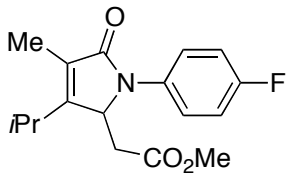
Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (m, 2H), 7.07 (m, 2H), 4.90 (m, 0.83H), 4.80 (dd, J = 7.0, 5.5 Hz, 0.17H), 3.57 (s, 0.5H), 3.55 (s, 2.5H), 2.64-2.49 (m, 2.83H), 2.29 (dd, J = 8.0, 7.5 Hz, 0.33H), 2.21 (m, 0.83H), 2.00 (s, 0.5H), 1.86 (s, 2.5H), 1.58 (m, 0.83H), 1.50–1.42 (m, 1.17H), 1.40–1.29 (m, 4H), 0.90 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.5, 161.0, 159.0, 153.3, 148.8, 133.8, 132.7, 132.7, 129.3, 124.8, 124.7, 124.6, 124.5, 115.8, 115.7, 60.5, 59.1, 51.9, 35.6, 35.6, 31.7, 31.6, 28.1, 28.0, 26.5, 23.5, 22.4, 223, 13.9, 13.9, 12.1, 8.7. IR (neat): 2955, 2932, 2872, 1738, 1733, 1694, 1674, 1511, 1383, 1222, 1157, 835 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{25}FNO_3$ ([M+H]$^+$): 334.1818. Found: 334.1813.

Methyl 2-(3-isopropyl-1-(4-methoxyphenyl)-4-methyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-acetate (5j).



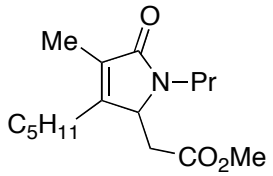
Colorless crystal, mp. 70–72 °C (CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (m, 2H), 6.90 (m, 2H), 4.86 (m, 1H), 3.79 (s, 3H), 3.48 (s, 3H), 2.76 (sept, J = 7.5 Hz, 1H), 2.64 (dd, J = 16.0, 5.5 Hz, 1H), 2.51 (dd, J = 16.0, 5.5 Hz, 1H), 1.93 (d, J = 2.0 Hz, 3H), 1.28 (d, J = 7.5 Hz, 3H), 1.25 (d, J = 7.5, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.6, 157.3, 157.0, 129.5, 128.5, 125.4, 114.2, 59.7, 55.4, 51.7, 35.9, 27.7, 21.4, 20.5, 9.4. IR (KBr): 2966, 2930, 1732, 1682, 1516, 1437, 1246, 1036, 840 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{24}NO_4$ ($[M+H]^+$): 318.1705. Found 318.1699.

Methyl 2-(1-(4-fluorophenyl)-3-isopropyl-4-methyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl)-acetate (5k).



Colorless crystal, mp. 108–109 °C (CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (m, 2H), 7.07 (m, 2H), 4.89 (m, 1H), 3.50 (s, 3H), 2.77 (sept, J = 7.5 Hz, 1H), 2.66 (dd, J = 16.0, 5.5 Hz, 1H), 2.53 (dd, J = 16.0, 5.0 Hz, 1H), 1.94 (d, J = 1.5 Hz, 3H), 1.29 (d, J = 7.0 Hz, 3H), 1.25 (d, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 170.4, 161.1 (d, J_{CF} = 243 Hz), 157.3, 132.6, 128.5, 125.2 (d, J_{CF} = 8.1 Hz), 115.8 (d, J_{CF} = 22.3 Hz), 59.4, 51.8, 35.7, 27.7, 21.3, 20.4, 9.4. IR (KBr): 2966, 2929, 1736, 1673, 1509, 1217, 1158, 842, 757 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{21}FNO_3$ ($[M+H]^+$): 306.1505. Found: 306.1500.

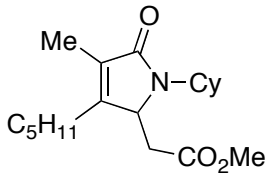
Methyl 2-(4-methyl-5-oxo-3-pentyl-1-propyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5m).



Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.31 (m, 1H), 3.73 (m, 1H), 3.69 (s, 3H), 2.95 (m, 1H), 2.61 (dd, J = 16.0, 5.5 Hz, 1H), 2.48 (dd, J = 16.0, 6.5 Hz, 1H), 2.43 (m, 1H), 2.14 (m, 1H), 1.79 (s, 3H), 1.59 (m, 1H), 1.53–1.45 (m, 2H), 1.40 (m, 1H), 1.36–1.24 (m, 4H), 0.89 (t, J = 7.5 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 171.0, 152.3, 129.2, 57.7, 52.0, 41.8, 35.5, 31.6, 28.1,

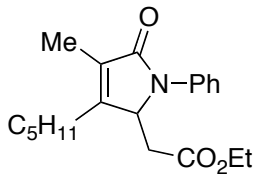
26.3, 22.3, 21.7, 13.9, 11.2, 8.8. IR (neat): 2958, 2932, 2873, 1737, 1686, 1455, 1415, 1159, 1095 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{28}NO_3$ ($[M+H]^+$): 282.2069. Found: 282.2064.

Methyl 2-(1-cyclohexyl-4-methyl-5-oxo-3-pentyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5n).



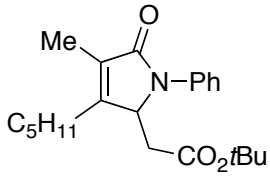
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (m, 1H), 3.68 (s, 3H), 3.55 (tt, *J* = 11.5, 4.0 Hz, 1H), 2.66 (dd, *J* = 15.5, 4.5 Hz, 1H), 2.58 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.42 (m, 1H), 2.08 (m, 1H), 1.90 (m, 1H), 1.83–1.70 (m, 8H), 1.48 (m, 1H), 1.40–1.22 (m, 8H), 1.16 (m, 1H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 170.9, 152.7, 129.4, 58.1, 53.7, 51.8, 36.5, 31.7, 31.1, 30.8, 28.0, 26.3, 26.2, 26.1, 25.4, 22.3, 13.9, 8.6. IR (neat): 2930, 2855, 1737, 1667, 1452, 1372, 1256, 1156, 1024 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{32}NO_3$ ($[M+H]^+$): 322.2382. Found: 322.2376.

Ethyl 2-(4-methyl-5-oxo-3-pentyl-1-phenyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5o).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (m, 2H), 7.39 (m, 2H), 7.16 (tt, *J* = 7.0, 1.5 Hz, 1H), 4.96 (m, 1H), 4.08–3.94 (m, 2H), 2.62 (dd, *J* = 16.0, 4.5 Hz, 1H), 2.52 (m, 1H), 2.50 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.23 (m, 1H), 1.87 (dd, *J* = 1.5, 1.0 Hz, 3H), 1.47 (m, 1H), 1.38–1.23 (m, 4H), 1.16 (t, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.2, 153.3, 136.7, 129.4, 129.0, 124.8, 122.5, 60.9, 58.6, 35.8, 31.7, 28.1, 26.5, 22.3, 14.0, 13.9, 8.7. IR (neat): 2984, 2938, 1666, 1643, 1499, 1371, 1293, 1155, 759, 694 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{28}NO_3$ ($[M+H]^+$): 330.2069. Found: 330.2063.

***tert*-Butyl 2-(4-methyl-5-oxo-3-pentyl-1-phenyl-2,5-dihydro-1H-pyrrol-2-yl)acetate (5p).**



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (m, 2H), 7.38 (m, 2H), 7.15 (tt, *J* = 7.0, 1.5 Hz, 1H), 4.90 (m, 1H), 2.58 (dd, *J* = 16.0, 4.0 Hz, 1H), 2.52 (m, 1H), 2.46 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.28 (m, 1H), 1.86 (s, 3H), 1.61 (m, 1H), 1.50 (m, 1H), 1.35 (s, 9H), 0.91 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

170.5, 169.1, 153.4, 136.9, 129.2, 129.0, 124.6, 122.2, 81.3, 58.6, 36.5, 31.7, 28.1, 27.8, 26.5, 22.4, 13.9, 8.7. IR (neat): 2957, 2931, 1725, 1693, 1501, 1381, 1143, 759, 693 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{32}NO_3$ ($[M+H]^+$): 358.2382. Found: 358.2376.

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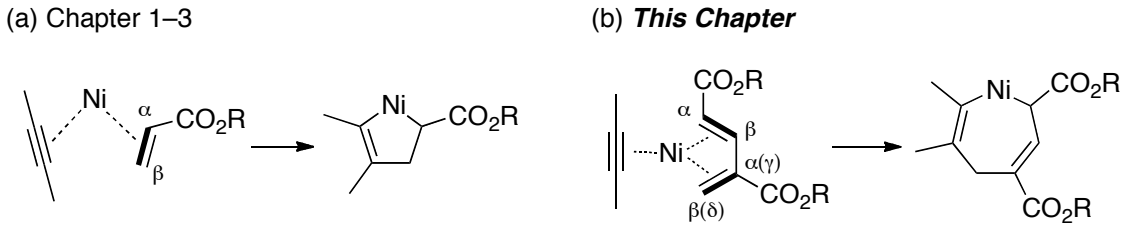
Chapter 4

Nickel-Catalyzed [4+2] Cycloaddition of Electron-Deficient Dienes with Alkynes for Highly Substituted Arenes

Nickel(0) efficiently catalyzed [4+2] cycloaddition of electron-deficient dienes with unactivated alkynes, and subsequent aromatization gave highly substituted arenes. This formal inverse electron-demand Diels–Alder cycloaddition is attributed to the formation of a seven-membered nickelacycle from a diene and an alkyne. The process is driven by two ester groups of the diene.

Introduction

In Chapters 1–3, the author described nickel-catalyzed reactions of acrylates with alkynes. The reactions are attributed to the oxidative cyclization of an acrylate and an alkyne, which results in the formation of a C–Ni bond at the α-position of the acrylate with the nickel complex and a C–C bond at the β-position with the alkyne (Scheme 1a). Based on the observations, he anticipated that a diene, which comprises two enoate moieties, could form a C–Ni bond at the α-position of one of the enoate moieties and a C–C bond at the β-position of the other enoate moiety to create a seven-membered nickelacycle intermediate. Following reductive elimination, this intermediate would change in to a six-membered carbocycle (Scheme 1b). According to this working hypothesis, he started his research and found nickel-catalyzed [4+2] cycloaddition of a γ-ester substituted α,β,γ,δ-unsaturated ester with an alkyne.

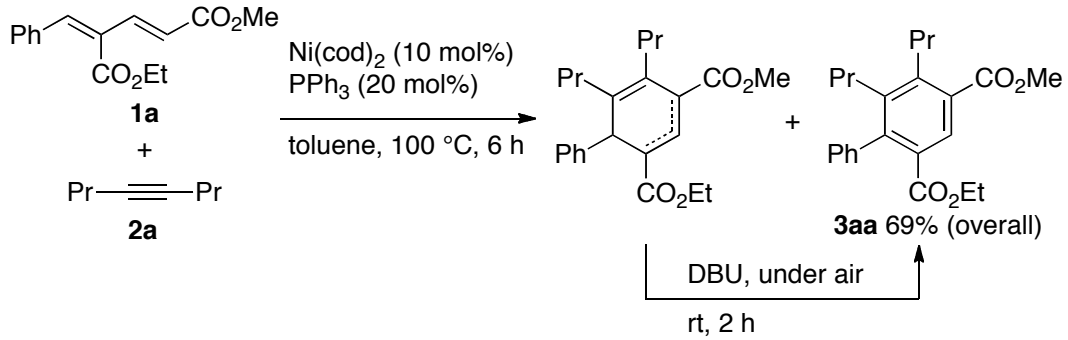


Scheme 1. Formation of nickelacycles.

Although many transition-metal complexes have also been catalyzed successfully through the [4+2] cycloaddition of dienes with alkynes,[1–5] most studies on this topic are limited to reactions with electron-rich or electronically neutral dienes. On the other hand, a reaction with electron-deficient dienes, namely inverse electron-demand Diels–Alder type cycloaddition, is rare.[2g,3b] In this Chapter, the author reports that the nickel-catalyzed [4+2] cycloaddition of electron-deficient dienes with alkynes and subsequent aromatization of the resultant cycloadducts results in the creation of highly substituted arenes.[6,7]

Results and Discussion

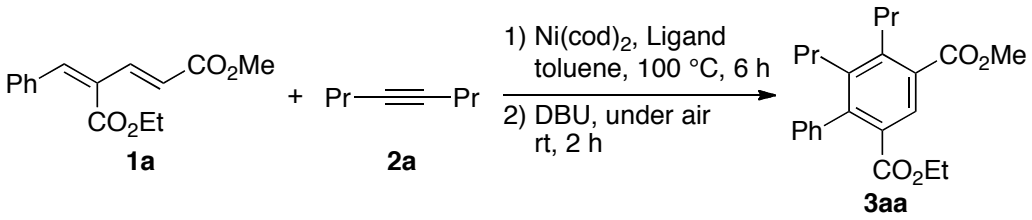
Initially, the author examined the reaction of diene **1a** with alkyne **2a** in the presence of $Ni(cod)_2$ (10 mol %) and PPh_3 (20 mol %) in toluene at 100 °C for 6 h. This reaction afforded several isomers of cyclohexadienes and aromatized cycloadduct **3aa** as an inseparable mixture. After nickel-catalyzed cycloaddition, adding DBU in one-pot followed by vigorous stirring under air for 2 h provided isophthalate **3aa** as single product in 69% yield (Scheme 2).[8]



Scheme 2. Nickel-catalyzed [4+2] cycloaddition of diene **1a** with alkyne **2a** and sequential aromatization.

To improve the yield of **3aa**, the use of several phosphine ligands was examined (Table 1). Alkyl-substituted phosphines were less effective than PPh_3 (Table 1, entries 2–4), while electron-rich triarylphosphines gave the product at similar yields (entries 5 and 6). On the contrary, an electron-deficient ligand resulted in a poor yield (entry 7). Decreasing the amount of ligand to 12 mol% did not affect the reaction (entry 8), while a low reaction rate was observed when the amount of ligand was increased to 30 mol% (entry 9). Decreasing the amount of $Ni(cod)_2$ to 5 mol% did not lower the yield (entry 10). Finally, it is found that the use of 3 equiv of **2a** improved drastically the yield and **3aa** was obtained at a yield of 84% (entry 11).

Table 1. Optimization of reaction conditions[a]



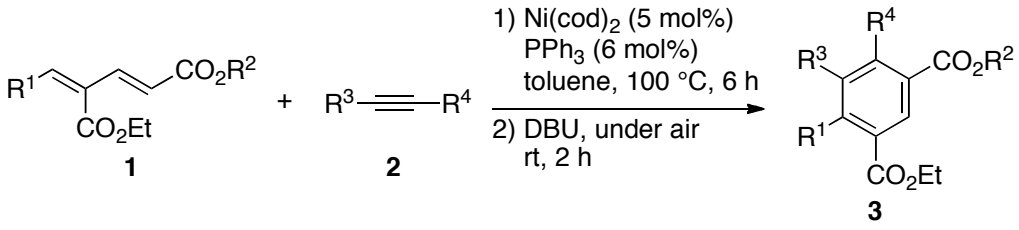
Entry	$Ni(cod)_2$ [mol%]	Ligand	[mol%]	Yield [%][b]
1	10	PPh_3	20	69
2	10	PCy_3	20	49
3	10	$PCyPh_2$	20	57
4	10	$PMePh_2$	20	16
5	10	$P(4\text{-}MeC_6H_4)_3$	20	70
6	10	$P(4\text{-}MeOC_6H_4)_3$	20	67
7	10	$P(4\text{-}FC_6H_4)_3$	20	31
8	10	PPh_3	12	68
9	10	PPh_3	30	47
10	5	PPh_3	6	68
11[c]	5	PPh_3	6	84 (82)

[a] Reactions were carried out using $Ni(cod)_2$, ligand, diene **1a** (0.50 mmol) and 4-octyne (**2a**; 1.0 mmol, 2 equiv) in 1 mL of toluene at 100 °C for 6 h, followed by addition of DBU (1.0 mmol, 2 equiv) and stirring under air at room temperature for 2 h. [b] Yield as determined by NMR spectroscopy. Yield of the isolated product is given in parentheses. [c] **2a** (1.5 mmol, 3 equiv).

With the optimized reaction conditions in hand, the author examined the substrate scope of this cycloaddition reaction (Table 2). Dienes with an aryl substituent at R^1 were effective participants. In the reactions of methoxyphenyl-substituted dienes **1b** and **1c**, deactivation of the nickel catalyst was observed. This was prevented by using 10 mol% of phosphine ligand (Table 2, entries 1 and 2). Among the aryl-groups that he examined, the electron-deficient groups afforded aromatized cycloadduct **3** in higher yields (entries 3 and 4). Sterically bulky 2-tolyl and 1-naphthyl groups also participated in the cycloaddition (entries 5 and 6).

Various internal alkynes were also examined for their reactivity. Alkyl-substituted symmetrical alkynes **2b** and **2c** reacted with **1a** to afford **3ab** and **3ac** in good yields (entries 7 and 8). The reaction with cycloalkynes gave ring-fused arenes. Whereas strained cyclododecyne (**2d**) resulted in a relatively low yield (entry 9), less strained cyclopentadecyne (**2e**) gave arene **3ae** at a yield of 81%. Of note, the aromatization step of this reaction was time intensive (entry 10). Unsymmetrical alkyne **2f** gave two corresponding regioisomers at a yield of 61% but its selectivity was low (entry 11). Aryl-substituted alkynes also participated in the [4+2] cycloaddition. Diphenylacetylene (**2g**) reacted with diene **1h** to afford **3hg** in 56% yield (entry 12). Although two regioisomers were possible outcomes in the reaction with 1-phenyl-1-propyne (**2h**), the product **3hh** was obtained as a single isomer (entry 13). Similar unsymmetrical alkyne a methoxy group or fluorine also reacted stereoselectively to afford arene **3** (entries 14 and 15). However, terminal alkynes failed to participate in the reaction.

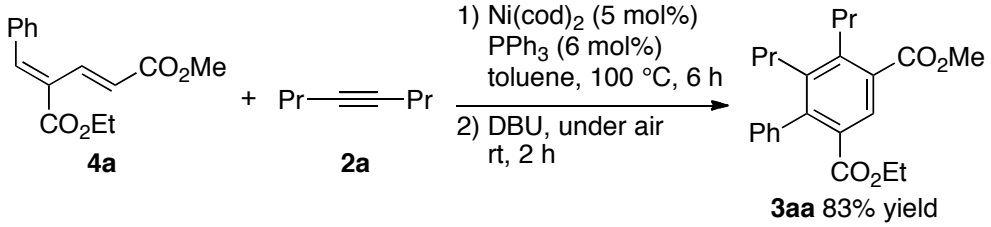
Table 2. Nickel-catalyzed [4+2] cycloaddition of electron-deficient dienes with alkynes[a]



Entry	**1**	R^1	R^2	**2**	R^3	R^4	**3**	Yield [%][b]
1[c]	**1b**	4-$MeOC_6H_4$	Me	**2a**	Pr	Pr	**3ba**	54
2[c]	**1c**	3-$MeOC_6H_4$	Me	**2a**	Pr	Pr	**3ca**	56
3	**1d**	4-FC_6H_4	Me	**2a**	Pr	Pr	**3da**	81
4	**1e**	4-$F_3CC_6H_4$	Me	**2a**	Pr	Pr	**3ea**	77
5	**1f**	2-MeC_6H_4	Me	**2a**	Pr	Pr	**3fa**	70
6	**1g**	1-Naphthyl	*t*Bu	**2a**	Pr	Pr	**3ga**	68
7	**1a**	Ph	Me	**2b**	Et	Et	**3ab**	71
8	**1a**	Ph	Me	**2c**	C_5H_{11}	C_5H_{11}	**3ac**	78
9	**1a**	Ph	Me	**2d**	–$(CH_2)_{10}$–		**3ad**	44
10[d]	**1a**	Ph	Me	**2e**	–$(CH_2)_{13}$–		**3ae**	81
11	**1a**	Ph	Me	**2f**	*i*Pr	Me	**3af**	61 (1/1)[e]
12	**1h**	Ph	Et	**2g**	Ph	Ph	**3hg**	56
13	**1h**	Ph	Et	**2h**	Me	Ph	**3hh**	43
14	**1a**	Ph	Me	**2i**	C_5H_{11}	4-$MeOC_6H_4$	**3ai**	67
15	**1a**	Ph	Me	**2j**	C_5H_{11}	4-FC_6H_4	**3aj**	46

[a] Reactions were carried out using $Ni(cod)_2$ (5 mol%), PPh_3 (6 mol%), diene **1** (0.50 mmol) and alkyne **2** (1.5 mmol, 3 equiv) in 1 mL of toluene at 100 °C for 6 h, followed by addition of DBU (1.0 mmol, 2 equiv) and stirring under air at room temperature for 2 h. [b] Yield of the isolated product. [c] PPh_3 (10 mol%). [d] The second step reaction was carried out for 15 h. [e] Ratio of the regioisomers.

As shown in Scheme 3, the [4+2] cycloaddition of (*E*)-isomer **4a** with alkyne **2a** also resulted in **3aa** at a yield of 83%. It is unclear which isomer gave the cycloadduct, because the isomerization between (*Z*)-isomer **1a** and (*E*)-isomer **4a** was rapid.



Scheme 3. Nickel-catalyzed [4+2] cycloaddition of (*E*)-isomer **4a** with alkyne **2a**.

Conclusion

In conclusion, the author developed a nickel-catalyzed [4+2] cycloaddition reaction that centers on electron-deficient dienes with alkynes. This reaction corresponds to an inverse electron-demand Diels–Alder reaction. In addition, subsequent aromatization by using base and air produces highly functionalized arenes. Activation of both olefins of the diene is essential for the cycloaddition reaction.

Experimental Section

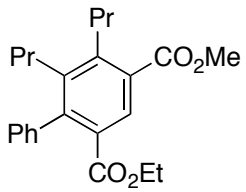
Chemicals. Triphenylphosphine was purchased from Wako Pure Chemical Co. and purified by recrystallization from ethanol. Dienes **1a–h**,[9] cyclododecyne (**2d**), and cyclopentadecyne (**2e**)[10] were prepared according to the literature.

Experimental procedure for nickel-catalyzed [4+2] cycloaddition of dienes with alkynes and sequential aromatization

General procedure. The reaction was performed in a 5 mL sealed vessel equipped with a Teflon-coated magnetic stirrer tip. A diene **1** (0.50 mmol) and an alkyne **2** (1.5 mmol) were added to a solution of bis(1,5-cyclooctadiene)nickel (7 mg, 0.025 mmol) and triphenylphosphine (8 mg, 0.030 mmol) in toluene (1 mL) in a dry box. The VIAL was taken outside the dry box and heated at 100 ºC for 6 h. After cooled to ambient temperature, DBU (0.15 mL, 1.0 mmol) was added to the mixture, and this was stirred vigorously under air at room temperature for 2 h. The resulting reaction mixture was filtered through a silica gel pad and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 10:1) to give the corresponding arene **3**.

Characterization data

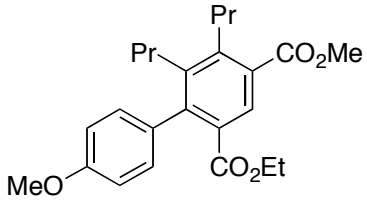
2-Ethyl 4-methyl 5,6-dipropyl-[1,1'-biphenyl]-2,4-dicarboxylate (3aa).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.36 (m, 3H), 7.16 (m, 2H), 3.95 (q, J = 7.0 Hz, 2H), 3.92 (s, 3H), 2.95 (t, J = 8.0 Hz, 2H), 2.42 (t, J = 8.0 Hz, 2H), 1.59 (m, 2H), 1.31 (m, 2H), 1.04 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H), 0.72 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.33, 167.83, 145.50, 144.89, 141.64, 140.18, 130.27, 130.07, 128.80, 128.74, 127.59, 127.02, 60.75, 52.13, 32.18, 32.04, 25.12, 24.38, 14.71, 14.51, 13.64. IR (neat): 2962, 1728, 1232, 703 cm^{-1}. HRMS

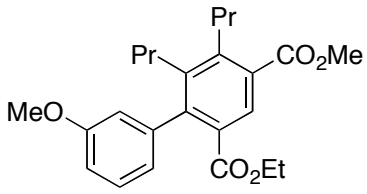
(APCI) calcd for $C_{23}H_{29}O_4$ ([M+H]$^+$): 369.2060. Found: 360.2053. Anal calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.91; H, 7.67.

2-Ethyl 4-methyl 4'-methoxy-5,6-dipropyl-[1,1'-biphenyl]-2,4-dicarboxylate (3ba).



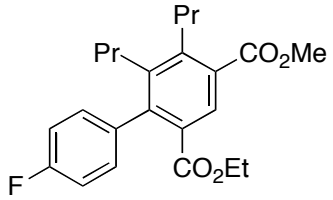
White powder, mp. 66–67 °C (hexane-AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 3.98 (q, *J* = 7.0 Hz, 2H), 3.91 (s, 3H), 3.85 (s, 3H), 2.93 (t, *J* = 8.0 Hz, 2H), 2.43 (t, *J* = 8.0 Hz, 2H), 1.58 (m, 2H), 1.30 (m, 2H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.98 (t, *J* = 7.0 Hz, 3H), 0.74 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.31, 167.99, 158.58, 145.38, 144.56, 142.07, 132.30, 130.43, 129.99, 129.80, 128.53, 113.02, 60.77, 55.19, 52.15, 32.19, 31.97, 25.10, 24.38, 14.75, 14.59, 13.79. IR (KBr): 2961, 1727, 1707, 1516, 1250, 1028, 841 cm^{-1}. HRMS (APCI) calcd for $C_{24}H_{31}O_5$ ([M+H]$^+$): 399.2166. Found: 399.2154. Anal calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.49; H, 7.75.

2-Ethyl 4-methyl 3'-methoxy-5,6-dipropyl-[1,1'-biphenyl]-2,4-dicarboxylate (3ca).



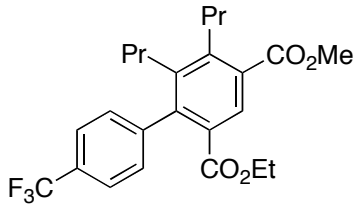
Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.28 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.90 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H), 6.76 (ddd, *J* = 7.0, 1.5, 1.0 Hz, 1H), 6.71 (dd, *J* = 2.5, 1.5 Hz, 1H), 3.97 (q, *J* = 7.0 Hz, 2H), 3.92 (s, 3H), 3.80 (s, 3H), 2.94 (t, *J* = 8.5 Hz, 2H), 2.43 (t, *J* = 8.0 Hz, 2H), 1.57 (m, 2H), 1.34 (m, 2H), 1.04 (t, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.0 Hz, 3H), 0.75 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.27, 167.78, 158.93, 145.59, 144.58, 141.55, 141.44, 130.17, 129.93, 128.72, 128.62, 121.42, 114.36, 112.67, 60.79, 55.24, 52.20, 32.15, 32.05, 25.12, 24.61, 14.78, 14.63, 13.69. IR (neat): 2960, 1727, 1589, 1465, 1233, 790, 708 cm^{-1}. HRMS (APCI) calcd for $C_{24}H_{31}O_5$ ([M+H]$^+$): 399.2166. Found: 399.2154.

2-Ethyl 4-methyl 4'-fluoro-5,6-dipropyl-[1,1'-biphenyl]-2,4-dicarboxylate (3da).



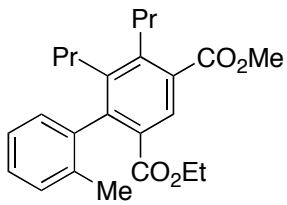
Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.14–7.06 (m, 4H), 3.99 (q, J = 7.0 Hz, 2H), 3.92 (s, 3H), 2.93 (t, J = 8.0 Hz, 2H), 2.39 (t, J = 8.0 Hz, 2H), 1.58 (m, 2H), 1.29 (m, 2H), 1.04 (t, J = 7.0 Hz, 3H), 0.99 (t, J = 7.0 Hz, 3H), 0.74 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.23, 167.56, 161.98 (d, J_{CF} = 245 Hz), 145.66, 143.84, 141.84, 135.99 (d, J_{CF} = 3.3 Hz), 130.46, 130.33 (d, J_{CF} = 7.6 Hz), 129.93, 128.87, 114.62 (d, J_{CF} = 21.5 Hz), 60.87, 52.23, 32.18, 32.02, 25.11, 24.34, 14.75, 14.57, 13.76. IR (neat): 2963, 1727, 1513, 838 cm^{-1}. HRMS (APCI) calcd for $C_{27}H_{28}FO_4$ ([M+H]$^+$): 387.1966. Found: 387.1951.

2-Ethyl 4-methyl 5,6-dipropyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2,4-dicarboxylate (3ea).



White powder, mp. 55–56 °C (hexane-AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 3.97 (q, J = 7.0 Hz, 2H), 3.93 (s, 3H), 2.94 (t, J = 8.0 Hz, 2H), 2.36 (t, J = 8.5 Hz, 2H), 1.59 (m, 2H), 1.29 (m, 2H), 1.04 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H), 0.72 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.14, 167.10, 146.02, 144.24, 143.50, 141.35, 130.86, 129.31 (q, J_{CF} = 32.4 Hz), 129.30, 129.21, 129.16, 124.58 (q, J_{CF} = 3.9 Hz), 124.22 (q, J_{CF} = 271 Hz), 60.94, 52.30, 32.14, 32.03, 25.11, 24.38, 14.75, 14.53, 13.54. IR (KBr): 2969, 1730, 1701, 1324, 1237, 1163, 1126, 842 cm^{-1}. HRMS (APCI) calcd for $C_{24}H_{28}F_3O_4$ ([M+H]$^+$): 437.1934. Found: 437.1926. Anal calcd for $C_{24}H_{27}F_3O_4$: C, 66.04; H, 6.24. Found: C, 66.32; H, 6.26.

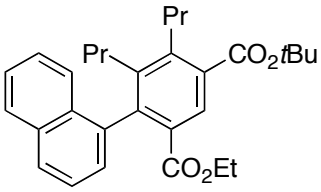
2-Ethyl 4-methyl 2'-methyl-5,6-dipropyl-[1,1'-biphenyl]-2,4-dicarboxylate (3fa).



Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.26–7.15 (m, 3H), 6.99 (dd, J = 7.5, 1.0 Hz, 1H), 3.96 (q, J = 7.0 Hz, 2H), 3.92 (s, 3H), 3.07 (m, 1H), 2.84 (m, 1H), 2.47 (m, 1H), 2.16 (m, 1H), 1.97 (s, 3H), 1.63 (m, 1H), 1.56 (m, 1H), 1.34–1.18 (m, 2H), 1.03 (t, J = 7.5 Hz, 3H),

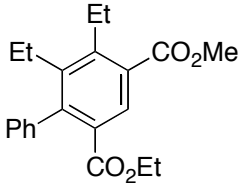
0.93 (t, J = 7.0 Hz, 3H), 0.69 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.38, 167.48, 145.84, 144.41, 141.54, 139.52, 135.66, 130.08, 129.41, 129.32, 129.19, 128.63, 127.35, 125.04, 60.71, 52.19, 32.09, 32.02, 25.17, 23.83, 19.97, 14.69, 14.67, 13.61. IR (neat): 2961, 1728, 1233, 730 cm^{-1}. HRMS (APCI) calcd for $C_{24}H_{31}O_4$ ([M+H]$^+$): 383.2217. Found: 383.2204.

1-*tert*-Butyl 3-ethyl 4-(naphthalen-1-yl)-5,6-dipropylisophthalate (3ga)



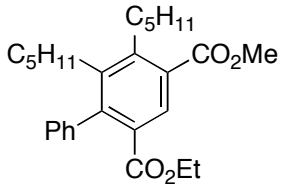
Pale yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.86 (m, 2H), 7.46 (m, 2H), 7.31 (m, 2H), 7.21 (dd, J = 7.0, 1.0 Hz, 1H), 3.68 (q, J = 7.5 Hz, 2H), 3.03 (m, 1H), 2.85 (m, 1H), 2.39 (m, 1H), 2.07 (m, 1H), 1.65 (m, 2H), 1.65 (s, 9H), 1.23 (m, 2H), 1.04 (t, J = 7.5 Hz, 3H), 0.56 (t, J = 7.5 Hz, 3H), 0.47 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.98, 167.60, 144.38, 142.25, 142.08, 138.00, 133.43, 133.13, 132.60, 130.47, 128.50, 128.03, 127.47, 126.34, 125.90, 125.84, 125.59, 124.83, 81.78, 60.39, 32.57, 32.07, 28.18, 25.24, 24.60, 14.71, 14.52, 13.04. IR (neat): 2964, 1722, 1251, 1153, 1028, 851, 802, 781 cm^{-1}. HRMS (EI) calcd for $C_{30}H_{36}O_4$ ([M]$^+$): 460.2614. Found: 460.2607.

2-Ethyl 4-methyl 5,6-diethyl-[1,1'-biphenyl]-2,4-dicarboxylate (3ab).



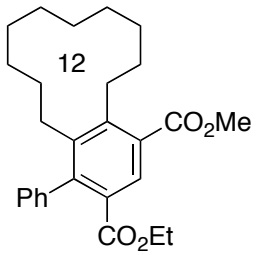
White powder, mp. 41–42 °C (hexane-AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.37 (m, 3H), 7.18 (m, 2H), 3.95 (q, J = 7.5 Hz, 2H), 3.93 (s, 3H), 3.03 (q, J = 7.5 Hz, 2H), 2.52 (q, J = 7.5 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.25, 167.75, 146.76, 144.90, 142.62, 140.07, 130.17, 130.01, 128.80, 128.75, 127.62, 127.03, 60.78, 52.20, 23.17, 22.64, 15.87, 15.32, 13.65. IR (KBr): 2984, 1725, 1711, 1244, 707 cm^{-1}. HRMS (APCI) calcd for $C_{21}H_{25}O_4$ ([M+H]$^+$): 341.1747. Found: 341.1733. Anal calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.17; H, 7.27.

2-Ethyl 4-methyl 5,6-dipentyl-[1,1'-biphenyl]-2,4-dicarboxylate (3ac).



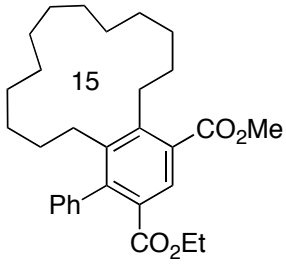
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.35 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 3.95 (q, *J* = 7.0 Hz, 2H), 3.92 (s, 3H), 2.95 (t, *J* = 8.0 Hz, 2H), 2.43 (t, *J* = 8.0 Hz, 2H), 1.56 (m, 2H), 1.45–1.34 (m, 4H), 1.27 (m, 2H), 1.08 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 6H), 0.75 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.34, 167.81, 145.68, 144.89, 141.72, 140.11, 130.19, 129.87, 128.77, 128.70, 127.57, 127.00, 60.76, 52.18, 32.49, 32.07, 31.52, 30.49, 30.11, 29.71, 22.41, 21.87, 14.05, 13.82, 13.64. IR (neat): 2956, 1727, 1234, 1031, 703 cm^{-1}. HRMS (APCI) calcd for $C_{27}H_{37}O_4$ ($[M+H]^+$): 425.2686. Found: 425.2675.

3-Ethyl 1-methyl 4-phenyl-5,6,7,8,9,10,11,12,13,14-decahydrobenzo[12]annulene-1,3-di-carboxylate (3ad).



White powder, mp. 83–85 °C (hexane-AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.35 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 3.94 (q, *J* = 7.0 Hz, 2H), 3.92 (s, 3H), 3.09 (t, *J* = 8.5 Hz, 2H), 2.55 (t, *J* = 8.5 Hz, 2H), 1.72 (m, 2H), 1.56 (m, 4H), 1.44 (m, 6H), 1.38 (m, 2H), 1.23 (m, 2H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.53, 167.81, 145.50, 145.18, 141.75, 140.17, 130.72, 129.93, 128.76, 128.55, 127.53, 127.02, 60.77, 52.22, 29.16, 28.79, 28.58, 28.44, 28.29, 27.88, 27.39, 22.86, 22.65, 13.66. IR (KBr): 2934, 1723, 1705, 1296, 1154, 1028, 702 cm^{-1}. HRMS (ESI^+) calcd for $C_{27}H_{35}O_4$ ($[M+H]^+$): 423.2530. Found: 423.2525. Anal calcd for $C_{27}H_{34}O_4$: C, 76.74; H, 8.11. Found: C, 76.72; H, 7.99.

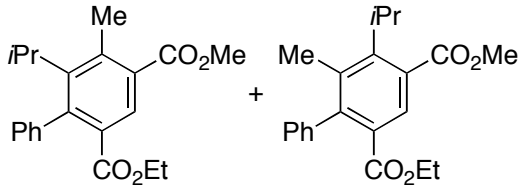
3-Ethyl 1-methyl 4-phenyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-5*H*-benzo[15]annulene-1,3-dicarboxylate (3ae).



White powder, mp. 104–105 °C (hexane-AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.36 (m, 3H), 7.15 (d, J = 8.0 Hz, 2H), 3.95 (q, J = 7.5 Hz, 2H), 3.92 (s, 3H), 2.93 (t, J = 8.0 Hz, 2H), 2.42 (t, J = 8.5 Hz, 2H), 1.67–1.55 (m, 4H), 1.45–1.23 (m, 16H), 1.10 (m, 2H), 0.92 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.28, 167.76, 145.84, 145.13, 141.83, 140.17, 130.26, 129.90, 128.85, 128.61, 127.60, 126.98, 60.76, 52.20, 30.08, 29.66, 29.30, 28.45, 27.92, 27.56, 26.56, 26.30, 26.27, 26.03, 24.94, 24.92, 13.64. IR (KBr): 2925, 1730, 1705, 1239, 1029, 709 cm^{-1}. HRMS (ESI$^+$) calcd for $C_{30}H_{41}O_4$ ([M+H]$^+$): 465.2999. Found: 465.2996. Anal calcd for $C_{30}H_{40}O_4$: C, 77.55; H, 8.68. Found: C, 77.29; H, 8.88.

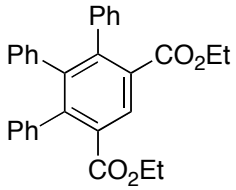
2-Ethyl 4-methyl 6-isopropyl-5-methyl-[1,1'-biphenyl]-2,4-dicarboxylate and

2-ethyl 4-methyl 5-isopropyl-6-methyl-[1,1'-biphenyl]-2,4-dicarboxylate (1:1 mixture) (3af).



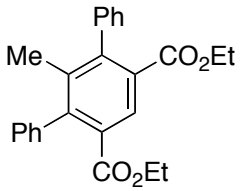
Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (s, 0.5H), 7.78 (s, 0.5H), 7.36 (m, 3H), 7.13 (m, 2H), 3.95 (q, J = 7.0 Hz, 2H), 3.92 (s, 3H), 3.46 (sept, J = 7.0 Hz, 0.5H), 3.20 (sept, J = 7.0 Hz, 0.5H), 2.65 (s, 1.5H), 2.11 (s, 1.5H), 1.37 (d, J = 7.0 Hz, 3H), 1.19 (d, J = 7.0 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.49, 168.58, 168.04, 167.61, 148.06, 146.20, 144.54, 140.70, 136.57, 132.14, 132.03, 129.51, 128.64, 128.58, 127.92, 127.75, 127.69, 127.46, 127.04, 126.96, 60.81, 60.75, 52.39, 52.19, 31.11, 30.57, 21.10, 20.93, 18.65, 17.92, 13.65, 13.64. IR (neat): 2959, 1728, 1257, 1235, 1030, 703 cm^{-1}. HRMS (APCI) calcd for $C_{21}H_{25}O_4$ ([M+H]$^+$): 341.1747. Found: 341.1735.

Diethyl 6'-phenyl-[1,1':2',1''-terphenyl]-3',5'-dicarboxylate (3hg).



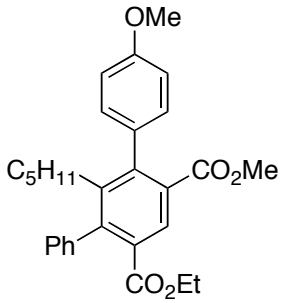
Pale red powder, mp. 128–130 °C (hexane-AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.10 (m, 6H), 6.97 (m, 4H), 6.87 (m, 3H), 6.68 (m, 2H), 4.02 (q, J = 7.0 Hz, 4H), 0.93 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.94, 143.77, 142.76, 139.29, 138.01, 131.95, 131.03, 129.43, 129.06, 127.17, 126.78, 126.62, 125.93, 61.15, 13.61. IR (KBr): 1730, 1318, 1200, 1085, 761, 699 cm^{-1}. HRMS (APCI) calcd for $C_{30}H_{27}O_4$ ($[M+H]^+$): 451.1904. Found: 451.1893. Anal calcd for $C_{30}H_{26}O_4$: C, 79.98; H, 5.82. Found: C, 79.98; H, 5.96.

Diethyl 2'-methyl-[1,1':3',1''-terphenyl]-4',6'-dicarboxylate (3hh).



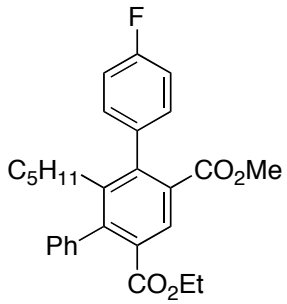
Pale red powder, mp. 68–72 °C (hexane-AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.39 (m, 6H), 7.19 (d, J = 8.0 Hz, 4H), 4.01 (q, J = 7.0 Hz, 4H), 1.81 (s, 3H), 0.96 (t, J = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.73, 144.68, 140.11, 136.71, 131.32, 128.54, 128.03, 127.60, 127.19, 60.96, 18.83, 13.66. IR (KBr): 1719, 1251, 1026, 765, 707 cm^{-1}. HRMS (APCI) calcd for $C_{25}H_{25}O_4$ ($[M+H]^+$): 389.1747. Found: 389.1736.

4'-Ethyl 6'-methyl 4-methoxy-2'-pentyl-[1,1':3',1''-terphenyl]-4',6'-dicarboxylate (3ai).



Pale yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.36 (m, 3H), 7.22 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 3.99 (q, J = 7.0 Hz, 2H), 3.85 (s, 3H), 3.60 (s, 3H), 2.25 (t, J = 8.0 Hz, 2H), 1.03 (m, 2H), 0.95 (t, J = 7.0 Hz, 3H), 0.82 (m, 2H), 0.70 (m, 2H), 0.57 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.04, 167.75, 158.64, 144.47, 144.42, 142.41, 139.55, 131.59, 131.53, 129.88, 128.89, 127.65, 127.30, 127.14, 113.14, 60.93, 55.18, 52.05, 31.62, 30.31, 29.80, 21.49, 13.67, 13.61. IR (neat): 2956, 1728, 1515, 1247, 1032, 833, 704 cm^{-1}. HRMS (APCI) calcd for $C_{29}H_{33}O_5$ ($[M+H]^+$): 461.2323. Found: 461.2310. Anal calcd for $C_{29}H_{32}O_5$: C, 75.63; H, 7.00. Found: C, 75.72; H, 7.02.

4'-Ethyl 6'-methyl 4-fluoro-2'-pentyl-[1,1':3',1''-terphenyl]-4',6'-dicarboxylate (3aj).



Pale yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.37 (m, 3H), 7.23–7.17 (m, 4H), 7.10 (m, 2H), 3.99 (q, J = 7.0 Hz, 2H), 3.61 (s, 3H), 2.22 (t, J = 8.0 Hz, 2H), 1.02 (m, 2H), 0.95 (t, J = 7.0 Hz, 3H), 0.81 (m, 2H), 0.70 (m, 2H), 0.57 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.66, 167.60, 162.01 (d, J_{CF} = 245 Hz), 144.71, 143.71, 142.19, 139.29, 135.24 (d, J_{CF} = 3.3 Hz), 132.06, 131.09, 130.42 (d, J_{CF} = 7.6 Hz), 128.84, 127.70, 127.61, 127.27, 114.75 (d, J_{CF} = 21.0 Hz), 61.02, 52.07, 31.60, 30.33, 29.78, 21.44, 13.66, 13.59. IR (neat): 2956, 1733, 1512, 838, 703 cm^{-1}. HRMS (APCI) calcd for $C_{28}H_{30}FO_4$ ($[M+H]^+$): 449.2123. Found: 449.2110. Anal calcd for $C_{28}H_{29}FO_4$: C, 74.98; H, 6.52. Found: C, 75.07; H, 6.38.

References and Notes

1. For iron-catalyzed [4+2] cycloaddition, see: (a) A. Carbonaro, A. Greco, G. Dall'Asta, *J. Org. Chem.* **1968**, *33*, 3948; (b) J. P. Genêt, J. Ficini, *Tetrahedron Lett.* **1979**, *20*, 1499; (c) H. tom Dieck, R. Diercks, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 778.
2. For rhodium-catalyzed [4+2] cycloaddition, see: (a) I. Matsuda, M. Shibata, S. Sato, Y. Izumi, *Tetrahedron Lett.* **1987**, *28*, 3361; (b) R. S. Jolly, G. Luedtke, D. Sheehan, T. Livinghouse, *J. Am. Chem. Soc.* **1990**, *112*, 4965; (c) M. Murakami, M. Ubukata, K. Itami, Y. Ito, *Angew. Chem. Int. Ed.* **1998**, *37*, 2248; (d) S.-J. Paik, S. U. Son, Y. K. Chung, *Org. Lett.* **1999**, *1*, 2045; (e) D. Motoda, H. Kinoshita, H. Shinokubo, K. Oshima, *Angew. Chem. Int. Ed.* **2004**, *43*, 1860; (f) W.-J. Yoo, A. Allen, K. Villeneuve, W. Tam, *Org. Lett.* **2005**, *7*, 5853; (g) A. Saito, T. Ono, A. Takahashi, T. Taguchi, Y. Hanzawa, *Tetrahedron Lett.* **2006**, *47*, 891.
3. For nickel-catalyzed [4+2] cycloaddition, see: (a) P. A. Wender, T. E. Jenkins, *J. Am. Chem. Soc.* **1989**, *111*, 6432; (b) P. A. Wender, T. E. Smith, *Tetrahedron*, **1998**, *54*, 1255.
4. For cobalt-catalyzed [4+2] cycloaddition, see: (a) G. Hilt, F.-X. du Mesnil, *Tetrahedron Lett.* **2000**, *41*, 6757; (b) G. Hilt, T. J. Korn, *Tetrahedron Lett.* **2001**, *42*, 2783. See also following review: (c) W. Hess, J. Treutwein, G. Hilt, *Synthesis* **2008**, 3537.
5. For other transition-metal-catalyzed [4+2] cycloaddition, see the following. Ti: (a) K. Mach, H. Antropiusová, L. Petrusová, F. Turecek, V. Hanus, *J. Organomet. Chem.* **1985**, *289*, 331. Pd: (b) K. Kumar, R. S. Jolly, *Tetrahedron Lett.* **1998**, *39*, 3047. Cu and Au: (c) A. Fürstner, C. C. Stimson, *Angew. Chem. Int. Ed.* **2007**, *46*, 8845. Au: (d) S. M. Kim, J. H. Park, Y. K. Chung, *Chem. Commun.* **2011**, *47*, 6719.
6. (a) P. A. Wender, T. E. Smith, *J. Org. Chem.* **1996**, *61*, 824; (b) G. Hilt, J. Janikowsky, W. Hess, *Angew. Chem. Int. Ed.* **2006**, *45*, 5204; (c) G. Hilt, M. Danz, *Synthesis* **2008**, 2257.
7. Another methodology to provide arenes *via* [4+2] cycloaddition, see following reviews: (a) V. Gevorgyan, Y. Yamamoto, *J. Organomet. Chem.* **1999**, *576*, 232; (b) S. Saito, Y.

Yamamoto, *Chem. Rev.* **2000**, *100*, 2901.

8. S. Ikeda, N. Mori, Y. Sato, *J. Am. Chem. Soc.* **1997**, *119*, 4779.
9. C. Dockendorff, S. Sahli, M. Olsen, L. Milhau, M. Lautens, *J. Am. Chem. Soc.* **2005**, *127*, 15028.
10. K. M. Brummond, K. D. Gesenberg, J. L. Kent, A. D. Kerekes, *Tetrahedron Lett.* **1998**, *39*, 8613.

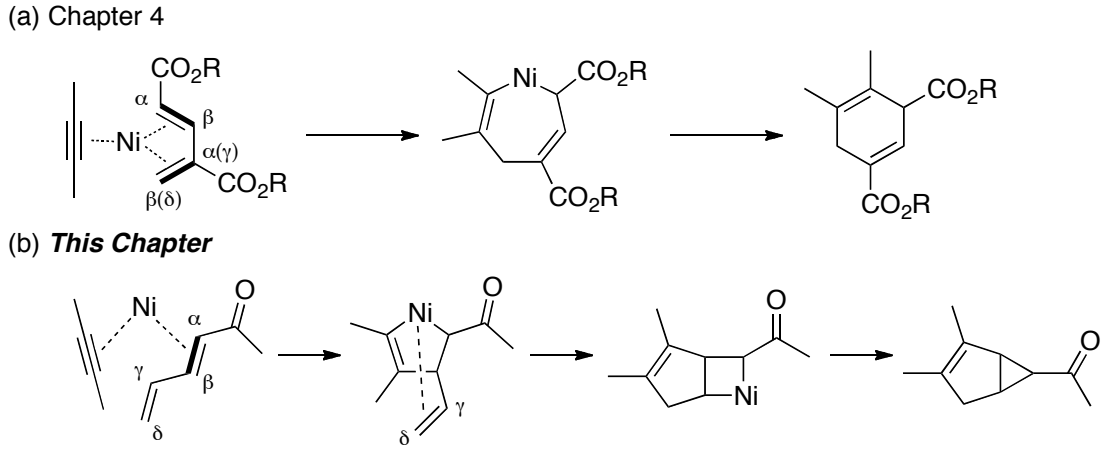
Chapter 5

Nickel-Catalyzed Cycloaddition of α,β,γ,δ-Unsaturated Ketones with Alkynes

Nickel(0) complex catalyzed unprecedented manner of cycloaddition of α,β,γ,δ-unsaturated ketones with alkynes to produce bicyclo[3.1.0]hexenes. Formation of nickelacycle from an α,β-double bond and an alkyne followed by intramolecular carbonickelation to the remaining γ,δ-double bond would construct such bicyclic compounds. The products were obtained as single diastereomers.

Introduction

α,β-Unsaturated carbonyl compounds, such as enones and enoates, have been widely used for substrates of nickel-catalyzed cycloaddition to furnish functionalized carbo- or heterocyclic compounds.[1–3] In Chapter 4, the author described nickel-catalyzed [4+2] cycloaddition of dienes, which have a structure combining two enoate moieties, with alkynes. The diene would form nickelacycle by construction of a C–Ni bond at the α-position of one of the enoate moieties and a C–C bond at the β-position of the other enoate moiety with an alkyne, which was the intermediate of the [4+2] cycloaddition (Scheme 1a). On the other hand, simple α,β,γ,δ-unsaturated carbonyl compounds have a structure combining an enone with an electron-rich olefin. In view of the potentially unique reactivity of α,β,γ,δ-unsaturated carbonyl compounds,[4,5] the author explored the nickel-catalyzed cycloaddition of α,β,γ,δ-unsaturated ketones with alkynes. As the result of this investigation, he found that the reaction proceeded through fomation of nickelacycle from an enone moiety and an alkyne followed by intramoleclar reaction of the remaining olefin to afford bicyclo[3.1.0]hexenes (Scheme 1b).[6,7]

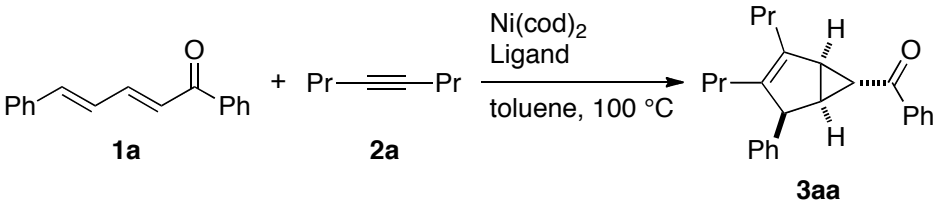


Scheme 1. Formation of C–Ni and C–C bond of α,β,γ,δ-unsaturated carbonyl compounds.

Results and Discussion

First, the author examined the reaction of α,β,γ,δ-unsaturated ketone **1a** with 4-octyne (**2a**) in the presence of $Ni(cod)_2$ (10 mol%) and PPh_3 (20 mol%) in toluene at 100 °C for 16 h (Table 1, entry1). The reaction took place stereoselectively to afford the bicyclo[3.1.0]hexene **3aa** as a

Table 1. Optimization of reaction conditions[a]

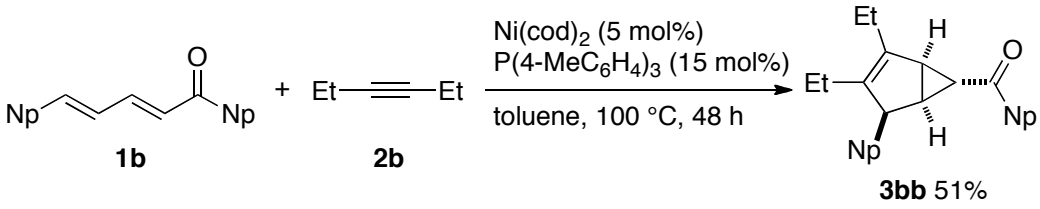


Entry	Ni [mol%]	Ligand	[mol%]	*t* [h]	Yield [%][b]
1	10	PPh_3	20	16	70 (57)
2	10	PCy_3	20	16	51
3	10	$PCyPh_2$	20	16	67
4	10	$PMePh_2$	20	16	<1
5	10	PPh_3	12	16	65
6	10	PPh_3	30	16	63
7	10	PPh_3	30	48	76 (64)
8	10	$P(4\text{-}MeC_6H_4)_3$	30	48	82 (71)
9	10	$P(2\text{-}MeC_6H_4)_3$	30	48	<1
10	10	$P(4\text{-}MeOC_6H_4)_3$	30	48	30
11	10	$P(4\text{-}FC_6H_4)_3$	30	48	79 (67)
12	5	$P(4\text{-}MeC_6H_4)_3$	15	48	(69)

[a] Reactions were carried out using $Ni(cod)_2$, ligand, **1a** (0.50 mmol) and 4-octyne (**2a**; 1.0 mmol, 2 equiv) in 2 mL of toluene at 100 °C. [b] Yield as determined by NMR spectroscopy. Yield of the isolated product is given in parentheses.

single diastereomer. Then, various ligands and the ratio of Ni(0) to ligands were investigated to improve the yield. When alkyl-substituted phosphines were used, the yield became lower (entries 2–4). Tuning the molar ratio of Ni(0) to ligand, the cycloadduct **3aa** was obtained in lower yield, along with some unreacted **1a**, when 30 mol% of PPh_3 was used (entry 6). By prolonging the reaction time to 48 h, the yield of **3aa** was increased (entry 7). Among triarylphosphines examined in this condition, $P(4\text{-}MeC_6H_4)_3$ gave the best yield of **3aa** (entries 8–11). Decreasing the amount of catalyst to 5 mol% did not lower the yield of bicyclo[3.1.0]hexene **3aa** (entry 12).

Having determined the optimal reaction conditions, the author next confirmed the stereochemistry of the cycloadduct by performing the reaction of **1b** with **2b** (Scheme 2). The reaction provided **3bb** in 51% yield as a single isomer. The molecular structure of **3bb** was confirmed using X-ray crystal structure analysis that showed that **3bb** has *cis-exo* stereochemistry at the ring fusion (Figure 1).



Scheme 2. Nickel-catalyzed reaction of **1b** with **2b**. Np = 2-naphthyl.

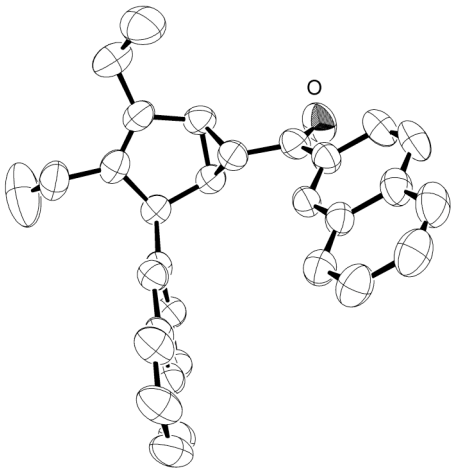
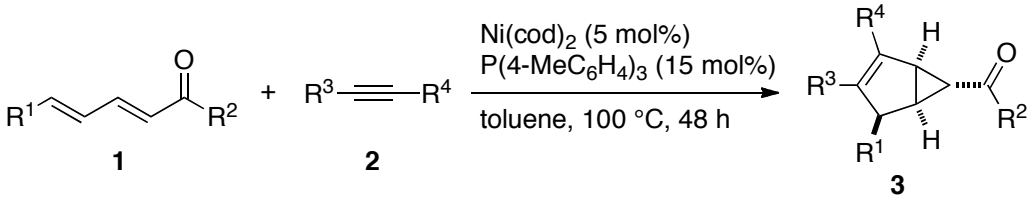


Figure 1. ORTEP drawing of cycloadduct **3bb**.

Then, the author examined the reaction of 4-octyne (**2a**) with various α,β,γ,δ-unsaturated carbonyl compounds **1** having different functional groups (Table 2). It was found that diarylsubstituted α,β,γ,δ-unsaturated ketones **1** reacted with 4-octyne (**2a**) in the presence of a nickel catalyst to stereoselectively provide the corresponding substituted bicyclo[3.1.0]hexenes **3**. Among the examined aryl substituents at R^2, an aryl group with an electron-withdrawing group afforded a higher yield of cycloadduct **3** (entry 1 versus entry 3). Meanwhile, among the examined aryl substituents at R^1, an electron-donating group substituted aryl group gave **3** in higher yield (entry 6 versus entries 7–10). In addition, heteroaryl substituents at R^2 were tolerated to yield bicyclo[3.1.0]hexenes **3** (entries 4 and 5). The reaction of thienyl-substituted dienone **1m** also provided cycloadduct **1ma** in 66% by using 10 mol% of nickel catalyst (entry 11). Alkyl substituent at R^1 afforded corresponding cycloadduct **3na** in 23% yield (entry 12). Acetyl-substituted diene (R^2 = Me) and α,β,γ,δ-unsaturated ester (R^2 = OMe) did not participate in the nickel-catalyzed reaction with **2a**.

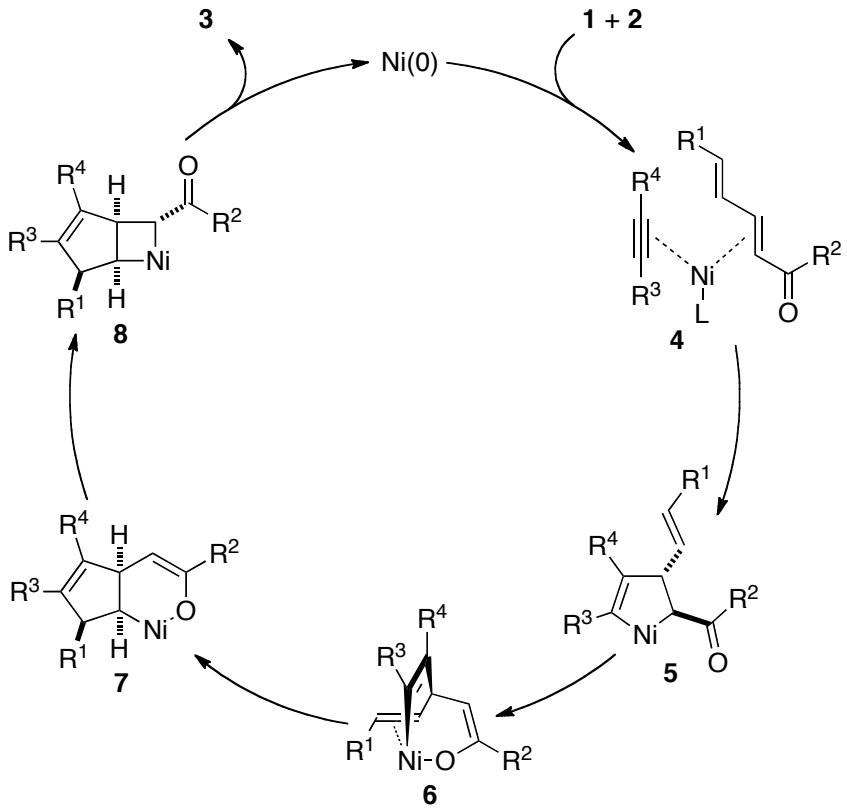
After demonstrating the scope of α,β,γ,δ-unsaturated ketones **1**, the author investigated the reaction scope with regards to alkynes **2**. Alkyl-substituted symmetrical alkynes **2b** and **2c** reacted with **1a** to afford bicyclo[3.1.0]hexenes **3** (Table 2, entries 13 and 14). Cycloalkynes also participated in the reaction with **1a**. Whereas the reaction of strained cyclododecyne (**2d**) resulted in low yield (entry 15), less strained cyclopentadecyne (**2e**) gave cycloadduct **3ae** in 68% yield (entry 16). Moderate regioselectivity of the reaction with an unsymmetrical alkyne **2f** was achieved by using $PCyPh_2$ in place of $P(4\text{-}MeC_6H_4)_3$ (entry 17). In the case of using $P(4\text{-}MeC_6H_4)_3$ as a ligand, **3af** was obtained in 57% yield with a regioselectivity ratio of 2:1. Terminal alkynes and aryl-substituted alkynes failed to participate in the reaction because of rapid oligomerization of the alkynes.

Table 2. Nickel-catalyzed reaction of α,β,γ,δ-unsaturated ketones **1** with alkynes **2**[a]



Entry	**1**	R^1	R^2	**2**	R^3	R^4	**3**	Yield [%][b]
1	**1c**	Ph	4-NCC_6H_4	**2a**	Pr	Pr	**3ca**	60
2	**1d**	Ph	2-MeC_6H_4	**2a**	Pr	Pr	**3da**	49
3	**1e**	Ph	4-$MeOC_6H_4$	**2a**	Pr	Pr	**3ea**	28
4	**1f**	Ph	2-furyl	**2a**	Pr	Pr	**3fa**	53
5	**1g**	Ph	3-pyridyl	**2a**	Pr	Pr	**3ga**	41
6	**1h**	4-$F_3CC_6H_4$	Ph	**2a**	Pr	Pr	**3ha**	19
7	**1i**	2-$MeOC_6H_4$	Ph	**2a**	Pr	Pr	**3ia**	66
8	**1j**	3-$MeOC_6H_4$	Ph	**2a**	Pr	Pr	**3ja**	54
9	**1k**	4-$MeOC_6H_4$	Ph	**2a**	Pr	Pr	**3ka**	74
10	**1l**	4-$Me_2NC_6H_4$	Ph	**2a**	Pr	Pr	**3la**	67
11	**1m**	2-thienyl	Ph	**2a**	Pr	Pr	**3ma**	66
12[c]	**1n**	Me	Ph	**2a**	Pr	Pr	**3na**	23
13	**1a**	Ph	Ph	**2b**	Et	Et	**3ab**	64
14	**1a**	Ph	Ph	**2c**	C_5H_{11}	C_5H_{11}	**3ac**	64
15	**1a**	Ph	Ph	**2d**	–$(CH_2)_{10}$–		**3ad**	30
16	**1a**	Ph	Ph	**2e**	–$(CH_2)_{13}$–		**3ae**	68
17[d]	**1a**	Ph	Ph	**2f**	Me	*i*Pr	**3af**	53 (7/2)[e]

[a] Reactions were carried out using $Ni(cod)_2$ (5 mol%), P(4-$MeC_6H_4)_3$ (15 mol%), **1** (0.50 mmol) and **2** (1.0 mmol, 2 equiv) in 2 mL of toluene at 100 °C for 48 h. [b] Yield of the isolated product. [c] $Ni(cod)_2$ (10 mol%) and P(4-$MeC_6H_4)_3$ (30 mol%). [d] The reaction was carried out using $PCyPh_2$ (15 mol%) in place of P(4-$MeC_6H_4)_3$. [e] Ratio of the regioisomers.



Scheme 3. Plausible reaction mechanism.

While the mechanism of this reaction has not been completely elucidated, based on the observed results the author propose the following reaction mechanism to account for the formation of bicyclo[3.1.0]hexenes **3**, and the stereochemical outcome of the reaction (Scheme 3). The reaction is initiated by the coordination of dienone **1** and alkyne **2** to Ni(0). Oxidative cyclization leading to the formation of nickelacycle **5** is followed by ring expansion to form a seven-membered oxanickelacycle **6** by 1,3-migration.[1h,8] The subsequent intramolecular insertion of the olefin affords bicyclic intermediate **7**, which undergoes 1,3-migration and reductive elimination to give cycloadduct **3** and regenerate the starting Ni(0) catalyst. The *cis* stereochemistry of the ring fusion in bicyclo[3.1.0]hexene **3** may be ascribed to an intramolecular *syn* carbonickelation of the olefin in intermediate **6**. The configuration of substituent R^1 is also established by this process. The stereochemistry of the arylcarbonyl substituent on the cyclopropane ring results from the steric repulsion between this substituent and the cyclopentene

ring. In the reaction of unsymmetrical alkyne **2f**, the sterically demanding environment among the alkyne substituents and the ligand may favor orientation of the small methyl group proximal to the ligand as in **4**.

Conclusion

The author developed an unprecedented reaction, which forms bicyclo[3.1.0]hexene by a nickel-catalyzed intermolecular stereoselective reaction of α,β,γ,δ-unsaturated ketones with alkynes. Although various diastereomers were possible, the product was obtained as a single diastereomer. The structure combining an enone with an electron-rich olefin would be essential for construction of such bicyclic skeleton.

Experimental Section

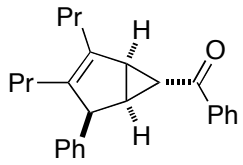
Chemicals. α,β,γ,δ-Unsaturated ketones **1a–n** were prepared by aldol condensation of corresponding acetophenone derivatives with enals.

Experimental procedure for the nickel-catalyzed cycloaddition of α,β,γ,δ-unsaturated ketones with alkynes

General procedure. The reaction was performed in a 5 mL sealed vessel equipped with a Teflon-coated magnetic stirrer tip. An α,β,γ,δ-unsaturated ketone **1** (0.50 mmol) and an alkyne **2** (1.0 mmol) were added to a solution of bis(1,5-cyclooctadiene)nickel (7 mg, 0.025 mmol) and tri(4-methylphenyl)phosphine (23 mg, 0.075 mmol) in toluene (2 mL) in a dry box. The VIAL was taken outside the dry box and heated at 100 ºC for 48 h. The resulting reaction mixture was cooled to ambient temperature and filtered through a silica gel pad, concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate = 40:1) to give the corresponding bicyclohexene **3**.

Characterization data

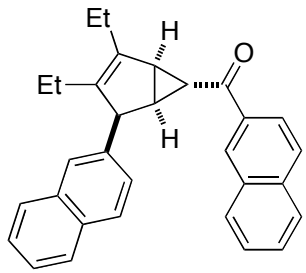
Phenyl((1*R,4*S**,5*R**,6*R**)-4-phenyl-2,3-dipropylbicyclo[3.1.0]hex-2-en-6-yl)methanone (3aa).**



Yellow Powder, mp. 37–39 °C (AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 4.43 (d, *J* = 7.0 Hz, 1H), 2.72 (dd, *J* = 7.0, 3.0 Hz, 1H), 2.53 (td, *J* = 7.0, 3.0 Hz, 1H), 2.36 (t, *J* = 3.0 Hz, 1H), 2.29-2.11 (m, 3H), 1.75 (m, 1H), 1.56 (m, 2H), 1.35 (m, 1H), 1.23 (m, 1H), 0.97 (t, *J* = 7.0 Hz, 3H), 0.82 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.19, 142.50, 141.44, 137.97, 136.90, 132.34, 128.50, 128.37, 128.29, 127.80, 126.36, 54.81, 39.39, 36.45, 32.52,

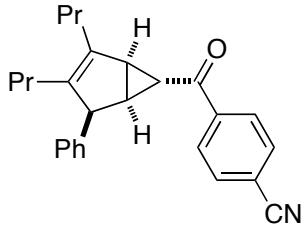
30.52, 28.32, 21.61, 21.15, 14.14, 13.96. IR (KBr): 2957, 1645, 1449, 1382, 1221, 704 cm^{-1}. HRMS (EI) calcd for $C_{25}H_{28}O$ ($[M]^+$): 344.2140. Found: 344.2134.

((1*R,4*S**,5*R**,6*R**)-2,3-Diethyl-4-(naphthalen-2-yl)bicyclo[3.1.0]hex-2-en-6-yl)(naphthalen-2-yl)methanone (3bb).**



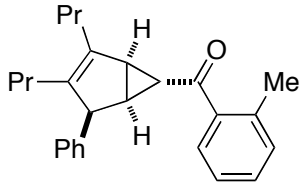
White crystal, mp. 128–130 °C (hexane-CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (m, 3H), 7.73 (m, 2H), 7.66 (m, 3H), 7.55 (m, 2H), 7.45 (m, 2H), 7.30 (t, *J* = 7.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 4.69 (d, *J* = 6.0 Hz, 1H), 2.95 (dd, *J* = 6.0, 3.5 Hz, 1H), 2.60 (t, *J* = 3.5 Hz, 1H), 2.58 (d, *J* = 3.5 Hz, 1H), 2.35 (m, 3H), 1.89 (sext, 7.5 Hz, 1H), 1.20 (t, *J* = 7.5 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.25, 142.72, 140.45, 137.03, 135.17, 135.10, 133.67, 132.45, 132.24, 129.61, 129.22, 128.11, 127.96, 127.92, 127.77, 127.76, 127.55, 127.43, 126.41, 126.24, 126.21, 125.53, 123.53, 54.56, 37.70, 36.88, 33.22, 21.55, 19.49, 13.39, 12.96. IR (KBr): 2961, 1656, 1390, 821, 749 cm^{-1}. HRMS (EI) calcd for $C_{31}H_{28}O$ ($[M]^+$): 416.2140. Found: 416.2137.

4-((1*R,4*S**,5*R**,6*R**)-4-Phenyl-2,3-dipropylbicyclo[3.1.0]hex-2-ene-6-carbonyl)benzonitrile (3ca).**



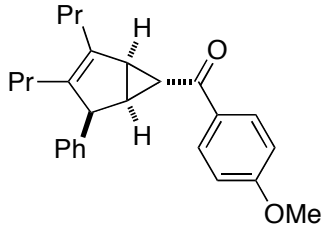
Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (m, 4H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 2H), 4.45 (d, *J* = 6.5 Hz, 1H), 2.79 (d, *J* = 6.5 Hz, 1H), 2.54 (t, *J* = 6.5 Hz, 1H), 2.26 (s, 1H), 2.26–2.13 (m, 3H), 1.76 (m, 1H), 1.55 (m, 2H), 1.35 (m, 1H), 1.23 (m, 1H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.93, 142.33, 141.28, 140.96, 137.18, 132.20, 128.51, 128.41, 128.15, 126.55, 118.03, 115.56, 54.76, 39.82, 37.74, 33.16, 30.45, 28.30, 21.62, 21.13, 14.13, 13.95. IR (neat): 2959, 2231, 1740, 1669, 1375, 1216, 1046, 734 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{27}NO$ ($[M]^+$): 369.2093. Found: 369.2096.

((1*R,4*S**,5*R**,6*R**)-4-Phenyl-2,3-dipropylbicyclo[3.1.0]hex-2-en-6-yl)(*o*-tolyl)methanone (3da).**



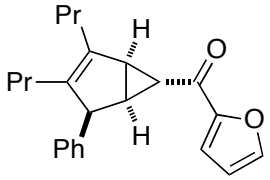
Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.24 (m, 1H), 7.12 (m, 3H), 7.01 (m, 2H), 4.43 (d, *J* = 6.5 Hz, 1H), 2.71 (dd, *J* = 6.5, 2.5 Hz, 1H), 2.53 (td, *J* = 6.5, 2.5 Hz, 1H), 2.25 (s, 3H), 2.23 (m, 2H), 2.12 (t, *J* = 2.5 Hz, 1H), 2.12 (m, 1H), 1.73 (m, 1H), 1.55 (m, 2H), 1.33 (m, 1H), 1.21 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.54, 142.34, 141.27, 139.33, 136.93, 131.24, 130.48, 128.55, 128.38, 126.35, 125.40, 54.79, 39.77, 36.98, 35.57, 30.50, 28.34, 21.65, 21.14, 20.36, 14.15, 13.95. IR (neat): 2958, 1668, 1454, 1378, 1212, 732, 704 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{30}O$ ($[M]^+$): 358.2297. Found: 358.2286.

(4-Methoxyphenyl)((1*R,4*S**,5*R**,6*R**)-4-phenyl-2,3-dipropylbicyclo[3.1.0]hex-2-en-6-yl)-methanone (3ea).**



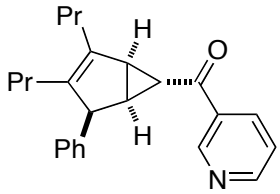
White powder, mp. 78–80 °C (AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.0 Hz, 2H), 7.25 (t, *J* = 7.0 Hz, 1H), 7.15 (d, *J* = 7.0 Hz, 2H), 6.79 (d, *J* = 7.5 Hz, 2H), 4.42 (d, *J* = 6.5 Hz, 1H), 3.82 (s, 3H), 2.67 (d, *J* = 6.5 Hz, 1H), 2.48 (td, *J* = 6.5, 3.0 Hz, 1H), 2.31 (s, 1H), 2.28–2.10 (m, 3H), 1.74 (m, 1H), 1.55 (m, 2H), 1.34 (m, 1H), 1.22 (m, 1H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.64, 163.00, 142.62, 141.55, 136.71, 131.02, 129.99, 128.50, 128.35, 126.31, 113.47, 55.38, 54.77, 38.90, 35.87, 32.07, 30.53, 28.33, 21.60, 21.14, 14.14, 13.94. IR (KBr): 2956, 1639, 1602, 1387, 1171, 1025, 707 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{30}O_2$ ($[M]^+$): 374.2246. Found: 374.2245.

Furan-2-yl((1*R,4*S**,5*R**,6*R**)-4-phenyl-2,3-dipropylbicyclo[3.1.0]hex-2-en-6-yl)methanone (3fa).**



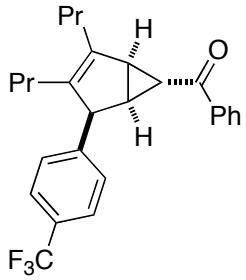
Yellow powder, mp. 61–65 °C (AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, *J* = 1.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.91 (d, *J* = 3.5 Hz, 1H), 6.43 (dd, *J* = 3.5, 1.5 Hz, 1H). 4.40 (d, *J* = 7.0 Hz, 1H), 2.65 (dd, *J* = 7.0, 3.0 Hz, 1H), 2.57 (td, *J* = 7.0, 3.0 Hz, 1H), 2.31 (t, *J* = 3.0 Hz, 1H), 2.28–2.08 (m, 3H), 1.71 (m, 1H), 1.56 (m, 2H), 1.32 (m, 1H), 1.20 (m, 1H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.50, 153.06, 146.01, 142.16, 141.13, 137.28, 128.52, 128.28, 126.40, 116.18, 111.95, 54.83, 39.59, 35.00, 32.04, 30.44, 28.27, 21.54, 21.11, 14.08, 13.92. IR (neat): 2956, 1637, 1468, 1403, 1054, 771, 704 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{26}O_2$ ([M]$^+$): 334.1933. Found: 334.1922.

((1*R,4*S**,5*R**,6*R**)-4-Phenyl-2,3-dipropylbicyclo[3.1.0]hex-2-en-6-yl)(pyridin-3-yl)methanone (3ga).**



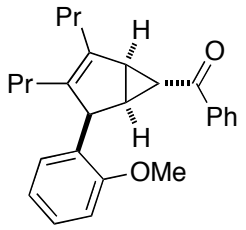
Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.67 (d, *J* = 2.5 Hz, 1H), 7.85 (d, *J* = 3.0 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.28 (m, 2H), 7.15 (d, *J* = 7.5 Hz, 2H), 4.44 (d, *J* = 6.5 Hz, 1H), 2.76 (d, *J* = 6.5 Hz, 1H), 2.59 (t, *J* = 6.5 Hz, 1H), 2.33 (s, 1H), 2.30–2.11 (m, 3H), 1.75 (m, 1H), 1.56 (m, 2H), 1.34 (m, 1H), 1.22 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.91, 152.84, 149.35, 142.25, 141.22, 137.36, 135.00, 133.15, 128.51, 128.40, 126.59, 123.35, 54.85, 40.20, 37.19, 32.77, 30.47, 28.31, 21.63, 21.12, 14.12, 13.94. IR (neat): 2958, 1667, 1586, 1381, 1231, 704 cm^{-1}. HRMS (EI) calcd for $C_{24}H_{27}NO$ ([M]$^+$): 345.2093. Found: 345.2087.

((1*R,4*S**,5*R**,6*R**)-2,3-Dipropyl-4-(4-(trifluoromethyl)phenyl)bicyclo[3.1.0]hex-2-en-6-yl)-(phenyl)methanone (3ha).**



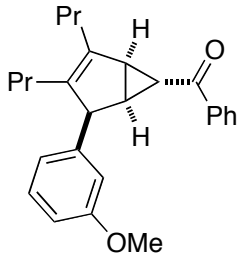
Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.47 (t, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 4.50 (d, J = 6.5 Hz, 1H), 2.74 (dd, J = 6.5, 2.5 Hz, 1H), 2.54 (td, J = 6.5, 2.5 Hz, 1H), 2.31 (t, J = 2.5 Hz, 1H), 2.29–2.15 (m, 3H), 1.70 (m, 1H), 1.57 (m, 2H), 1.34 (m, 1H), 1.22 (m, 1H), 0.98 (t, J = 7.5 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.58, 146.77, 142.45, 137.77, 136.02, 132.57, 128.84 (q, J_{CF} = 33 Hz), 128.72, 128.37, 127.69, 125.36 (q, J_{CF} = 3.9 Hz), 124.28 (q, J_{CF} = 267 Hz), 54.52, 39.30, 35.73, 32.37, 30.51, 28.28, 21.59, 21.12, 14.12, 13.91. IR (neat): 2960, 1665, 1326, 1125, 1069, 698 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{27}F_3O$ ([M]$^+$): 412.2014. Found: 412.2011.

((1*R,4*R**,5*R**,6*R**)-4-(2-Methoxyphenyl)-2,3-dipropylbicyclo[3.1.0]hex-2-en-6-yl)(phenyl)-methanone (3ia).**



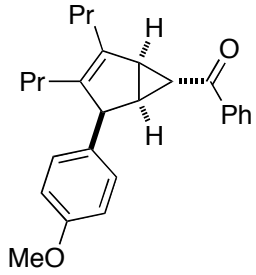
Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.5 Hz, 1H), 7.26 (m, 3H), 6.97 (t, J = 7.5 Hz, 1H), 6.87 (m, 2H), 4.78 (d, J = 6.5 Hz, 1H), 3.82 (s, 3H), 2.72 (dd, J = 6.5, 2.5 Hz, 1H), 2.66 (td, J = 6.5, 2.5 Hz, 1H), 2.30–2.14 (m, 3H), 2.20 (t, J = 2.5 Hz, 1H), 1.80 (m, 1H), 1.55 (m, 2H), 1.35 (m, 1H), 1.23 (m, 1H), 0.96 (t, J = 7.5 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.56, 157.69, 141.36, 138.12, 137.35, 132.18, 131.35, 128.35, 128.23, 127.78, 127.20, 120.03, 110.23, 55.41, 47.56, 39.17, 35.73, 32.84, 30.61, 28.58, 21.65, 21.37, 14.11, 14.03. IR (neat): 2957, 1663, 1217, 1023, 756, 699 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{30}O_2$ ([M]$^+$): 374.2246. Found: 374.2243.

((1*R,4*S**,5*R**,6*R**)-4-(3-Methoxyphenyl)-2,3-dipropylbicyclo[3.1.0]hex-2-en-6-yl)(phenyl)-methanone (3ja).**



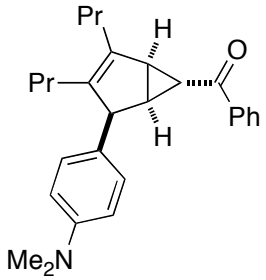
Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 6.81 (m, 1H), 6.75 (d, *J* = 7.5 Hz, 1H), 6.72 (t, *J* = 2.0 Hz, 1H), 4.40 (d, *J* = 6.5 Hz, 1H), 3.81 (s, 3H), 2.70 (dd, *J* = 6.5, 2.5 Hz, 1H), 2.52 (td, *J* = 6.5, 2.5 Hz, 1H), 2.39 (t, *J* = 2.5 Hz, 1H), 2.28–2.10 (m, 3H), 1.77 (m, 1H), 1.55 (m, 2H), 1.36 (m, 1H), 1.23 (m, 1H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.82 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.14, 159.73, 144.16, 141.49, 138.01, 136.90, 132.35, 129.26, 128.30, 127.84, 120.94, 114.64, 111.42, 55.18, 54.84, 39.31, 36.28, 32.57, 30.51, 28.40, 21.61, 21.21, 14,12, 13.97. IR (neat): 2957, 1665, 1217, 1044, 699 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{30}O_2$ ($[M]^+$): 374.2246. Found: 374.2243.

((1*R,4*S**,5*R**,6*R**)-4-(4-Methoxyphenyl)-2,3-dipropylbicyclo[3.1.0]hex-2-en-6-yl)(phenyl)-methanone (3ka).**



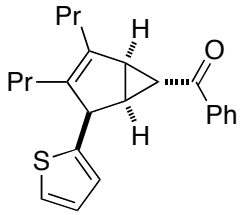
Yellow powder, mp. 55–58 °C (AcOEt).^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.5 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.38 (d, *J* = 6.5 Hz, 1H), 3.81 (s, 3H), 2.69 (dd, *J* = 6.5, 2.5 Hz, 1H), 2.51 (td, *J* = 6.5, 2.5 Hz, 1H), 2.34 (t, *J* = 2.5 Hz, 1H), 2.27–2.09 (m, 3H), 1.72 (m, 1H), 1.55 (m, 2H), 1.34 (m, 1H), 1.19 (m, 1H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.19, 158.26, 141.11, 138.06, 137.24, 134.54, 132.34, 129.40, 128.31, 127.83, 113.84, 55.28, 54.09, 39.50, 36.46, 32.58, 30.54, 28.33, 21.62, 21.13, 14.13, 13.96. IR (neat): 2957, 1664, 1511, 1248, 1039, 829, 699 cm^{-1}. HRMS (EI) calcd for $C_{26}H_{30}O_2$ ($[M]^+$): 374.2246. Found: 374.2243.

((1*R,4*S**,5*R**,6*R**)-4-(4-(Dimethylamino)phenyl)-2,3-dipropylbicyclo[3.1.0]hex-2-en-6-yl)-(phenyl)methanone (3la).**



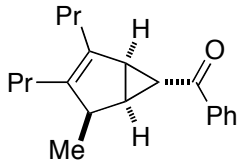
Yellow viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 4.34 (d, *J* = 6.5 Hz, 1H), 2.94 (s, 6H), 2.68 (dd, *J* = 6.5, 2.5 Hz, 1H), 2.51 (td, *J* = 6.5, 2.5 Hz, 1H), 2.36 (t, *J* = 2.5 Hz, 1H), 2.27–2.05 (m, 3H), 1.75 (m, 1H), 1.55 (m, 2H), 1.35 (m, 1H), 1.22 (m, 1H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.41, 149.41, 140.63, 138.18, 137.67, 132.21, 130.45, 129.14, 128.25, 127.90, 112.82, 54.05, 40.80, 39.46, 36.68, 32.78, 30.56, 28.35, 21.63, 21.18, 14.12, 13.96. IR (neat): 2956, 1662, 1515, 1216, 816, 699 cm^{-1}. HRMS (EI) calcd for $C_{27}H_{33}NO$ ($[M]^+$): 387.2562. Found: 387.2553.

((1*R,4*R**,5*S**,6*R**)-2,3-Dipropyl-4-(thiophen-2-yl)bicyclo[3.1.0]hex-2-en-6-yl)(phenyl)methanone (3ma).**



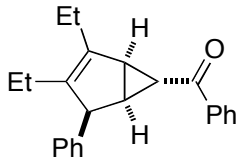
Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, *J* = 7.5 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.20 (d, *J* = 5.0 Hz, 1H), 6.98 (m, 1H), 6.89 (d, *J* = 3.5 Hz, 1H), 4.71 (d, *J* = 6.5 Hz, 1H), 2.69 (dd, *J* = 6.5, 2.5 Hz, 1H), 2.63 (td, *J* = 6.5, 2.5 Hz, 1H), 2.53 (t, *J* = 2.5 Hz, 1H), 2.20 (m, 2H), 2.06 (m, 1H), 1.77 (m, 1H), 1.54 (m, 2H), 1.39 (m, 1H), 1.24 (m, 1H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.80, 145.40, 140.56, 137.86, 137.50, 132.54, 128.43, 128.00, 126.38, 125.35, 123.73, 50.39, 39.88, 35.61, 34.14, 30.43, 28.26, 21.50, 21.28, 14.04, 13.93. IR (neat): 2957, 1648, 1449, 1388, 1227, 700 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{26}OS$ ($[M]^+$): 350.1704. Found: 350.1713.

((1*R,4*R**,5*S**,6*R**)-4-Methyl-2,3-dipropylbicyclo[3.1.0]hex-2-en-6-yl)(phenyl)methanone (3na).**



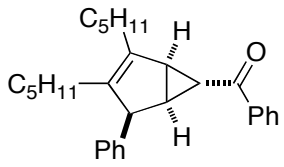
Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.5 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.20 (qd, *J* = 7.0, 6.5 Hz, 1H), 2.56 (dd, *J* = 6.5, 2.0 Hz, 1H), 2.46 (td, *J* = 6.5, 3.0 Hz, 1H), 2.16–2.02 (m, 4H), 1.78 (m, 1H), 1.46 (m, 3H), 1.28 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.49, 139.94, 138.38, 138.24, 132.41, 128.44, 127.85, 43.11, 40.39, 35.58, 32.89, 30.27, 27.94, 21.63, 21.15, 16.22, 14.09, 14.06. IR (neat): 2958, 1662, 1383, 1216, 698 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{26}O$ ([M]$^+$): 282.1984. Found: 282.1973.

((1*R,4*S**,5*R**,6*R**)-2,3-Diethyl-4-phenylbicyclo[3.1.0]hex-2-en-6-yl)(phenyl)methanone (3ab).**



Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.33 (m, 4H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.0 Hz, 2H), 4.47 (d, *J* = 6.5 Hz, 1H), 2.73 (dd, *J* = 6.5, 2.5 Hz, 1H), 2.53 (td, *J* = 6.5, 2.5 Hz, 1H), 2.37 (t, *J* = 2.5 Hz, 1H), 2.25 (m, 3H), 1.73 (qd, *J* = 15.0, 7.5 Hz, 1H), 1.12 (t, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.20, 142.46, 142.25, 138.05, 137.55, 132.34, 128.50, 128.38, 128.30, 127.82, 126.40, 54.48, 38.92, 36.21, 32.67, 21.46, 19.33, 13.35, 12.90. IR (neat): 2964, 1668, 1449, 1386, 1217, 702 cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{25}O$ ([M+H]$^+$): 317.1900. Found: 317.1891.

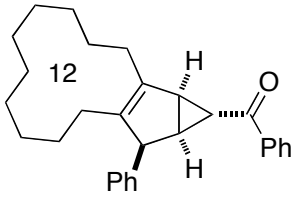
((1*R,4*S**,5*R**,6*R**)-2,3-Dipentyl-4-phenylbicyclo[3.1.0]hex-2-en-6-yl)(phenyl)methanone (3ac).**



Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.33 (m, 4H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 2H), 4.43 (d, *J* = 6.5 Hz, 1H), 2.71 (dd, *J* = 6.5, 2.5 Hz, 1H), 2.54 (td,

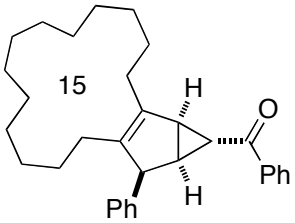
J = 6.5, 2.5 Hz, 1H), 2.36 (t, *J* = 2.5 Hz, 1H), 2.29-2.14 (m, 3H), 1.73 (m, 1H), 1.53 (m, 2H), 1.33 (m, 5H), 1.26–1.11 (m, 5H), 0.90 (t, *J* = 7.5 Hz, 3H), 0.83 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.16, 142.51, 141.44, 138.00, 136.90, 132.34, 128.51, 138.36, 128.28, 127.80, 126.35, 54.84, 39.47, 36.36, 32.60, 31.89, 31.61, 28.42, 28.15, 27.63, 26.18, 22.57, 22.45, 14.07, 13.94. IR (neat): 2931, 1666, 1449, 1383, 1218, 703 cm^{-1}. HRMS (EI) calcd for $C_{29}H_{36}O$ ([M]$^+$): 400.2766. Found: 400.2758.

Phenyl((1*R,1a*R**,12*S**,12a*R**)-12-phenyl-1,1a,2,3,4,5,6,7,8,9,10,11,12,12a-tetradecahydrocyclopropa[3,4]cyclopenta[1,2][12]annulen-1-yl)methanone (3ad).**



White powder, mp. 107–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 2H), 4.43 (d, *J* = 6.5 Hz, 1H), 2.84 (dd, *J* = 6.5, 2.5 Hz, 1H), 2.56 (td, *J* = 6.5, 2.5 Hz, 1H), 2.53 (m, 1H), 2.43 (t, *J* = 2.5 Hz, 1H), 2.37 (m, 1H), 2.08 (m, 1H), 1.73 (m, 2H), 1.65–1.48 (m, 3H), 1.43–1.18 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.29, 142.45, 141.55, 138.01, 137.35, 132.30, 128.57, 128.32, 128.25, 127.82, 126.39, 54.45, 38.41, 36.87, 32.44, 25.44, 24.80, 24.66, 24.60, 24.53, 24.43, 24.21, 22.73, 22.43, 22.20. IR (KBr): 2924, 2851, 1667, 1452, 1219, 708 cm^{-1}. HRMS (EI) calcd for $C_{29}H_{34}O$ ([M]$^+$): 398.2610. Found: 398.2621.

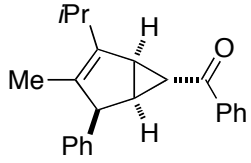
Phenyl((1*R,1a*R**,15*S**,15a*R**)-15-phenyl-1a,2,3,4,5,6,7,8,9,10,11,12,13,14,15,15a-hexadecahydro-1*H*-cyclopropa[3,4]cyclopenta[1,2][15]annulen-1-yl)methanone (3ae).**



Pale yellow solid, mp.110–114 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.34 (m, 4H), 7.27 (t, *J* = 7.0 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 4.45 (d, *J* = 6.5 Hz, 1H), 2.80 (dd, *J* = 6.5, 2.5 Hz, 1H), 2.54 (td, *J* = 6.5, 2.5 Hz, 1H), 2.38 (t, *J* = 2.5 Hz, 1H), 2.33 (m, 1H), 2.17 (m, 2H), 1.71 (m, 1H), 1.56 (m, 2H), 1.43–1.23 (m, 20H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.29, 142.57, 141.56, 138.02, 136.98, 132.31, 128.54, 128.35, 128.26, 127.82,

126.36, 55.11, 39.07, 36.65, 32.56, 27.75, 27.68, 27.64, 27.22, 27.06, 26.91, 26.86, 26.37, 26.30, 26.23, 25.97. IR (KBr): 2927, 2855, 1664, 1640, 1450, 1383, 1222, 1023, 703 cm^{-1}. HRMS (ESI) calcd for $C_{32}H_{41}O$ ($[M+H]^+$): 441.3152. Found: 441.3140.

((1*R,4*S**,5*R**,6*R**)-2-Isopropyl-3-methyl-4-phenylbicyclo[3.1.0]hex-2-en-6-yl)(phenyl)methanone (3af, major)**



Yellow viscous oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.33 (m, 4H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 2H), 4.31 (d, *J* = 6.5 Hz, 1H), 2.79 (m, 2H), 2.53 (td, *J* = 6.5, 3.0 Hz, 1H), 2.33 (t, *J* = 3.0 Hz, 1H), 1.54 (s, 3H), 1.13 (d, *J* = 6.5 Hz, 3H), 1.12 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.07, 146.84, 142.34, 138.02, 132.36, 130.52, 128.50, 128.40, 128.32, 127.80, 126.37, 57.16, 36.16, 35.89, 33.10, 27.30, 21.69, 21.18, 12.26. IR (KBr): 2956, 1665, 1449, 1219, 698 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{24}O$ ($[M]^+$): 316.1827. Found: 316.1833.

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Publication List

1. Parts of present Thesis have been or are to be published in the following journals.

Chapter 1 Selective Synthesis of Trienes and Dienes *via* Nickel-Catalyzed Intermolecular Cotrimerization of Acrylates and Alkynes
Hiroaki Horie, Takuya Kurahashi, and Seijiro Matsubara
Chem. Commun. **2010**, *46*, 7229–7231.

Chapter 2 Nickel-Catalyzed Intermolecular Codimerization of Acrylates and Alkynes
Hiroaki Horie, Ichiro Koyama, Takuya Kurahashi, and Seijiro Matsubara
Chem. Commun. **2011**, *47*, 2658–2660.

Chapter 3 Nickel-Catayzed [2+2+1] Cycloaddition of Alkynes, Acrylates and Isocyanates
Takuya Ozawa, Hiroaki Horie, Takuya Kurahashi, and Seijiro Matsubara
Chem. Commun. **2010**, *46*, 8055–8057.

Chapter 4 Nickel-Catalyzed Formal Inverse Electron-Demand Diels–Alder Type Cycloaddition for Highly Substituted Arenes
Hiroaki Horie, Takuya Kurahashi, and Seijiro Matsubara
Chem. Commun. in press

Chapter 5 Nickel-Catalyzed Cycloaddition of α,β,γ,δ-Unsaturated Ketones with Alkynes
Hiroaki Horie, Takuya Kurahashi, and Seijiro Matsubara
Angew. Chem. Int. Ed. **2011**, *50*, 8956–8959.

2. Following publication is not included in this Thesis.

Sequential Introduction of Carbon Nucleophiles onto Silicon Atoms Using Metyl as a Leaving Group
Hiroaki Horie, Yuichi Kajita, and Seijiro Matsubara
Chem. Lett. **2009**, *38*, 116–117.

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