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<tr>
<td>校名</td>
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<td>学部</td>
<td>博士(工学)</td>
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Studies on Regio- and Stereoselective Multicomponent Coupling Reaction via Nickelacycles

ニッケラサイクルを介した位置および立体選択的 多成分連結反応に関する研究

September 2014
2014 年 9 月

Graduate School of Engineering
Nagasaki University
長崎大学大学院工学研究科

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Preface

The studies presented in this thesis have been carried out under the direction of Professor Dr. Masanari Kimura at the Graduate School of Engineering, Nagasaki University during April 2009 to September 2014. This thesis is concerned with the development of Highly Regio- and Stereoselective Multi-Component Coupling Reaction via Nickelacycles. The author has been a Research Fellow of the Japan Society for the Promotion of Science during April 2012 to March 2015.

The author would like to express his grateful gratitude to Professor Dr. Masanari Kimura for his kind guidance, valuable suggestions, and continuous encouragement throughout this work.

He is sincerely grateful to Associate Professor Shyuji Tanaka, Associate Professor Yasuhiro Arikawa and Dr. Gen Onodera for his pertinent guidance and helpful discussions. He is also grateful to Ms. Mariko Togawa (up to March 2010) and Mr. Toshiyuki Nakamura (up to March 2013) for their valuable comments and discussions.

Furthermore, he wishes to thank Mr. Yushichiro Ohama, NMR Facility, for his helpful suggestions and splendid assistance throughout this study, Ms. Junko Nagaoka for their assistance with X-ray crystallographic analysis, and Mr. Noriaki Yamaguchi and Mr. Nobuaki Tsuda of Joint Research Division for their measurements of mass spectra and elemental analysis. He is also grateful to all of his colleagues and members of Professor Kimura’s research group for his encouragement and helpful discussions.

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Finally, the author thanks his family, Mr. Kingo Mori, Ms. Miyuki Mori, Ms. Sayaka Mori, Ms. Saori Mori, Mr. Taisuke Mori, and Ms. Yoko Sakimoto for their constant encouragement and affectionate assistance.

September 2014

Takamichi Mori
**General Introduction**

Synthetic organic chemistry creates ways important organic compounds, such as physiologically active substances and functionalized molecules. Carbon–carbon bond formation is the most meaningful strategy in synthetic organic chemistry.

Catalytic reactions using transition metals, such as Suzuki-Miyaura cross coupling reaction\(^1\) and Negishi cross coupling reaction\(^2\), are the most powerful tools for the efficient and selective carbon–carbon bond formations. Transition-metal catalyzed organic reactions have been developed for the efficient synthesis of useful compounds in many practical ways\(^3\).

Especially, nickelacycles and heteronickelacycles made from unsaturated hydrocarbons and Ni-complex are attractive and convenient intermediates for C–C bond formation (Scheme 1)\(^4\).

![Scheme 1](image)

Metalacycles are well-known as an important active intermediate for synthetic organic chemistry\(^5\). However, oxametalacycles, in which carbon atom replaced by the oxygen atom, have not been used as active intermediates.

Recently, it became clear that oxanickelacycle could be used as a very useful
active intermediate for the catalytic reactions. In 1997, Montgomery and co-workers have found a reductive coupling reaction of alkyne and aldehyde via oxanickelacycle to provide allylalcohols 1 (eq. 1)\textsuperscript{6}. Kimura, Tamaru and co-workers have reported that the reductive coupling reaction of conjugated diene and aldehyde via oxanickelacycle to provide bishomoallylalcohols 2 in 1998 (eq. 2)\textsuperscript{7}. Furthermore, Kimura and Tamaru developed multicomponent coupling reaction of unsaturated hydrocarbon and carbonyl compounds via oxanickelacycle as active intermediates\textsuperscript{8}. The first example of the isolation oxanickelacycle has been reported by Ogoshi and Kurosawa in 2004 (eq. 3, Figure 1)\textsuperscript{9}. Since then, many reports on the catalytic reaction via oxanickelacycles have been appeared. And the related organic synthesis have been developed to construct complicated molecules.
This thesis is composed of three chapters.

Chapter 1: Multicomponent coupling reaction of alkyne, Me₂Zn and vinylic cyclic compounds via oxanickelacycle is described.

Chapter 2: Multicomponent coupling reaction of alkyne, Et₃B and N,O-acetals prepared from cyclic hemiacetals and primary amines via azanickelacycle is developed.

Chapter 3: Selective formation of unsaturated carboxylic acid and phenyl acetic acid from diketene via nickelacycles as active intermediates is demonstrated.

Chapter 1 deals with Ni-catalyzed three-component coupling reaction of alkynes, Me₂Zn, and vinyloxyacyclopropane or vinylcyclopropane through oxanickelacycle intermediates to provide dienyl homoallylalcohols and α-dienyl malonates (Scheme 2)¹⁰. The reaction is readily conducted by exposing of Me₂Zn to a mixture of vinyloxyacyclopropane and alkynes at room temperature under nitrogen atmosphere. Alkynes tends to attack on the terminal carbon atom of the vinylic group to afford heptadienyl alcohols with mixture of E and Z isomers. Furthermore, the coupling
reactions of alkynes, Me₂Zn, and vinylcyclopropane derived from dimethyl malonate and 1,4-dichloro-2-butene under similar catalytic conditions are also investigated. The reaction proceeds smoothly at room temperature within several hours and the coupling products are obtained with excellent $E$-stereoselectivities.

![Scheme 2]

Chapter 2 describes that Ni-catalyzed homoallylation of $N,O$-acetals prepared from cyclic hemiacetals and primary amines to provide $\omega$-hydroxybischomoallylamines in high regio- and stereoselectivity (Scheme 3). In similar catalytic reaction systems, $N,O$-acetals from carbohydrates with primary amines give rise to the polyhydroxy-bischomoallylamines as physiologically active molecules for development of medicinal and synthetic chemistry.
Chapter 3 deals with selective formation of unsaturated carboxylic acids and phenyl acetic acids from diketene (Scheme 4). It’s shown that Ni-catalyzed multicomponent coupling reaction of alkyne, dimethylzinc, and diketene (as butenoic acid equivalent) to provide 3-methylene-4-hexenoic acids in a single manipulation (path A)\textsuperscript{12}. On the other hand, in the presence of Ni catalyst, a formal [2+2+2] cycloaddition reaction with diketene and two equivalents of alkynes proceeds to give phenylacetic acid derivatives by use of Et\textsubscript{2}Al(OEt) instead of Me\textsubscript{2}Zn (path B). Furthermore, in the presence of Ni catalyst and PPh\textsubscript{3} under the similar catalytic conditions, the regioselectivity was changed dramatically to provide the symmetrical substituted phenylacetic acid as a single product via C–C double bond cleavage of diketene (path C, D).

Ni-catalyzed oxidative cyclization of alkyne and diketene seems to form nickelacyclopentene intermediate. In the absence of phosphine ligand, the ring expansion reaction undergoes to form oxanickelacycle intermediate, whereas, in the presence of phosphine ligand, the active nickelacycle bearing PPh\textsubscript{3} ligand invokes C–C bond cleavage reaction via nickel carbene cyclopropane rearrangement\textsuperscript{13}.
References


(5) (a) 中村晃，安田源，有機合成化学協会誌，**1980**, 38, 975.

(b) 山崎博史，岩槻康雄，化学総説「有機金属錯体の化学」，日本化学会，**1981**, No. 32, 161.


*Angew. Chem. Int. Ed.*, accepted for publication (ASAP).

(13) Palladacyclopentene rearrangements involving Pd carbene complex have been reported by B. M. Trost et al:


Chapter 1

Multicomponent Coupling Reaction via Oxanickelacycle:
Stereoselective Coupling Reaction of Dimethylzinc and Alkyne toward Nickelacycles

Summary: Ni-catalyzed three-component coupling reaction of Me₂Zn, alkynes, and vinyloxacyclopropanes and vinylecyclopropanes to afford dienyl alcohols and α-heptadienyldimethyl malonates in excellent yields with high stereoselectivities.
Introduction

Multicomponent coupling reaction is among the most efficient and straightforward synthetic strategies for C–C bond transformation. Especially, Ni-catalyzed coupling reactions, which have involving unsaturated hydrocarbons, are widely utilized for the synthesis of physiologically active compounds and complicated molecules. We previously reported the Ni(0) catalyst accelerated oxidative cyclization of aldehydes and conjugated dienes in the presence of Et$_3$B and Et$_2$Zn, with subsequent reductive coupling, to provide bis-homoallyl alcohols with excellent regio- and stereoselectivities through key oxanickelacycle intermediates. Furthermore, we demonstrated that similar catalytic systems promoted the four-component coupling of 1,3-butadiene, alkynes, aldehydes, and dimethylzinc to provide 3,6-octadienyl alcohols with excellent regio- and stereoselectivities (Scheme 1).

Ikeda et al. reported the Ni-catalyzed three-component coupling reaction of allyl chloride, an alkyne, and Me$_2$Zn in the presence of Ni catalyst via the syn stereoselective addition manner of π-allylnickel species followed by methyl group transfer to the alkyne carbon atom to construct 1,4-pentadiene skeletons (Scheme 2).
Furthermore, the Ni(0) metal-catalyzed coupling reaction of alkyne-tethered vinylcyclopropanes with allyl chloride has been reported. In this case, the addition of the π-allylnickel species to the alkyne moiety proceeds with β-syn elimination of the cyclopropyl C–C bond giving the (E)-1,3-diene with excellent regio- and
stereoselectivities. Encouraged by these multicomponent coupling reactions involving \( \pi \)-allylnickel species by Ikeda’s protocols and our previous strategies utilizing oxanickelacycles with alkynes and organozinc reagents, we were prompted to develop stereodefined functionalizations using allylating agents and alkynes based on the structural variety of oxanickelacycles.

Herein, we would like to report highly regio- and stereocontrolled three-component coupling reaction of alkynes, dimethylzinc, and vinyloxacyclopropane, vinylcyclopropanes involving the addition of \( \pi \)-allylnickel species toward the alkynes to provide 2,5-heptadienyl alcohols and 2,5-heptadienyl malonates.
Results and Discussion

The reaction was readily conducted by exposing Me$_2$Zn to a mixture of vinyloxacyclopropane and alkynes at room temperature under nitrogen atmosphere. The results using various kinds of ligands and solvents are shown in Table 1. The initial investigation using vinyloxacyclopropane and 3-hexyne made it clear that THF was the most effective solvent (entries 1-8, Table 1). In all cases, the alkynes tended to attack on the terminal carbon atom of the vinylic group to afford heptadienyl alcohol 3aa via methyl group transfer from Me$_2$Zn in a 3:1 ratio of $E$ and $Z$ isomers with respect to the C-2 olefin geometry. Among these results with various kinds of ligands using monodentate, bidentate phosphine ligands, and NHC ligands, no ligands at room temperature provided the best result in the formation of the desired product (entries 9-13, Table 1).

Next, we conducted the multicomponent coupling reaction of substituted vinyloxacyclopropane, various alkynes, and Me$_2$Zn under the optimized conditions of Table 1. Although diphenylacetylene participated in the coupling reaction in good yield to afford a mixture of $E$ and $Z$ isomers (entry 1, Table 2), bis(trimethylsilyl)acetylene and an electron-deficient alkyne did not provide the desired results (entries 2 and 3, Table 2). An unsymmetrical alkyne took part in the coupling reaction in excellent yields to give 3ae as four inseparable regio- and stereoisomers and 3af as two stereoisomers (entries 4 and 5, Table 2).
Table 1. Optimization of Reaction Conditions for the Nickel-Catalyzed Three-Component Coupling Reaction of Alkyne, Vinyloxacyclopropane and \( \text{Me}_2\text{Zn} \)\(^a\)

![Chemical reaction image](image-url)

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>solvent</th>
<th>condition</th>
<th>yield of 3aa (%) [E/Z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>THF</td>
<td>r.t., 24 h</td>
<td>92 [3:1]</td>
</tr>
<tr>
<td>2(^b)</td>
<td>none</td>
<td>THF</td>
<td>r.t., 24 h</td>
<td>90 [3:1]</td>
</tr>
<tr>
<td>3</td>
<td>none</td>
<td>THF</td>
<td>50 °C, 24 h</td>
<td>89 [3:1]</td>
</tr>
<tr>
<td>4</td>
<td>none</td>
<td>toluene</td>
<td>80 °C, 24 h</td>
<td>81 [3:1]</td>
</tr>
<tr>
<td>5</td>
<td>none</td>
<td>toluene</td>
<td>110 °C, 24 h</td>
<td>82 [3:1]</td>
</tr>
<tr>
<td>6</td>
<td>none</td>
<td>ether</td>
<td>r.t., 24 h</td>
<td>84 [3:1]</td>
</tr>
<tr>
<td>7</td>
<td>none</td>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>r.t., 24 h</td>
<td>59 [3:1]</td>
</tr>
<tr>
<td>8</td>
<td>none</td>
<td>dioxane</td>
<td>r.t., 24 h</td>
<td>20 [3:1]</td>
</tr>
<tr>
<td>9</td>
<td>Ph(_3)P</td>
<td>THF</td>
<td>r.t., 48 h</td>
<td>71 [3:1]</td>
</tr>
<tr>
<td>10</td>
<td>n-Bu(_3)P</td>
<td>THF</td>
<td>r.t., 48 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>11(^c)</td>
<td>dppf</td>
<td>THF</td>
<td>r.t., 48 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>12(^d)</td>
<td>dppbz</td>
<td>THF</td>
<td>r.t., 48 h</td>
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(Table 1, continued)

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<tr>
<th>13c</th>
<th>NHC</th>
<th>THF</th>
<th>r.t., 24 h</th>
<th>81 [1:1]</th>
</tr>
</thead>
</table>

\(^a\) The reaction was conducted in the presence of vinyloxacyclopropane (1 mmol), Ni(acac)$_2$ (0.1 mmol), ligand (0.2 mmol), 3-hexyne (1 mmol), and dimethylzinc (1.2 mmol; 1 M hexane) in solvent (3 mL) under nitrogen atmosphere.

\(^b\) Ni(cod)$_2$ (0.1 mmol) was used instead of Ni(acac)$_2$.

\(^c\) dppf: diphenylphosphinoferrocene (0.1 mmol) was used.

\(^d\) dppbz: diphenylphosphinobenzene (0.1 mmol) was used.

\(^e\) NHC ligand was prepared from 1,3-bis(2,6-diisopropylphenyl)-imidazolium chloride with 0.2 mmol of \(t\)-BuOK.

Two equivalents of terminal alkynes were required to afford the products 3ag and 3ah in modest yields along with the branched regioisomers 4ag and 4ah, which were produced by attack of the terminal alkynes on the internal allylic position of vinyloxacyclopropane (entries 6 and 7, Table 2). 2-Methyl-2-vinyloxacyclopropane underwent a similar coupling reaction in good to excellent yields, and employment of 3-hexyne and diphenylacetylene led to the formation of the desired product 3ba and 3bb in high yields in a 1:2 to 1:3 ratios of \(E\) and \(Z\) stereoisomers (entries 8 and 9, Table 2). Bis(trimethylsilyl)acetylene showed the modest yield and selectivity as well as the result of butadiene monoxide (entry 10, Table 2).
Table 2. Scope of the Nickel-Catalyzed Three-Component Coupling Reaction of Vinyloxacyclopropane 1 with Alkyne 2\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>epoxide R</th>
<th>alkyne R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>yield of 3 and 4 (%) [E/Z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H (1a)</td>
<td>Ph</td>
<td>Ph (2b)</td>
<td>3ab: 84 [2:1]</td>
</tr>
<tr>
<td>2</td>
<td>H (1a)</td>
<td>TMS</td>
<td>TMS (2c)</td>
<td>3ac: 35 [2:1]</td>
</tr>
<tr>
<td>3</td>
<td>H (1a)</td>
<td>CO\textsubscript{2}Me</td>
<td>CO\textsubscript{2}Me (2d)</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>H (1a)</td>
<td>Et</td>
<td>Ph (2e)</td>
<td>3ae: 93 [4 isomers]</td>
</tr>
<tr>
<td>5</td>
<td>H (1a)</td>
<td>Me</td>
<td>TMS (2f)</td>
<td>3af: 97 [2:1]</td>
</tr>
<tr>
<td>6\textsuperscript{b}</td>
<td>H (1a)</td>
<td>H</td>
<td>Ph (2g)</td>
<td>3ag: 81 [2:1], 4ag: 15</td>
</tr>
<tr>
<td>7\textsuperscript{b}</td>
<td>H (1a)</td>
<td>H</td>
<td>TMS (2h)</td>
<td>3ah: 64 [2:1], 4ah: 33</td>
</tr>
<tr>
<td>8</td>
<td>Me (1b)</td>
<td>Et</td>
<td>Et (2a)</td>
<td>3ba: &gt;99 [1:2]</td>
</tr>
<tr>
<td>9</td>
<td>Me (1b)</td>
<td>Ph</td>
<td>Ph (2b)</td>
<td>3bb: 73 [1:3]</td>
</tr>
<tr>
<td>10</td>
<td>Me (1b)</td>
<td>TMS</td>
<td>TMS (2c)</td>
<td>3bc: 61 [1:1]</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The reaction was undertaken in the presence of vinyloxacyclopropane (1 mmol), Ni(acac)\textsubscript{2} (0.1 mmol), alkyne (1 mmol), and dimethylzinc (1.2 mmol; 1 M hexane) in THF (3 mL) under nitrogen atmosphere.

\textsuperscript{b} Alkyne (4 mmol) was used.
Based on the optimized catalytic systems, we examined the multicomponent coupling reaction of vinyloxacyclopropane and substituted alkynes, and dimethylzinc in the multi-grams scale to give the corresponding dienyl alcohols 3 and 4 in good to reasonable yields. In that case, even if it reduces catalyst quantity to 1 mol%, it is satisfactory (Table 3).

**Table 3.** Scope of the Nickel-Catalyzed Three-Component Coupling Reaction of Vinyloxacyclopropane 1 with Alkyne 2 on a 15-mmol Scale\(^a\)

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>epoxide R</th>
<th>alkyne R(^1)</th>
<th>R(^2)</th>
<th>yield of 3 and 4 (%) [E/Z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H (1a)</td>
<td>Et</td>
<td>Et (2a)</td>
<td>3aa: 99 [3:1]</td>
</tr>
<tr>
<td>2</td>
<td>H (1a)</td>
<td>Ph</td>
<td>Ph (2b)</td>
<td>3ab: 99 [2:1]</td>
</tr>
<tr>
<td>3</td>
<td>H (1a)</td>
<td>TMS</td>
<td>TMS (2c)</td>
<td>3ac: 41 [2:1]</td>
</tr>
<tr>
<td>4</td>
<td>H (1a)</td>
<td>Et</td>
<td>Ph (2e)</td>
<td>3ae: 95 [4 isomers]</td>
</tr>
<tr>
<td>5</td>
<td>H (1a)</td>
<td>Me</td>
<td>TMS (2f)</td>
<td>3af: 97 [2:1]</td>
</tr>
</tbody>
</table>
(Table 3, continued)

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</thead>
<tbody>
<tr>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>H (1a)</td>
<td>H</td>
<td>Ph (2g)</td>
<td>3ag: 37 [2:1], 4ag: 18</td>
</tr>
<tr>
<td>7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>H (1a)</td>
<td>H</td>
<td>TMS (2h)</td>
<td>3ah: 27 [2:1], 4ah: 10</td>
</tr>
<tr>
<td>8</td>
<td>Me (1b)</td>
<td>Et</td>
<td>Et (2a)</td>
<td>3ba: 93 [1:2]</td>
</tr>
<tr>
<td>9</td>
<td>Me (1b)</td>
<td>Ph</td>
<td>Ph (2b)</td>
<td>3bb: 84 [1:3]</td>
</tr>
<tr>
<td>10</td>
<td>Me (1b)</td>
<td>TMS</td>
<td>TMS (2c)</td>
<td>3bc: 41 [1:1]</td>
</tr>
</tbody>
</table>

<sup>a</sup> The reaction was undertaken in the presence of vinyloxacyclopropane (18 mmol), Ni(acac)<sub>2</sub> (0.15 mmol), alkyne (15 mmol), and dimethylzinc (15 mmol; 1 M hexane) in THF (30 mL) under nitrogen atmosphere.

<sup>b</sup> Alkyne (45 mmol) was used.
A plausible reaction mechanism for the multicomponent coupling reaction of vinyloxacyclop propane, alkyne, and dimethylzinc is displayed in Scheme 3. Low stereoselectivities for the coupling reactions using vinyloxacyclop propane might originate from the formation of the $\pi$-allyloxanickelacycle intermediate I in equilibrium with the 6-membered oxanickelacycle II. It is known that vinyloxacyclop propane readily undergoes oxidative addition toward Ni(0) metal species coordinated by alkynes to form four- or six-membered oxanickelacycles. This is followed by methyl group transfer from the Zn atom to the Ni metal center, leading to C–C bond formation and a mixture of E and Z isomers. Terminal carbons of phenylacetylene and trimethylsilylacetylene attack on the allylic position of vinyloxacyclop propane to afford the branched regiosomers 4 owing to less steric repulsion between the H atom of the terminal alkyne and the allylic moiety of intermediate III (Scheme 3).
Scheme 3. Reaction Mechanism for Three-Component Coupling Reaction of Vinyloxacyclopropane, Alkyne and Me₂Zn

In case of R¹ = H
The coupling reaction with various alkynes, dimethylzinc, and vinylcyclopropane, which is prepared from dimethyl malonate with 1,4-dichloro-2-butene, are summarized in Table 4. In most cases, the reaction proceeded smoothly at room temperature within several hours and the coupling products were obtained with excellent $E$-stereoselectivities (entries 1 and 2, Table 4). The trimethylsilyl group also took part in efficient coupling to give the corresponding desired product 5ce in moderate yield with $E$-stereoselectivity (entry 3, Table 4). And an electron-deficient alkyne did not provide the desired result (entry 4, Table 4). Unsymmetrical internal alkynes participated in the coupling reaction giving rise to a mixture of regioisomers with exclusive $E$-stereoselectivities (entries 5 and 6, Table 4). In all cases, the stereochemistry with respect to the Me group and the olefinic main chain is the Z-form, as in the reaction of vinylcyclopropane. The reaction feature using terminal alkyne such as phenylacetylene and trimethylsilylacetylene were changed dramatically and the desired product 5 was not obtained at all. Instead, the dienynes 7cg and 7ch, involving dimerization of the terminal alkynes, were produced as major products by the stereoselective coupling reaction with vinylcyclopropane (entries 7 and 8, Table 4).
Table 4. Scope of the Nickel-Catalyzed Three-Component Coupling Reaction of Vinylcyclopropane 1c with Alkyne 2

![Reaction diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne $\text{R}^1$</th>
<th>alkyne $\text{R}^2$</th>
<th>time (h)</th>
<th>yield of 5, 6 and 7 (%) [E/Z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>Et ($\text{2a}$)</td>
<td>1</td>
<td>$\text{5ca}$: 84 [E only]</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph ($\text{2b}$)</td>
<td>3</td>
<td>$\text{5cb}$: 73 [E only]</td>
</tr>
<tr>
<td>3</td>
<td>TMS</td>
<td>TMS ($\text{2c}$)</td>
<td>3</td>
<td>$\text{5cc}$: 63 [E only]</td>
</tr>
<tr>
<td>4</td>
<td>CO$_2$Me</td>
<td>CO$_2$Me ($\text{2d}$)</td>
<td>24</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>Ph ($\text{2e}$)</td>
<td>6</td>
<td>$\text{5ce}$: 92 [E only]$^b$</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>TMS ($\text{2f}$)</td>
<td>1</td>
<td>$\text{5cf}$: 83 [E only]</td>
</tr>
<tr>
<td>7$^c$</td>
<td>H</td>
<td>Ph ($\text{2g}$)</td>
<td>24</td>
<td>$\text{7cg}$: 71 [E only]</td>
</tr>
<tr>
<td>8$^c$</td>
<td>H</td>
<td>TMS ($\text{2h}$)</td>
<td>6</td>
<td>$\text{7ch}$: 56 [E only], $\text{6ch}$: 24</td>
</tr>
</tbody>
</table>

$^a$ The reaction was undertaken in the presence of vinylcyclopropane (1 mmol), Ni(acac)$_2$ (0.1 mmol), alkyne (1 mmol), and dimethylzinc (1.2 mmol; 1 M hexane) in THF (3 mL) under nitrogen atmosphere.

$^b$ Product $\text{5ce}$ was obtained as a mixture of regioisomer in a 3:1 ratio.

$^c$ Alkyne (4 mmol) was used.
Moreover, also in a multi-gram scale, a reaction advances equal, and this reaction gives the same products. In that case, even if it reduces catalyst quantity to 1 mol%, it is satisfactory (Table 5).

**Table 5.** Scope of the Nickel-Catalyzed Three-Component Coupling Reaction of Vinylcyclopropane 1c with Alkyne 2 on a 15-mmol Scale

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne R¹</th>
<th>R²</th>
<th>time (h)</th>
<th>yield of 5, 6 and 7 (%) [E/Z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>Et (2a)</td>
<td>24</td>
<td>5ca: 80 [E only]</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph (2b)</td>
<td>24</td>
<td>5cb: 68 [E only]</td>
</tr>
<tr>
<td>3</td>
<td>TMS</td>
<td>TMS (2c)</td>
<td>24</td>
<td>5cc: 59 [E only]</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>Ph (2e)</td>
<td>24</td>
<td>5ce: 83 [E only]</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>TMS (2f)</td>
<td>24</td>
<td>5cf: 91 [E only]</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>Ph (2g)</td>
<td>24</td>
<td>7cg: 65 [E only]</td>
</tr>
</tbody>
</table>

*a The reaction was undertaken in the presence of vinylcyclopropane (1 mmol), Ni(acac)₂ (0.1 mmol), alkyne (1 mmol), and dimethylzinc (1.2 mmol; 1 M hexane) in THF (3 mL) under nitrogen atmosphere.  
*b Product 5ce was obtained as a mixture of regioisomer in a 3:1 ratio.  
*c Alkyne (4 mmol) was used.
The stereochemistry of the products was unequivocally determined on the basis of NOE experiments. The results of irradiation at the bold protons are illustrated in Figure 1. According to the NOE results, irrespective of the kinds of regioisomers derived from the symmetrical and unsymmetrical alkynes, it was apparent that methyl group transfer from Me₂Zn to the acetylenic triple bond proceeded in a syn manner to deliver Z-stereochemistry with respect to the C5 olefinic geometry and E-stereochemistry with respect to the C2 position by the ring expanding reaction processes of the vinylcyclopropyl groups.

**Figure 1.** NOE Data for the Irradiation at the Bold Methylene Protons.
A reaction mechanism for the coupling reaction of alkyne, vinlycyclopropane, and Me₂Zn is displayed in Scheme 4. The exclusive \( E \)-stereochemistry might stem from the stability of the produced nickelacycles. Formation of allylnickel species \( \text{IV} \) would predominate over that of 8-membered ring species \( \text{V} \) owing to the entropy effect for the ring-closing reaction. This is followed by insertion of the alkyne to the allylic terminus of the allylnickel species to provide \((E)-5\) isomer exclusively. As in the case of using terminal alkyne, zinc acetylide derived from dimethylzinc and terminal alkyne might preferentially participate in the coupling reaction via transmetalation with allylnickel species \( \text{VI} \) to give rise to diene-yne \( 7 \) as the major products. Since Ni(0) catalysts tend to promote a head-to-tail dimerization of terminal alkynes in the presence of organozinc reagents to give the enyne framework, the alternative coupling reaction involving dimerization of terminal alkyne followed by carbonickelation toward vinlycyclopropane to provide diene-yne \( 7 \) might be probable⁸.
Scheme 4. Reaction Mechanism for Three-Component Coupling Reaction of Vinylcyclopropane, Alkyne and Me$_2$Zn
In summary, we have demonstrated Ni-catalyzed multicomponent coupling reaction of vinyloxacyclopropane, alkyne, and dimethylzinc to provide 2,5-heptadienyl alcohols as a mixture of $E$ and $Z$ isomers in high yields. Furthermore, vinylcyclopropane participated in highly regio- and stereoselective multicomponent coupling reaction to afford dimethyl($\alpha$-2,5-heptadienyl)malonates with excellent $E$-stereoselectivity. And we have succeeded to extend these reactions in multi-grams scale for the efficient synthesis of dienyl alcohols and steredefined dienyl esters$^9$. These reactions could be performed with standard laboratories glassware and equipment and did no require the expensive and specialized chemicals and catalysts.
Experimental Section

Reactions employed oven-dried glassware unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator (Merck, Silica gel 60F\textsubscript{254}). Flash chromatography columns were packed with 230-400 mesh silica gel as a slurry in hexane. Gradient flash chromatography was conducted eluting with a continuous gradient from hexane to the indicated solvent. Distillation were carried out in a Kugelrohr apparatus (SIBATA glass tube oven GTO-350RG). Boiling points are meant to refer to the oven temperature (± 1 °C). Microanalyses were performed by the Instrumental Analysis Center of Nagasaki University. Analysis agreed with the calculated values within ± 0.4%. Proton and carbon NMR data were obtained with a JEOL-GX400 with tetramethylsilane as an internal standard. Chemical shift values were given in ppm downfield from the internal standard. Infrared spectra were recorded with a JASCO A-100 FT-IR or SHIMAZU FTIR-8700 spectrophotometer. High resolution mass spectra (HRMS) were measured with a JEOL JMS-DX303.

Solvents and Reagents

Tetrahydrofuran, diethyl ether, and 1,4-dioxane were dried and distilled from benzophenone and sodium immediately prior to use under nitrogen atmosphere. Anhydrous toluene and dichloromethane were purchased (Aldrich) and used without further purification. Ni(acac)\textsubscript{2}, PPh\textsubscript{3}, n-Bu\textsubscript{3}P, dpff \textsubscript{[1,1’-bis(diphenylphosphino)ferro-}
cene], 1,3-bis(2,6-di-isopropylphenyl)imidazolium chloride, and Me₂Zn (1.0 M hexane solution) (Kanto Kagaku) were purchased and used without further purification. 3-Hexyne, dimethylacetylene, bis(methoxycarbonyl)ethyne, 1-phenyl-1-butyne, phenylacetylene, trimethylsilylacetylene, bistrimethylacetylene, and diphenylacetylene (Tokyo Kasei Kogyo Co., Ltd) were purchased and distilled prior to use. Butadiene monoxide and isoprene oxide (Aldrich) were purchased and distilled prior to use. Dimethyl 2-vinylcyclopropane-1,1-dicarboxylate was prepared according to the literature¹⁰.
General procedure 1: for the Nickel-catalyzed three-component coupling reaction of alkynes, vinyloxacyclopropane and Me₂Zn (entry 1, Table 1)

An oven-dried, 25 mL, three-necked round-bottomed flask equipped with a dropping funnel, a rubber septum cap, an air condenser (fitted with a three-way stopcock connected into nitrogen balloon), and a Teflon-coated magnetic stir bar was charged with Ni(acac)₂ (25.7 mg, 0.1 mmol). The apparatus was purged with nitrogen and the flask was charged successively via syringe with freshly dry THF (3 mL), vinyloxacyclopropane (70.1 mg, 1 mmol), and 3-hexyne (82.1 mg, 1 mmol). Dimethylzinc (1.2 mmol, 1.0 M hexane solution) was added slowly at room temperature via the dropping funnel over a period of 10 min (the reaction temperature should not be exceeded 50 °C). The mixture was stirred at room temperature for 24 h and monitored by TLC. After the reaction was completed, the reaction mixture was cooled to 0 °C, and then poured into ice-water. The resulting solution was diluted with 30 mL of EtOAc and carefully washed with 2 M HCl, with sat. NaHCO₃, and brine. The aqueous layer was extracted with 30 mL of EtOAc. The combined organic phases were dried (MgSO₄) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (eluent; hexane/EtOAc = 16/1 v/v) to afford 3aa as a colorless oil (155.6 mg, 92%; \( R_f = 0.45 \); hexane/EtOAc = 4/1 v/v); bp 100 °C /0.1 mmHg.
(2E,5E)-5-Ethyl-6-methylocta-2,5-dien-1-ol : (3aa)

![Structure of (2E,5E)-5-Ethyl-6-methylocta-2,5-dien-1-ol (3aa)](image)

(2E,5E)-5-Ethyl-6-methylocta-2,5-dien-1-ol (3aa): (a mixture of E- and Z- isomers in a ratio of 3 : 1): IR (neat) 3319 (m), 2962 (s), 2931 (s), 2872 (s), 1655 (w), 1458 (m), 1373 (m), 1070 (m), 1004 (m), 970 (m), 792 (w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, (E)-) δ 0.94 (t, J = 7.6 Hz, 3 H), 0.97 (t, J = 7.6 Hz, 3 H), 1.62 (s, 3 H), 2.03 (q, J = 7.6 Hz, 2 H), 2.04 (q, J = 7.6 Hz, 2 H), 2.75 (br m, 2 H), 5.62 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃, (E)-) δ 13.3, 13.6, 17.5, 24.9, 27.0, 34.7, 63.8, 127.9, 128.8, 131.2, 131.6; ¹H-NMR (400 MHz, CDCl₃, (Z)-): δ 0.94 (t, J = 7.6 Hz, 3 H), 0.97 (t, J = 7.6 Hz, 3 H), 1.58 (s, 3 H), 2.03 (q, J = 7.6 Hz, 2 H), 2.04 (q, J = 7.6 Hz, 2 H), 2.80 (d, J = 7.3 Hz, 2 H), 5.45 (dt, J = 11.0, 7.3 Hz, 1 H), 5.58 (dm, J = 11.0 Hz, 1 H); ¹³C-NMR (100 MHz, CDCl₃, (Z)-) δ 13.2, 13.6, 17.5, 24.8, 27.1, 30.2, 58.7, 127.9, 128.8, 131.0, 131.4; High-resolution MS, calcd for C₁₁H₂₀O: 168.1514. Found m/z (relative intensity): 169(M⁺+1, 1), 168.1497 (M⁺, 8), 167 (20), 151 (27), 150 (31), 139 (100).

(2E,5Z)-5,6-Diphenylhepta-2,5-dien-1-ol : (3ab)

Following General Procedure 1. Purification by flash chromatography (eluent; hexane/EtOAc = 8/1 v/v) afforded 3ab as a colorless oil. bp 180 °C/0.1 mmHg.
(2E,5Z)-5,6-Diphenylhepta-2,5-dien-1-ol (3ab): (a mixture of E- and Z- isomers in a ratio of 2 : 1): IR (neat) 3350 (s), 3055 (s), 3020 (s), 2993 (s), 2928 (s), 2870 (m), 1717 (s), 1682 (s), 1599 (m), 1489 (s), 1443 (s), 1026 (m), 970 (m), 912 (m), 764 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, (E)-) δ 2.17 (s, 3 H), 3.31 (br m, 2 H), 4.10 (br m, 2 H), 5.72 (m, 2 H), 7.00 (m, 10 H); ¹³C NMR (100 MHz, CDCl₃, (E)-) δ 21.1, 37.9, 63.6, 125.6, 127.4, 127.5, 128.9, 129.0, 129.4, 129.5, 129.6, 134.7, 142.8, 143.1, 144.1; ¹H NMR (400 MHz, CDCl₃, (Z)-): δ 2.20 (s, 3 H), 3.34 (d, J = 6.6 Hz, 2 H), 4.00 (d, J = 6.3 Hz, 2 H), 5.57 (dt, J = 10.2, 6.6 Hz, 1 H), 5.72 (dt, J = 10.2, 6.3 Hz, 1 H), 7.00 (m, 10 H); ¹³C NMR (100 MHz, CDCl₃, (Z)-) δ 20.9, 33.5, 58.4, 125.8, 127.4, 127.5, 128.9, 129.3, 129.4, 129.5, 129.6, 135.4, 142.8, 143.1, 144.0; High-resolution MS, calcd for C₁₉H₂₀O: 264.1514. Found m/z (relative intensity): 264.1440 (M⁺, 42), 263 (100), 262 (51), 246 (57).

(2E,5Z)-5,6-Bis(trimethylsilyl)hepta-2,5-dien-1-ol : (3ac)

Following General Procedure 1. Purification by flash chromatography (eluent; hexane/EtOAc = 12/1 v/v) afforded 3ac as a colorless oil. bp 110 °C/0.1 mmHg.

(2E,5Z)-5,6-Bis(trimethylsilyl)hepta-2,5-dien-1-ol (3ac): (a mixture of E- and Z-
isomers in a ratio of 2:1): IR (neat) 3329 (m), 2955 (s), 2899 (m), 2864 (m), 1456 (w), 1248 (s), 1001 (m), 968 (m), 837 (m), 756 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.12 (s, 18 H), 1.26 (br, 1 H), 1.78 (s, 3 H), 2.89 (d, J = 7.6 Hz, 2 H), 4.26 (d, J = 6.3 Hz, 2 H), 5.60-5.68 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃, (E)-) δ 0.4, 17.6, 33.4, 63.8, 128.6, 130.3, 142.9; ¹³C NMR (100 MHz, CDCl₃, (Z)-) δ 0.4, 17.6, 31.6, 60.3, 128.6, 130.3, 143.3; High-resolution MS, calcd for C₁₃H₂₈OSi₂: 256.1679. Found m/z (relative intensity): 257 (M⁺+1, 24), 256.1679 (M⁺, 100), 225 (9).

(2E,5E)-5-Ethyl-6-phenylhepta-2,5-dien-1-ol : (3ae)

Following General Procedure 1. Purification by flash chromatography (eluent; hexane/EtOAc = 8/1 v/v) afforded 3ae as a colorless oil. bp 150 °C/0.1 mmHg.

(2E,5E)-5-Ethyl-6-phenylhepta-2,5-dien-1-ol (3ae): (a mixture of 4 isomers, the ratio was not determined): IR (neat) 3350 (s), 3057 (m), 3020 (m), 2968 (s), 2933 (s), 2873 (s), 1717 (s), 1682 (s), 1599 (m), 1491 (s), 1441 (s), 1026 (s), 972 (m), 766 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, (2E)-) δ 0.89 (t, J = 7.6 Hz, 3 H), 1.58 (br s, 1 H), 1.89 (q, J = 7.6 Hz, 2 H), 1.93 (s, 3 H), 2.94 (br m, 2 H), 4.14 (br m, 2 H), 5.73 (m, 2 H), 7.10 (t, J = 7.6 Hz, 2 H), 7.21 (d, J = 7.6 Hz, 2 H), 7.30 (t, J = 7.6 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃, (2E)-) δ 13.4, 21.0, 26.2, 33.8, 63.7, 125.8, 127.8, 127.9, 128.5, 129.3, 130.4, 130.9, 144.9; ¹H NMR (400 MHz, CDCl₃, (2Z)-) δ 0.90 (t, J = 7.6 Hz, 3 H),
1.31 (br s, 1 H), 1.89 (q, $J = 7.6$ Hz, 2 H), 1.95 (s, 3 H), 2.98 (d, $J = 7.3$ Hz, 2 H), 4.31 (d, $J = 6.6$ Hz, 2 H), 5.56 (dt, $J = 10.7$, 7.3 Hz, 1 H), 5.67 (dt, $J = 10.7$, 6.6 Hz, 1 H), 7.10 (t, $J = 7.6$ Hz, 2 H), 7.21 (d, $J = 7.6$ Hz, 2 H), 7.29 (t, $J = 7.6$ Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$, (2Z)-) $\delta$ 13.3, 20.9, 26.1, 29.4, 58.7, 125.8, 127.9, 127.9, 128.6, 129.2, 130.4, 130.9, 144.9; High-resolution MS, calcd for C$_{15}$H$_{20}$O: 216.1514. Found $m/z$ (relative intensity): 217 (M$^+$+1, 16), 216.1496 (M$^+$, 100), 214 (15), 199 (36).

(2E,5E)-5-methyl-6-(trimethylsilyl)hepta-2,5-dien-1-ol: (3af)

Following General Procedure 1, Purification by distillation afforded 3af as a color less oil. bp 115 °C/0.1mmHg.

(2E,5E)-5-methyl-6-(trimethylsilyl)hepta-2,5-dien-1-ol (3af): (a mixture of 2E- and 2Z- isomers in a ratio of 2 : 1): IR (neat): 3312 (s), 2953 (s), 2912 (s), 2860 (m), 1612 (m), 1445 (m), 1247 (s), 1001 (m), 835 (s), 756 (s), 687 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, (E)-): $\delta$ 0.12 (s, 9 H), 1.26 (brs, 1 H), 1.70 (s, 3 H), 1.78 (s, 3 H), 2.84 (d, $J = 7.4$ Hz, 2 H), 4.09 (d, $J = 6.3$ Hz, 2 H), 5.45-5.65 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, (E)-): $\delta$ 0.4, 17.6, 21.1, 37.9, 63.7, 128.4, 129.2, 131.9, 142.9; $^1$H NMR (400 MHz, CDCl$_3$, (Z)-): $\delta$ 0.13 (s, 9 H), 1.35 (brs, 1 H), 1.71 (s, 3 H), 1.85 (s, 3 H), 2.89 (d, $J = 7.4$ Hz, 2 H), 4.25 (d, $J = 6.3$ Hz, 2 H), 5.45-5.65 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, (Z)-): $\delta$ 0.7, 17.6, 22.9, 34.3, 58.6, 128.6, 129.8, 130.3, 144.7; High-resolution MS, calcd for C$_{11}$H$_{22}$OSi: 198.1440. Found $m/z$ (relative intensity): 199 (M$^+$+1, 10), 38
General procedure 2: for the Nickel-catalyzed three-component coupling reaction of alkynes, vinyloxacyclopropane and Me₂Zn (entry 6, Table 1)

An oven-dried, 25 mL, three-necked round-bottomed flask equipped with a dropping funnel, a rubber septum cap, an air condenser (fitted with a three-way stopcock connected into nitrogen balloon), and a Teflon-coated magnetic stir bar was charged with Ni(acac)₂ (25.7 mg, 0.1 mmol). The apparatus was purged with nitrogen and the flask was charged successively via syringe with freshly dry THF (3 mL), vinyloxacyclopropane (70.1 mg, 1 mmol), and phenylacetylene (409 mg, 4 mmol). Dimethylzinc (1.2 mmol, 1.0 M hexane solution) was added slowly at room temperature via the dropping funnel over a period of 10 min (the reaction temperature should not be exceeded 50 °C). The mixture was stirred at room temperature for 24 h and monitored by TLC. After the reaction was completed, the reaction mixture was cooled to 0 °C, and then poured into ice-water. The resulting solution was diluted with 30 mL of EtOAc and carefully washed with 2 M HCl, with sat. NaHCO₃, and brine. The aqueous layer was extracted with 30 mL of EtOAc. The combined organic phases were dried (MgSO₄) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (eluent; hexane/EtOAc = 16/1 v/v) to afford 3ag as a colorless oil (152.4 mg, 81%; \( R_f = 0.40; \) hexane/EtOAc = 4/1 v/v).

\((2E,5E)-6\text{-Phenylhepta-2,5-dien-1-ol} : (3ag)\)
(2E,5E)-6-Phenylhepta-2,5-dien-1-ol (3ag): (a mixture of E- and Z- isomers in a ratio of 2 : 1): IR (neat) 3371 (br), 3024 (s), 2926 (s), 2872 (s), 1719 (m), 1647 (m), 1495 (s), 1447 (s), 1028 (s), 927 (s), 760 (s), 698 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, (E)-): δ 1.55 (br, 1 H), 2.05 (t, J = 1.0 Hz, 3 H), 2.99 (t, J = 7.0 Hz, 2 H), 4.12 (d, J = 5.3 Hz, 1 H), 4.27 (d, J = 5.3 Hz, 1 H), 5.60-5.80 (m, 3 H), 7.21 (tt, J = 7.0, 2.0 Hz, 1 H), 7.30 (td, J = 7.0, 1.5 Hz, 2 H), 7.36 (dt, J = 7.0, 1.3 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, (E)-) δ 15.8, 31.4, 63.6, 125.5, 126.6, 128.0, 128.2, 129.4, 130.7, 135.9, 143.5; ¹H NMR (400 MHz, CDCl₃, (Z)-): δ 1.55 (br, 1 H), 2.05 (t, J = 1.0 Hz, 3 H), 2.95 (t J = 7.0 Hz, 2 H), 4.12 (d, J = 5.3 Hz, 1 H), 4.27 (d, J = 5.3 Hz, 1 H), 5.60-5.80 (m, 3 H), 7.21 (tt, J = 7.0, 2.0 Hz, 1 H), 7.30 (td, J = 7.0, 1.5 Hz, 2 H), 7.36 (dt, J = 7.0, 1.3 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, (Z)-) δ 15.8, 27.3, 58.6, 125.5, 126.6, 128.0, 128.2, 128.8, 130.7, 135.6, 143.4; High-resolution MS, calcd for C₁₃H₁₆O: 188.1183. Found m/z (relative intensity): 189 (M⁺+1, 8), 188.1183 (M⁺, 54), 171 (13), 157 (48).

(E)-4-Phenyl-2-vinylpent-3-en-1-ol: (4ag)

Following General Procedure 2, Purification by flash column chromatography afforded 4ag as a color less oil.

(E)-4-Phenyl-2-vinylpent-3-en-1-ol (4ag): IR (neat): 3362 (br), 3080 (s), 2928 (s), 2872 (s), 1726 (s), 1636 (m), 1597 (m), 1493 (m), 914 (m), 758 (s), 696 (s) cm⁻¹; ¹H
NMR (400 MHz, CDCl₃): δ 1.54 (s, 1 H), 2.09 (d, J = 1.5 Hz, 3 H), 3.38 (ddt, J = 10.3, 9.0, 7.4 Hz 1 H), 3.62 (d, J = 7.4 Hz, 2 H), 5.17 (dd, J = 7.6, 1.5 Hz, 1 H), 5.20 (dd, J = 17.3, 1.5 Hz, 1 H), 5.63 (dq, J = 9.0, 1.5 Hz, 1 H), 5.78 (ddd, J = 17.3, 10.3, 7.6 Hz, 1 H), 7.24 (tt, J = 7.9, 2.3 Hz, 1 H), 7.31 (td, J = 7.9, 1.5 Hz, 2 H), 7.39 (dt, J = 7.9, 1.3 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃): δ 16.4, 46.3, 65.5, 116.5, 125.6, 125.9, 126.9, 128.1, 137.4, 138.0, 143.3; High-resolution MS, calcd for C₁₃H₁₆O: 188.1183. Found m/z (relative intensity): 189 (M⁺+1, 7), 188.1183 (M⁺, 46), 157 (100), 142 (76).

**(2E,5E)-6-(Trimethylsilyl)hepta-2,5-dien-1-ol: (3ah)**

Following General Procedure 2, Purification by flash column chromatography afforded 3ah as a color less oil.

**(2E,5E)-6-(Trimethylsilyl)hepta-2,5-dien-1-ol (3ah): (a mixture of E- and Z-isomers in a ratio of 2:1):** IR (neat): 3317 (br), 3009 (s), 2955 (s), 2899 (s), 1614 (m), 1404 (m), 1248 (s), 1013 (s), 970 (s), 837 (s), 750 (s), 689 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, (E)-): δ 0.01 (s, 9 H), 1.28 (s, 1 H), 1.63 (d, J = 0.9 Hz, 3 H), 2.84 (t, J = 6.9 Hz, 2 H), 4.06 (d, J = 5.6 Hz, 2 H), 5.62 (m, 3 H); ¹³C NMR (100 MHz, CDCl₃, (E)-): δ -2.1, 14.4, 31.2, 63.7, 128.5, 129.1, 131.0, 135.9; ¹H NMR (400 MHz, CDCl₃, (Z)-): 0.01 (s, 9 H), 1.28 (s, 1 H), 1.65 (d, J = 0.9 Hz, 3 H), 2.81 (t, J = 6.9 Hz, 2 H), 4.19 (d, J = 5.6 Hz, 2 H), 5.62 (m, 3 H); ¹³C NMR (100 MHz, CDCl₃, (Z)-): δ -2.1, 14.4, 27.0, 58.6, 128.5, 129.1, 131.0, 135.9; High-resolution MS, calcd for C₁₀H₂₀OSi: 184.1283.
Found m/z (relative intensity): 185 (M$^+$+1, 16), 184.1261 (M$^+$, 100), 170 (12), 169 (82), 166(34).

\( (E)-4\)-(Trimethylsilyl)-2-vinylpent-3-en-1-ol: (4ah) \)

Following General Procedure 2, Purification by flash column chromatography afforded 4ah as a color less oil.

\( (E)-4\)-(Trimethylsilyl)-2-vinylpent-3-en-1-ol (4ah): \) IR (neat): 3313 (br), 3080 (m), 2955 (s), 2874 (m), 1618 (m), 1406 (m), 1248 (s), 1028 (s), 991 (m), 835 (s), 750 (s), 689 (m) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.07 (s, 9 H), 1.43 (s, 1 H), 1.73 (d, $J$ = 1.7 Hz, 3 H), 3.38 (tdd, $J$ = 8.5, 7.8, 6.7 Hz, 1 H), 3.52 (d, $J$ = 7.8 Hz, 2 H), 5.11 (dd, $J$ = 17.6, 1.7 Hz, 1 H), 5.12 (dd, $J$ = 9.8, 1.7 Hz, 1 H), 5.53 (dq, $J$ = 8.5, 1.7 Hz, 1 H), 5.72 (ddd, $J$ = 17.6, 9.8, 6.7 Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 1.6, 15.4, 46.3, 65.6, 116.7, 136.5, 137.9, 140.9; High-resolution MS, calcd for C$_{10}$H$_{20}$OSi: 184.1283. Found m/z (relative intensity): 185 (M$^+$+1, 16), 184.1261 (M$^+$, 100), 170 (12), 169 (82), 166(34).

\( (2Z,5E)-5\)-Ethyl-2,6-dimethylocta-2,5-dien-1-ol: (3ba) \)

Following General Procedure 1, Purification by distillation afforded 3ba as a color less oil. bp 105 °C/0.1mmHg.
(2Z,5E)-5-Ethyl-2,6-dimethylocta-2,5-dien-1-ol (3ba): (a mixture of E- and Z-isomers in a ratio of 1 : 2): IR (neat): 3336 (m), 2964 (s), 2934 (s), 2872 (s), 1653 (m), 1456 (s), 1375 (s), 1005 (s), 951 (w), 785 (w) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), (Z)-): \(\delta\) 0.94 (t, \(J = 7.6\) Hz, 3 H), 0.96 (t, \(J = 7.6\) Hz, 3 H), 1.64 (s, 3 H), 1.80 (d, \(J = 1.2\) Hz, 3 H), 1.99 (q, \(J = 7.6\) Hz, 2 H), 2.02 (q, \(J = 7.6\) Hz, 2 H), 2.77 (d, \(J = 7.1\) Hz, 2 H), 4.19 (s, 2 H), 5.21 (tq, \(J = 7.1, 1.2\) Hz, 1 H); \(^1\)C NMR (100 MHz, CDCl\(_3\), (Z)-): \(\delta\) 13.2, 13.6, 17.5, 21.3, 24.6, 27.1, 30.2, 61.7, 127.2, 130.5, 132.2, 133.7; \(^1\)H NMR (400 MHz, CDCl\(_3\), (E)-): \(\delta\) 0.94 (t, \(J = 7.6\) Hz, 3 H), 0.96 (t, \(J = 7.6\) Hz, 3 H), 1.64 (s, 3 H), 1.72 (s, 3 H), 1.99 (q, \(J = 7.6\) Hz, 2 H), 2.02 (q, \(J = 7.6\) Hz, 2 H), 2.75 (d, \(J = 6.6\) Hz, 2 H), 4.00 (s, 2 H), 5.31 (t, \(J = 6.6\) Hz, 1 H); \(^1\)C NMR (100 MHz, CDCl\(_3\), (E)-): \(\delta\) 13.2, 13.6, 13.8, 17.6, 24.9, 27.1, 30.4, 69.1, 125.4, 130.5, 132.3, 134.2; High-resolution MS, calcd for C\(_{12}\)H\(_{22}\)O: 182.1671. Found \(m/z\) (relative intensity): 183 (M\(^+\) + 1, 10), 182.1669 (M\(^+\), 69), 164 (100).

(2Z,5Z)-2-Methyl-5,6-diphenylhepta-2,5-dien-1-ol: (3bb)

Following General Procedure 1, Purification by distillation afforded 3bb as a color less oil. bp 170 °C /0.1mmHg.

(2Z,5Z)-2-Methyl-5,6-diphenylhepta-2,5-dien-1-ol (3bb): (a mixture of E- and Z-
isomers in a ratio of 1 : 3): IR (neat): 3350 (s), 3057 (m), 3024 (s), 2968 (s), 2933 (s), 2876 (s), 1719 (s), 1701 (s), 1670 (m), 1599 (m), 1491 (s), 1437 (s), 1026 (m), 912 (m), 760 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, (Z)-): δ 1.55 (br s, 1 H), 1.74 (d, J = 1.2 Hz, 3 H), 2.20 (s, 3 H), 3.30 (d, J = 7.6 Hz, 2 H), 3.91 (s, 2 H), 5.31 (tq, J = 7.6, 1.2 Hz, 1 H), 6.92 - 7.08 (m, 10 H); ¹³C NMR (100 MHz, CDCl₃, (Z)-): δ 20.9, 21.3, 33.8, 61.5, 124.6, 125.7, 127.4, 127.5, 128.9, 129.6, 135.2, 136.0, 143.0, 144.1. ¹H NMR (400 MHz, CDCl₃, (E)-): δ 1.55 (br s, 1 H), 1.63 (s, 3 H), 2.18 (s, 3 H), 3.30 (d, J = 7.6 Hz, 2 H), 3.97 (s, 2 H), 5.41 (t, J = 7.6 Hz, 1 H), 6.92 - 7.08 (m, 10 H); ¹³C NMR (100 MHz, CDCl₃, (E)-): δ 13.8, 21.1, 33.8, 68.8, 123.5, 125.5, 127.4, 127.5, 129.0, 129.4, 135.2, 136.0, 143.0, 144.1; High-resolution MS, calcd for C₂₀H₂₂O: 278.1671. Found m/z (relative intensity): 279 (M⁺+1, 17), 278.1658 (M⁺, 73), 260 (100).

(2Z,5Z)-2-methyl-5,6-bis(trimethylsilyl)hepta-2,5-dien-1-ol: (3bc)

Following General Procedure 1, Purification by distillation afforded 3bc as a color less oil. bp 170 °C /0.1mmHg.

(2Z,5Z)-2-methyl-5,6-bis(trimethylsilyl)hepta-2,5-dien-1-ol (3bc): (a mixture of E- and Z- isomers in a ratio of 1 : 1): IR (neat): 3396 (br), 2955 (s), 2899 (s), 1717 (s), 1699 (s), 1437 (m), 1248 (s), 1047 (s), 1009 (s), 839 (s), 756 (s), 689 (m) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, (Z)-): δ 0.14 (s, 9 H), 0.18 (s, 9 H), 1.72 (s, 3 H), 1.80 (brs, 1 H), 1.83 (s, 3 H), 2.85 (d, J = 6.7 Hz, 2 H), 4.19 (d, J = 4.2 Hz, 2 H), 5.04 (t, J = 6.7 Hz,
$^1$H NMR (400 MHz, CDCl$_3$, (E)-): $\delta$ 0.13 (s, 9 H), 0.17 (s, 9 H), 1.72 (s, 3 H), 1.80 (brs, 1 H), 1.83 (s, 3 H), 2.83 (d, $J$ = 6.8 Hz, 2 H), 4.19 (d, $J$ = 4.2 Hz, 2 H), 5.02 (t, $J$ = 6.8 Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$, (E)-): $\delta$ 0.81, 1.93, 18.7, 20.2, 25.4, 61.9, 125.9, 133.5, 143.9, 151.2; High-resolution MS, calcd for C$_{14}$H$_{30}$OSi$_2$: 270.1835. Found m/z (relative intensity): 270.1812 (M$^+$, 100), 269 (72), 254 (94).

**General procedure 3: for the Nickel-catalyzed three-component coupling reaction of alkynes, vinylcyclopropane and Me$_2$Zn (entry 1, Table 3)**

An oven-dried, 25 mL, three-necked round-bottomed flask equipped with a dropp- ing funnel, a rubber septum cap, an air condenser (fitted with a three-way stopcock connected into nitrogen balloon), and a Teflon-coated magnetic stir bar was charged with Ni(acac)$_2$ (25.7 mg, 0.1 mmol). The apparatus was purged with nitrogen and the flask was charged successively via syringe with freshly dry THF (3 mL), vinylcyclo- propane (184 mg, 1 mmol), and 3-hexyne (82.1 mg, 1 mmol). Dimethylzinc (1.2 mmol, 1.0 M hexane solution) was added slowly at room temperature via the dropping funnel over a period of 10 min (the reaction temperature should not be exceeded 50 °C). The mixture was stirred at room temperature for 1 h and monitored by TLC. After the reaction was completed, the reaction mixture was cooled to 0 °C, and then poured into ice-water. The resulting solution was diluted...
with 30 mL of EtOAc and carefully washed with 2 M HCl, with sat. NaHCO₃, and brine. The aqueous layer was extracted with 30 mL of EtOAc. The combined organic phases were dried (MgSO₄) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (eluent; hexane/EtOAc = 16/1 v/v) to afford 5ca as a colorless oil (236.6 mg, 84%; Rf = 0.60; hexane/EtOAc = 4/1 v/v). bp 130 °C /0.1mmHg.

**Dimethyl-2-((2E,5E)-5-ethyl-6-methylocta-2,5-dienyl)malonate: (5ca)**

![Structure of 5ca]

**Dimethyl-2-((2E,5E)-5-ethyl-6-methylocta-2,5-dienyl)malonate (5ca):** IR (neat): 2959 (s), 2882 (m), 1738 (s), 1655 (w), 1437 (s), 1340 (m), 1269 (m), 1161 (m), 974 (m), 698 (w) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, (E)-): δ 0.91 (t, J = 7.6 Hz, 3 H), 0.96 (t, J = 7.6 Hz, 3 H), 1.54 (s, 3 H), 1.97 (q, J = 7.6 Hz, 2 H), 2.02 (q, J = 7.6 Hz, 2 H), 2.58 (ddd, J = 7.8, 6.8, 1.2 Hz, 2 H), 2.67 (d, J = 6.1 Hz, 2 H), 3.40 (t, J = 7.8 Hz, 1 H), 3.71 (s, 6 H), 5.32 (dt, J = 15.1, 6.8 Hz, 1 H), 5.46 (dtt, J = 15.1, 6.1, 1.2 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃, (E)-): δ 13.3, 13.6, 17.5, 24.7, 27.0, 31.9, 35.0, 52.1, 52.3, 52.7, 124.9, 127.7, 131.1, 131.8, 169.2, 172.4; High-resolution MS, calcd for C₉H₁₅O₄: 282.1831. Found m/z (relative intensity): 282.1829 (M⁺, 100), 253 (64), 251 (25).

**Dimethyl-2-((2E,5Z)-5,6-diphenylhepta-2,5-dienyl)malonate: (5cb)**
Following General Procedure 3, Purification by distillation afforded 5cb as a colorless oil. bp 190 °C /0.1mmHg

Dimethyl-2-((2E,5Z)-5,6-diphenylhepta-2,5-dienyl)malonate (5cb): IR (neat): 3078 (w), 3020 (s), 2999 (m), 1599 (w), 1491 (m), 1435 (s), 1339 (m), 1267 (m), 1232 (m), 1198 (m), 1155 (s), 972 (w), 764 (s), 700 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.13 (s, 3 H), 2.60 (ddd, J = 7.6, 6.8, 1.0 Hz, 2 H), 3.23 (d, J = 5.9 Hz, 2 H), 3.38 (t, J = 7.6 Hz, 1 H), 3.69 (s, 6 H), 5.46 (dt, J = 15.1, 6.8 Hz, 1 H), 5.58 (dtt, J = 15.1, 5.9, 1.0 Hz, 1 H), 6.90-7.06 (m, 10 H); ¹³C NMR (100 MHz, CDCl₃): δ 21.0, 31.9, 38.2, 52.0, 52.3, 52.4, 125.5, 125.6, 127.3, 127.4, 128.6, 128.9, 129.4, 134.5, 134.9, 138.9, 143.3, 144.2, 169.1; High-resolution MS, calcd for C₂₄H₂₆O₄: 378.1831. Found m/z (relative intensity): 379 (M⁺+1, 27), 378.1835 (M⁺, 100), 360 (3).

Dimethyl-2-((2E,5Z)-5,6-bis(trimethylsilyl)hepta-2,5-dienyl)malonate: (5cc)

Following General Procedure 3, Purification by distillation afforded 5cc as a colorless oil. bp 120 °C /0.1mmHg.

Dimethyl-2-((2E,5Z)-5,6-bis(trimethylsilyl)hepta-2,5-dienyl)malonate (5cc): IR (neat): 2957 (s), 1736 (s), 1456 (m), 1437 (m), 1340 (m), 1248 (s), 1198 (s), 1155 (s), 972 (m), 839 (m) cm⁻¹; ¹H NMR (400MHz, CDCl₃): δ 0.15 (s, 18 H), 1.76 (s, 3 H),
2.62 (d, J = 6.4 Hz, 2 H), 2.62 (t, J = 7.5 Hz, 2 H), 3.42 (t, J = 7.5 Hz, 1 H), 3.75 (s, 6 H), 5.64-5.46 (m, 2 H); 13C NMR (100 MHz, CDCl3): δ -2.1, 22.8, 32.1, 52.3, 125.5, 130.1, 143.2, 150.5, 169.3; High-resolution MS, calcd for C18H34O4Si2: 370.1996. Found m/z (relative intensity): 371 (M++1, 22), 370.2006 (M+, 78), 355 (100), 339 (6).

**Dimethyl-2-((2E,5E)-5-ethyl-6-phenylhepta-2,5-dienyl)malonate: (5ce)**

Following General Procedure 3, Purification by distillation afforded 5ce as a color less oil. bp 140 °C/0.1 mmHg.

\[ \text{Ph} \quad \text{Et} \quad \text{CO}_2\text{Me} \quad \text{CO}_2\text{Me} \]

**Dimethyl-2-((2E,5E)-5-ethyl-6-phenylhepta-2,5-dienyl)malonate (5ce): (a mixture of regioisomers in a ratio of 3:1):** IR (neat): 3020 (m), 2959 (s), 2934 (s), 1738 (s), 1491 (m), 1437 (s), 1232 (s), 1153 (s), 1026 (m), 970 (m), 768 (s), 704 (s) cm⁻¹; 1H NMR (400 MHz, CDCl₃, (major)-): δ 0.86 (t, J = 7.4 Hz, 3 H), 1.85 (q, J = 7.4 Hz, 2 H), 1.90 (s, 3 H), 2.63 (td, J = 7.3, 1.2 Hz, 2 H), 2.85 (d, J = 6.2 Hz, 2 H), 3.44 (t, J = 7.3 Hz, 1 H), 3.72 (s, 6 H), 5.46 (dtt, J = 15.4, 7.3, 1.5 Hz, 1 H), 5.57 (dtt, J = 15.4, 6.2, 1.5 Hz, 1 H), 7.09 (dd, J = 7.5, 1.4 Hz, 2 H), 7.19 (tt, J = 7.5, 1.4 Hz, 1 H), 7.29 (td, J = 7.5, 1.4 Hz, 2 H); 13C NMR (100 MHz, CDCl₃, (major)-): δ 13.4, 20.9, 26.1, 31.9, 34.1, 52.0, 52.3, 125.5, 125.7, 127.7, 127.9, 128.5, 131.2, 134.5, 145.0, 169.2; 1H NMR (400 MHz, CDCl₃, (minor)-): δ 0.90 (t, J = 7.4 Hz, 3 H), 1.75 (s, 3 H), 1.91 (q, J = 7.4 Hz, 2 H), 2.55 (td, J = 7.3, 1.2 Hz, 2 H), 2.98 (d, J = 6.2 Hz, 2 H), 3.35 (t, J = 7.3 Hz, 1 H), 3.69 (s, 6 H), 5.32 (dtt, J = 15.4, 7.3, 1.5 Hz, 1 H), 5.45 (dtt, J = 15.4, 6.2,
1.5 Hz, 1 H), 7.03 (dd, $J = 7.5, 1.4$ Hz, 2 H), 7.19 (tt, $J = 7.5, 1.4$ Hz, 1 H), 7.27 (td, $J = 7.5, 1.4$ Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, (minor)-): $\delta$ 13.2, 17.0, 28.5, 31.8, 37.9, 52.0, 52.3, 125.4, 125.7, 127.9, 128.5, 130.7, 131.9, 134.4, 143.8, 169.2; High-resolution MS, calcd for C$_{20}$H$_{26}$O$_4$: 330.1831. Found m/z (relative intensity): 371 (M$^+$+1, 23), 330.1832 (M$^+$, 100), 315 (2), 301 (4), 299 (4).

**Dimethyl-2-((2$E$,5$E$)-5-methyl-6-(trimethylsilyl)hepta-2,5-dienyl)malonate: (5cf)**

Following General Procedure 3, Purification by distillation afforded 5cf as a color less oil. bp 120 °C/0.1mmHg.

![Dimethyl-2-((2$E$,5$E$)-5-methyl-6-(trimethylsilyl)hepta-2,5-dienyl)malonate](image)

**Dimethyl-2-((2$E$,5$E$)-5-methyl-6-(trimethylsilyl)hepta-2,5-dienyl)malonate (5cf):**

IR (neat): 2955 (s), 1740 (s), 1612 (w), 1437 (m), 1340 (w), 1248 (m), 1155 (m), 972 (w), 856 (m), 837 (m), 756 (w), 689 (w) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.12 (s, 9 H), 1.62 (d, $J = 1.2$ Hz, 3 H), 1.74 (q, $J = 1.2$ Hz, 3 H), 2.58 (ddd, $J = 1.2$, 6.8, 7.6 Hz, 2 H), 2.76 (d, $J = 6.3$ Hz, 2 H), 3.41 (t, $J = 7.6$ Hz, 1 H), 3.71 (s, 6 H), 5.34 (dt, $J = 15.1, 6.8$ Hz, 1 H), 5.46 (dt, $J = 15.1, 6.3, 1.2$ Hz, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 0.40, 17.4, 22.9, 26.8, 31.9, 38.1, 52.0, 52.3, 125.5, 127.6, 130.6, 143.2, 169.2; High-resolution MS, calcd for C$_{16}$H$_{28}$O$_4$Si: 312.1757. Found m/z (relative intensity): 313 (M$^+$+22), 312.1743 (M$^+$, 100), 297 (81).
General procedure 4: for the Nickel-catalyzed three-component coupling reaction of alkynes, vinylcyclopropane and Me₂Zn (entry 7, Table 3)

An oven-dried, 25 mL, three-necked round-bottomed flask equipped with a dropping funnel, a rubber septum cap, an air condenser (fitted with a three-way stopcock connected into nitrogen balloon), and a Teflon-coated magnetic stir bar was charged with Ni(acac)₂ (25.7 mg, 0.1 mmol). The apparatus was purged with nitrogen and the flask was charged successively via syringe with freshly dry THF (3 mL), vinylcyclopropane (184 mg, 1 mmol), and phenylacetylene (409 mg, 4 mmol). Dimethylzinc (1.2 mmol, 1.0 M hexane solution) was added slowly at room temperature via the dropping funnel over a period of 10 min (the reaction temperature should not be exceeded 50 °C). The mixture was stirred at room temperature for 24 h and monitored by TLC. After the reaction was completed, the reaction mixture was cooled to 0 °C, and then poured into ice-water. The resulting solution was diluted with 30 mL of EtOAc and carefully washed with 2 M HCl, with sat. NaHCO₃, and brine. The aqueous layer was extracted with 30 mL of EtOAc. The combined organic phases were dried (MgSO₄) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (eluent; hexane/EtOAc = 16/1 v/v) to afford 7cg as a colorless oil (276.7 mg, 71%; $R_f = 0.55$; hexane/EtOAc = 4/1 v/v).

Dimethyl-2-[\((2E,5Z)\)-6,8-diphenylocta-2,5-dien-7-ynyl]malonate: (7cg)
Dimethyl-2-[(2E,5Z)-6,8-diphenylocta-2,5-dien-7-ynyl]malonate (7cg): IR (neat): 
3028 (s), 2953 (s), 2843 (m), 1738 (s), 1597 (m), 1489 (s), 1435 (s), 1155 (s), 1028 (s), 970 (m), 914 (m), 758 (s), 692 (s) cm⁻¹; ¹H NMR (400MHz, CDCl₃): δ 2.63 (td, J = 7.6, 1.0 Hz, 2 H), 3.25 (td, J = 6.9, 1.0 Hz, 2 H), 3.43 (t, J = 7.6 Hz, 1 H), 3.71 (s, 6 H), 5.53 (dtt, J = 15.4, 6.9, 1.3 Hz, 1 H), 5.65 (dtt, J = 15.4, 7.6, 1.3 Hz, 1 H), 6.37 (t, J = 7.6 Hz, 1 H), 7.27-7.37 (m, 6 H), 7.50-7.55 (m, 2 H), 7.62-7.65 (m, 2 H); ¹³C NMR (100MHz, CDCl₃): δ 31.9, 34.4, 51.8, 52.4, 86.4, 95.5, 123.3, 124.1, 125.9, 126.8, 127.5, 128.2, 130.4, 131.4, 135.2, 137.9, 169.1; High-resolution MS, calcd for C₂₅H₂₄O₄: 388.1675. Found m/z (relative intensity): 389 (M⁺+1, 28), 388.1689 (M⁺, 100), 373 (6), 357 (92), 329 (22).

Dimethyl 2-[(2E,5E)-6,8-bis(trimethylsilyl)octa-2,5-dien-7-ynyl]malonate: (7ch)

Following General Procedure 4, Purification by flash column chromatography afforded 7ch as a color less oil.

Dimethyl 2-[(2E,5E)-6,8-bis(trimethylsilyl)octa-2,5-dien-7-ynyl]malonate (7ch): IR (neat) 3003 (m), 2957 (s), 2899 (s), 2847(m), 2127 (s), 1738 (s), 1582 (m), 1435 (s),
1250 (s), 1155 (s), 970 (m), 841 (s), 758 (m), 698 (m) cm$^{-1}$; $^1$H NMR (400MHz, CDCl$_3$) δ 0.13 (s, 9 H), 0.18 (s, 9 H), 2.60 (td, $J = 7.6$, 0.9 Hz, 2 H), 3.06 (td, $J = 6.8$, 1.0 Hz 2 H), 3.42 (t, $J = 7.6$ Hz, 1 H), 3.72 (s, 6 H), 5.42 (dt, $J = 15.3$, 7.6 Hz, 1 H), 5.53 (dt, $J = 15.3$, 6.8 Hz, 1 H), 6.00 (t, $J = 6.8$ Hz, 1 H); $^{13}$C NMR (100MHz, CDCl$_3$) δ -2.0, 0.3, 32.0, 35.8, 51.9, 52.4, 102.8, 104.1, 125.7, 126.7, 130.5, 148.7, 169.2; High-resolution MS, calcd for C$_{19}$H$_{32}$O$_4$Si$_2$: 380.1841. Found m/z (relative intensity): 381 (M$^+$+1, 31), 380.1841 (M$^+$, 100), 365 (44), 349 (8).

**Dimethyl 2-[(E)-4-(trimethylsilyl)-2-vinylpent-3-enyl]malonate: (6ch)**

Following General Procedure 4, Purification by flash column chromatography afforded **6ch** as a color less oil.

![Dimethyl 2-[(E)-4-(trimethylsilyl)-2-vinylpent-3-enyl]malonate](image)

**Dimethyl 2-[(E)-4-(trimethylsilyl)-2-vinylpent-3-enyl]malonate (6ch):** IR (neat) 3074 (m), 3003 (m), 2955 (s), 2855 (s), 1740 (s), 1616 (m), 1437 (s), 1248 (s), 1157 (s), 1024 (m), 837 (s), 752 (m), 691 (m) cm$^{-1}$; $^1$H NMR (400MHz, CDCl$_3$) δ 0.05 (s, 9 H), 1.65 (d, $J = 1.7$ Hz, 3 H), 1.96 (t, $J = 7.4$ Hz 1 H), 2.02 (t, $J = 7.4$ Hz, 1 H), 3.14 (dt, $J = 8.7$, 7.4, 7.2 Hz, 1 H), 3.38 (t, $J = 7.4$ Hz, 1 H), 3.72 (s, 3 H), 3.73 (s, 3 H), 4.99 (dd, $J = 17.3$, 1.3 Hz, 1 H), 5.00 (dd, $J = 10.0$, 1.3 Hz, 1 H), 5.45 (dq, $J = 8.7$, 1.7 Hz, 2 H), 5.64 (ddd, $J = 17.3$, 10.0, 7.2 Hz, 1 H); $^{13}$C NMR (100MHz, CDCl$_3$) δ -2.1, 14.6, 33.6, 40.5, 49.5, 52.4, 114.5, 138.3, 138.8, 139.5, 169.7, 169.7; High-resolution MS, calcd for
C_{15}H_{26}O_4Si: 298.1600. Found m/z (relative intensity): 299 (M^+1, 18), 298.1591 (M^+, 45), 283 (100), 267 (64).
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Chapter 2

Multicomponent Coupling Reaction via Azanickelacycle:
Ni-Catalyzed Homoallylation of Polyhydroxy N,O-Acetals with Conjugated Dienes Promoted by Triethylborane

Summary: In the presence of Ni-catalyst and triethylborane, N,O-acetals prepared from glycolaldehyde and glyceraldehyde with primary amines in situ underwent homoallylation with conjugated dienes to provide 2-amino-5-hexenols in high regio- and stereoselectivity. Under similar reaction conditions, N,O-acetals from carbohydrates with primary amines provided the corresponding polyhydroxy-bishomoallylamines in good to reasonable yields.
**Introduction**

Ni-catalyzed C–C bond formation is a useful strategy for organic syntheses\(^1\). Cross-coupling of organometallic compounds with aromatic halides, as well as allylation and vinylation of carbonyls, is widely utilized for the synthesis of physiologically active molecules and fine chemicals\(^2\). Compared to catalytically C–C bond transformations involving allylation and vinylation, homoallylation of carbonyls providing bis-homoallyl alcohols have serious limitations, which may be due to the unavailability and low stability of homoallyl anion species that can react with electrophiles\(^3\).

Recently, a Ni catalyst was developed that could promote the homoallylation of benzaldehyde with a wide variety of 1,3-dienes in the presence of triethylborane to afford bis-homoallyl alcohols (Eq. 1)\(^4\). For these processes, isoprene reacts at the C1 position with an aromatic aldehyde to give 3-methyl-4-penten-1-ol with excellent 1,3-\textit{anti} stereoselectivity. A similar homoallylation to produce aliphatic aldehydes and ketones was successful using diethylzinc instead of triethylborane\(^5\). Results indicated that diethylzinc functions as a more effective promoter than triethylborane for the homoallylation of aliphatic aldehydes and ketones. In contrast, triethylborane is compatible with water and alcohols, and even promotes homoallylation of aqueous aldehyde (\textit{e.g.}, glutaraldehyde) and \(\omega\)-hydroxyaldehyde (lactol) with conjugated dienes to afford \(\omega\)-hydroxyhomoallyl alcohols (Eq. 2)\(^6\). Thus, triethylborane and diethylzinc
can be used in a complementary manner to accelerate homoallylation of carbonyl compounds.

\[
\begin{align*}
\text{RCHO} + \text{Et}_3\text{B or Et}_2\text{Zn} & \quad \text{cat. Ni(0)} \\
\text{1,3-anti selective} & \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{HO} + \text{Et}_3\text{B} & \quad \text{cat. Ni(0)} \\
\text{1,3-anti selective} & \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1\text{NH}_2 + \text{R}^2\text{CHO} & \quad \text{Et}_3\text{B} \\
\text{1,3-syn selective} & \quad \text{HN}^+ \text{R}^1 \quad \text{R}^2 \\
\end{align*}
\]

In addition, Ni-catalyzed homoallylation of aldimeses prepared from aldehydes and primary amines in situ with conjugated dienes provided bis-homoallylamines in high regio- and stereoselectivity (Eq. 3)\(^7\). Thus, the C1 position of isoprene reacts with aldimeses to afford 3-methyl-4-pentenlamines with excellent 1,3-syn stereoselectivity, compared to 1,3-anti stereoselectivity when using aldehydes.

This report describes a similar reaction system involving a Ni catalyst and
triethylborane that was extended successfully to the homoallylation of $N,O$-acetals prepared from cyclic hemiacetals and primary amines to provide $\omega$-hydroxybishomoallylamines in high regio- and stereoselectivity (Eq. 4). In similar catalytic reaction systems, $N,O$-acetals from carbohydrates with primary amines gave the polyhydroxybishomoallylamines in good to reasonable yields.

$$\text{R} + \text{R}^1\text{NH}_2 + \text{HO-\text{C}}\text{H}_2\text{O}_\text{n} \xrightarrow{\text{cat. Ni(0)}} \text{Et}_3\text{B} \rightarrow \text{HO-\text{C}}\text{H}_2\text{O}_\text{n}$$
Results and Discussion

Results of reactions of isoprene with \(N,O\)-acetals prepared from cyclic hemiacetals and \(p\)-methoxyaniline are summarized in Table 1. Reactions were conducted at room temperature using isoprene, Ni(cod)\(_2\) catalyst, triethylborane, and \(N,O\)-acetals under nitrogen atmosphere. Isoprene reacted at the C1 position with \(N,O\)-acetals and underwent homoallylation to provide hydroxybishomoallylamines. 2-Hydroxytetrahydrofuran provided 1-(3-hydroxypropyl)-3-methyl-4-pentenylamine 4a in reasonable yield along with a mixture of diastereomers in a 5:1 ratio (entry 1, Table 1). 5-Naphthyl-2-hydroxytetrahydrofuran provided the desired product 4b in 71% yield along with two diastereomers in a 2:1 ratio (entry 2, Table 1). 5-Methyl-5-\(n\)-hexyl-2-hydroxytetrahydrofuran participated in the homoallylation to afford hydroxylamine 4c, which possessed a tertiary alcohol moiety (entry 3, Table 1). Six-membered cyclic hemiacetals could be used for homoallylation to form amino alcohols 4d and 4e in 6:1 and 4:1 ratios, respectively (entries 4-5, Table 1). 2-Hydroxychroman served as an \(N,O\)-acetal precursor by treatment with a primary amine to provide \(o\)-aminoalkyl phenol 4f, (entry 6, Table 1). \(N\)-Boc-2-hydroxypiperidine acted as an aldimine in the presence of \(p\)-methoxyaniline to participate in the coupling reaction with isoprene to provide 2-butenylaminobishomoallylamine 4g (entry 7, Table 1). Seven-membered cyclic hemiacetal underwent a similar homoallylation to provide 1-(5-hydroxypentyl)-3-methyl-4-pentenylamine 4h in reasonable yield (entry 8, Table 1).
Table 1. Scope of the Nickel-Catalyzed Homoallylation of N,O-Acetals with Isoprene\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>hemiacetal</th>
<th>product</th>
<th>yield of 4 (%) [ratio]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a: (\text{HO} - \text{O} - \text{PMP})</td>
<td>4a: (\text{HN} - \text{PMP})</td>
<td>58 [5:1]</td>
</tr>
<tr>
<td>2</td>
<td>3b: (\text{HO} - \text{O} - \text{Naphtyl})</td>
<td>4b: (\text{HN} - \text{PMP})</td>
<td>71 [2:1]</td>
</tr>
<tr>
<td>3</td>
<td>3c: (\text{HO} - \text{O} - n\text{-C}<em>6\text{H}</em>{13})</td>
<td>4c: (\text{HN} - \text{PMP})</td>
<td>59 [3:1]</td>
</tr>
<tr>
<td>4</td>
<td>3d: (\text{HO} - \text{O})</td>
<td>4d: (\text{HN} - \text{PMP})</td>
<td>91 [6:1]</td>
</tr>
<tr>
<td>5</td>
<td>3e: (\text{HO} - \text{O})</td>
<td>4e: (\text{HN} - \text{PMP})</td>
<td>69 [4:1]</td>
</tr>
<tr>
<td>6</td>
<td>3f: (\text{HO} - \text{O})</td>
<td>4f: (\text{HN} - \text{PMP})</td>
<td>61 [7:1]</td>
</tr>
</tbody>
</table>
Glycolaldehyde dimer is a two-carbon monosaccharide (diese) that is an important component of biologically active molecules. The reaction of glycolaldehyde dimer as an N,O-acetal precursor with conjugated dienes to furnish 1-hydroxymethyl-4-pentenylamines also was examined. Results using various conjugated dienes and N,O-acetals prepared from primary amines and glycolaldehyde dimer are summarized in Table 2. 1,3-Butadiene reacted with N,O-acetal prepared from p-methoxyaniline to yield 47% of 1-hydroxymethyl-4-pentenylamine 6aa along with 23% of the internal olefin isomer 6'aa (entry 1, Table 2). N,O-Acetal from aniline underwent homoolallylation with isoprene to provide 1-hydroxymethyl-3-methyl-4-pentenylamine 6bb in reasonable yield with a diastereomeric mixture in a 8:1 ratio (entry 2, Table 2). p-Methoxy and o-methoxyaniline participated in similar homoallylations to provide hydroxyamines 6ba and 6bc, respectively, with high stereoselectivity in an 8:1 ratio.

\[ \text{Table 1, continued} \]

<table>
<thead>
<tr>
<th>7</th>
<th>3g:</th>
<th>4g: 41 [3:1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>3h:</td>
<td>4h: 58 [4:1]</td>
</tr>
</tbody>
</table>

\[ *N,O-Acetals were prepared from cyclic hemiacetals (1 mmol) and amines (2 mmol) stirring in THF (2 mL). A solution of isoprene (4 mmol), Ni(cod)\(_2\) (0.1 mmol) in THF (2 mL) and Et\(_3\)B (3.6 mmol) were introduced to the N,O-acetals, and the reaction mixture was stirred at room temperature for 24 h under nitrogen atmosphere. \]
Table 2. Scope of the Nickel-Catalyzed Homoallylation of N,O-Acetals, Prepared from Glycolaldehyde Dimer, with Isoprene

\[
\begin{align*}
\text{entry} & \quad \text{diene: } R \quad \text{amine: } R^1 \quad \text{yield of 6 (%) [ratio]} \\
1 & 1a: H \quad 2a \quad 6aa: 47^b \\
2 & 1b: Me \quad 2b: \text{phenyl} \quad 6bb: 64 [8:1] \\
3 & 1b: Me \quad 2a \quad 6ba: 59 [single] \\
4 & 1b: Me \quad 2c: o\text{-methoxyphenyl} \quad 6bc: 64[8:1] \\
5 & 1b: Me \quad 2d: p\text{-bromophenyl} \quad 6bd: 50 [single] \\
6 & 1b: Me \quad 2e: \text{benzyl} \quad \text{intractable mixture} \\
7 & 1c: -(\text{CH}_2)_2\text{CH}==\text{CMe}_2 \quad 2a \quad 6ca: 49 [single]
\end{align*}
\]

*\text{R, O-Acetals were prepared from glycolaldehyde dimer (1 mmol) and amines (4 mmol) stirring in THF (2 mL). A solution of conjugated diene (8 mmol), Ni(cod)\_2 (0.1 mmol) in THF (2 mL) and Et}_3B (6 mmol) were introduced to the N,O-acetals, and the reaction mixture was stirred at room temperature for 48 h under N}_2.*

*\text{Internal olefin isomer 6'}aa was obtained in 23%.*
and as a single isomer, respectively (entries 3-4, Table 2). \( p \)-Bromoaniline underwent homoallylation effectively to afford the desired hydroxylamine \( 6\text{bd} \) as the sole product (entry 5, Table 2). Benzylamine yielded an intractable mixture; the expected reaction was not observed (entry 6, Table 2). Myrcene also participated in homoallylation with \( N,O \)-acetal to produce the corresponding hydroxylamine \( 6\text{ca} \) as a single product (entry 7, Table 2).

Glyceraldehyde is a triose monosaccharide generally used for the enzymatic synthesis of D-fructose and L-sorbose with aldolases\(^9\). The glyceraldehyde can serve as an important electrophilic component for coupling reactions to form a physiologically active molecules. The Ni-catalyzed homoallylation of glyceraldehyde dimer was accomplished using primary amines and conjugated dienes in the presence of triethylborane (Table 3). In this reaction, \( N,O \)-acetals prepared from glyceraldehyde dimer and primary amines in DMF via azeotropic distillation underwent homoallylation with conjugated dienes to furnish dihydroxybishomoallylamines. 1,3-Butadiene reacted with \( N,O \)-acetal from \( p \)-methoxyaniline to provide 1-(1,2-dihydroxyethyl)-4-pentenyl-amine \( 8\text{aa} \) in 56% yield along with the internal olefin isomer \( 8'\text{aa} \) in 17% yield (entry 1, Table 3). \( N,O \)-Acetal from aniline participated in homoallylation with isoprene to provide 1-(1,2-dihydroxyethyl)-3-methyl-4-pent-enylamine \( 8\text{bb} \) in 62% yield in a 2:1 ratio of diastereomers (entry 2, Table 3). \( p \)-Methoxyaniline gave a similar homoallylation product \( 8\text{ba} \) with a mixture of diastereoisomers in a 2:1 ratio (entry 3, Table 3). Benzylamine provided an intractable mixture in the same way as
**Table 3.** Scope of the Nickel-Catalyzed Homoallylation of \(N, O\)-Acetals, Prepared from Glyceraldehyde Dimer, with Isoprene

\[
\begin{align*}
\text{entry} & \quad \text{diene: } \text{R} & \quad \text{amine: } \text{R}^1 & \quad \text{yield of } \text{8} \text{ (%)} [\text{ratio}] \\
1 & 1a & 2a & 8aa: 56 [3:1] \\
2 & 1b & 2b & 8bb: 62 [2:1] \\
3 & 1b & 2a & 8ba: 69 [2:1] \\
4 & 1b & 2e & \text{intractable mixture} \\
5 & 1c & 2a & 8ca: 64 [2:1]
\end{align*}
\]

\* \(N, O\)-Acetals were prepared from glyceraldehyde dimer (1 mmol) and amines (4 mmol) in DMF (2 mL) via azeotropic distillation. A solution of conjugated diene (8 mmol), Ni(cod)\(_2\) (0.1 mmol) in THF (2 mL) and Et\(_3\)B (6 mmol) were introduced to the residual oil of \(N, O\)-acetals, and then the reaction mixture was stirred at room temperature for 48 h under \(N_2\).

\*\* Internal olefin isomer 8'aa was obtained in 17% with 3:1 diastereoisomeric ratio.
the result of glycolaldehyde with aliphatic amine (entry 4, Table 3). Myrcene underwent homoallylation with $N,O$-acetal to produce the corresponding hydroxylamine $8\text{ca}$ in reasonable yield with diastereomers in a 2:1 ratio, as well as isoprene (entry 5, Table 3).

Next, homoallylation of $N,O$-acetals from carbohydrates, such as 2-deoxy-D-ribose, D-ribose, and 2-deoxy-D-glucose, was investigated. Various $N,O$-acetals prepared from carbohydrates and aromatic amines underwent homoallylation with conjugated dienes in one pot to provide polyhydroxyamines (Table 4). 1,3-Butadiene reacted with $N,O$-acetal from 2-deoxy-D-ribose and $p$-methoxyaniline to afford the homoallylation product $9\text{aa}$ in moderate yield along with the allylation product as a diastereoisomeric mixture of internal olefin isomers $9'\text{aa}$ (entry 1, Table 4). Isoprene reacted at the C1 position with $N,O$-acetals derived from 2-deoxy-D-ribose and various aromatic amines to provide the desired polyhydroxyamines $9\text{ba}$-$9\text{bg}$ as mixtures of two diastereomers in a nearly 2:1 ratio (entries 2-6, Table 4). Myrcene also participated in homoallylation as a conjugated diene and afforded the desired product $9\text{ca}$ in 56% in a 1:1 ratio (entry 7, Table 4). Since D-ribose and 2-deoxy-D-glucose are insoluble in THF, a series of $N,O$-acetals with D-ribose and 2-deoxy-D-glucose were prepared from amines in DMF via azeotropic distillation, and were used for homoallylation with isoprene to produce the expected polyhydroxyamines $10\text{ba}$ and $11\text{ba}$, respectively (entries 8 and 9, Table 4). Although carbohydrates were expected
Table 4. Scope of the Nickel-Catalyzed Homoallylation of \( N,O \)-Acetals, Prepared from Carbohydrate, with Isoprene

\[
\begin{align*}
\text{entry} & \quad \text{carbohydrate} & \quad \text{diene: R} & \quad \text{amine: R}^1 & \quad \text{yield of 9, 10 and 11 (%)} & \quad \text{ratio} \\
1 & 2\text{-deoxy-D-ribose} & 1\text{a} & 2\text{a} & 9\text{aa}: 27 [1:1]^b \\
2 & 2\text{-deoxy-D-ribose} & 1\text{b} & 2\text{a} & 9\text{ba}: 74 [2:1] \\
3 & 2\text{-deoxy-D-ribose} & 1\text{b} & 2\text{c} & 9\text{bc}: 80 [2:1] \\
4 & 2\text{-deoxy-D-ribose} & 1\text{b} & 2\text{f}: 3,4\text{-dimethoxyphenyl} & 9\text{bf}: 58 [2:1] \\
5 & 2\text{-deoxy-D-ribose} & 1\text{b} & 2\text{b} & 9\text{bb}: 75 [2:1] \\
6 & 2\text{-deoxy-D-ribose} & 1\text{b} & 2\text{g}: p\text{-chlorophenyl} & 9\text{bg}: 30 [2:1] \\
7 & 2\text{-deoxy-D-ribose} & 1\text{c} & 2\text{a} & 9\text{ca}: 56 [1:1] \\
8 & D\text{-ribose} & 1\text{b} & 2\text{a} & 10\text{ba}: 57 [2:1] \\
9 & 2\text{-deoxy-D-glucose} & 1\text{b} & 2\text{a} & 11\text{ba}: 64 [1:1] \\
\end{align*}
\]

\( N,O \)-Acetals were prepared from carbohydrate (1 mmol) and amines (2 mmol) in THF (5 mL, entries 1-7) or DMF (5 mL, entries 8 and 9) via azeotropic distillation. A solution of conjugated diene (8 mmol), \( \text{Ni(cod)}_2 \) (0.1 mmol) in THF (2 mL) and Et\textsubscript{3}B (6 mmol) were introduced to the \( N,O \)-acetals, and the reaction mixture was stirred at room temperature (entries 1-7) or 50 °C for 48 h (entries 8 and 9) under N\textsubscript{2}.

\( b \) Internal olefin isomer 9'aa was obtained in 32% with 3:1 diastereoisomeric ratio.
to serve as carbonyl electrophiles and chiral auxiliaries to induce stereoselectivity of
the homoallylation, the consecutive homoallylations of $N,O$-acetals did not proceed
with high stereoselectivity.

Although all product absolute configurations have not yet been determined, a
plausible reaction mechanism based on the homoallylation of aldimines prepared from
aldehydes and primary amines with isoprene is illustrated in Scheme 1. $N,O$-Acetals
were readily prepared from cyclic hemiacetals with primary amines in situ, and the low
concentration of $\omega$-hydroxyimine tautomers in equilibrium with the $N,O$-acetals
appeared to promote reaction with conjugated dienes (Scheme 2). As triethylborane
coordinates to the nitrogen atom of $N,O$-acetals as a Lewis acid, the formation of
$\omega$-hydroxyimine tautomers might predominate over $N,O$-acetals. Formation of an
azanickelacycle intermediate via oxidative cyclization with isoprene and $\omega$-hydroxy-
imine in the presence of Ni(0) catalyst results in a quasi-equatorial position of the
nitrogen atom substituent to avoid the steric repulsion toward the $\omega$-hydroxyalkyl main
chain. As a result, the aldimine moiety assumed a diaxial configuration resulting in
1,3-\textit{syn} stereoselectivity with respect to the methyl group of isoprene and amino groups.
**Scheme 1.** Ni-Catalyzed Homoallylation of $N,O$-Acetal with Isoprene Promoted by Triethylborane

**Scheme 2.** Equilibrium between Cyclic $N,O$-Acetal and ω-Hydroxyamine
Experimental Section

Reactions employed oven-dried glassware unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator (Merck, Silica gel 60F$_{254}$). Flash chromatography columns were packed with 230-400 mesh silica gel as a slurry in hexane. Gradient flash chromatography was conducted eluting with a continuous gradient from hexane to the indicated solvent. Distillation were carried out in a Kugelrohr apparatus (SIBATA glass tube oven GTO-350RG). Boiling points are meant to refer to the oven temperature (± 1 °C). Microanalyses were performed by the Instrumental Analysis Center of Nagasaki University. Analysis agreed with the calculated values within ± 0.4%. Proton and carbon NMR data were obtained with a JEOL-GX400 with tetramethylsilane as an internal standard. Chemical shift values were given in ppm downfield from the internal standard. Infrared spectra were recorded with a JASCO A-100 FT-IR or SHIMAZU FTIR-8700 spectrophotometer. High resolution mass spectra (HRMS) were measured with a JEOL JMS-DX303.

Solvents and Reagents

Tetrahydrofuran, toluene, and diethyl ether were dried and distilled from benzophenone-sodium immediately prior to use under nitrogen atmosphere. DMF was distilled over calcium chloride. Triethylborane (1 M THF, Aldrich), Ni(cod)$_2$ (KANTO Kagaku) were used without further purification. Isoprene, myrcene,
glycolaldehyde dimer, glyceraldehyde dimer, 2-deoxy-D-ribose, D-ribose, 2-deoxy-D-glucose, aniline, \( p \)-methoxyaniline, \( o \)-methoxyaniline, \( p \)-bromoaniline, benzylamine were purchased and used without purification. 1,3-Butadiene (Tokyo Kasei Kogyo Co., Ltd) was purchased, and was liquefied by cooling at -78 °C (dry ice/isopropanol) prior to use under argon atmosphere. 1,3-Butadiene could be measured by syringe kept cool in the freezer as well beforehand, and then was introduced into the reaction mixture at room temperature. Tetrahydrofuran-2-ol, tetrahydro-2\( H \)-pyran-2-ol, oxepane-2-ol, 5-(naphthalen-2-yl)tetrahydrofuran-2-ol, and all of these substrates in Table 1 were prepared according to the literature\(^{10}\). 
**General procedure 1: for the Nickel-catalyzed homoallylation of N,O-acetals with isoprene (entry 4, Table 1)**

An oven-dried, 25 mL, three-necked round-bottomed flask equipped with a dropping funnel, a rubber septum cap, an air condenser (fitted with a three-way stopcock connected into nitrogen balloon), and a Teflon-coated magnetic stir bar was charged. A solution of tetrahydro-2H-pyran-2-ol (102 mg, 1 mmol) and p-anisidine (246 mg, 2 mmol) in dry THF (2 mL) was stirred overnight under nitrogen. A mixture of Ni(cod)$_2$ (27.5 mg, 0.1 mmol) and isoprene (400 µL, 4 mmol) dissolved in THF (2 mL) and triethylborane (3.6 mmol, 1.0 M THF solution) were successively added to the N,O-acetal solution via the dropping funnel over a period of 10 min. The reaction mixture was stirred at room temperature for 24 h and monitored by TLC. After the reaction was completed, the reaction mixture was cooled to 0 °C, and then poured into ice-water. The resulting solution was diluted with 30 mL of EtOAc and carefully washed with 2 M HCl, with sat. NaHCO$_3$, and brine. The aqueous layer was extracted with 30 mL of EtOAc. The combined organic phases were dried (MgSO$_4$) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (eluent; hexane/EtOAc = 2/1 v/v) to afford 4d (258 mg, 91%; $R_f = 0.30$; hexane/EtOAc = 4/1 v/v) in a 6:1 ratio.
5-[(4-Methoxyphenyl)amino]-7-methylnon-8-en-1-ol: (4d)

IR (neat) 3368 (s), 2934 (s), 1514 (m), 1458 (s), 1236 (s), 1040 (s), 820 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, major-isomer) δ 1.00 (d, J = 6.6 Hz, 3 H), 1.37 – 1.58, (m, 8 H), 2.33 – 2.38 (m, 1 H), 3.31 (m, 1 H), 3.62 (t, J = 6.3 Hz, 2 H), 3.73 (s, 3 H), 4.92 (dd, J = 10.4, 1.1 Hz, 1 H), 4.93 (dd, J = 17.0, 1.1 Hz, 1 H), 5.65 (ddd, J = 17.0, 10.4, 8.1 Hz, 1 H), 6.52 (d, J = 8.9 Hz, 2 H), 6.74 (d, J = 8.9 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, major-isomer) δ 21.1, 22.0, 32.8, 35.0, 35.2, 42.5, 52.1, 55.8, 62.8, 113.2, 114.4, 114.9, 142.1, 144.3, 151.6; ¹H NMR (400 MHz, CDCl₃, minor-isomer) δ 0.98 (d, J = 6.8 Hz, 3 H), 1.37 – 1.58, (m, 8 H), 2.33 – 2.38 (m, 1 H), 3.31 (m, 1 H), 3.61 (t, J = 6.5 Hz, 2 H), 3.74 (s, 3 H), 4.92 (dd, J = 10.4, 1.1 Hz, 1 H), 4.93 (dd, J = 17.0, 1.1 Hz, 1 H), 5.65 (ddd, J = 17.0, 10.4, 8.1 Hz, 1 H), 6.52 (d, J = 8.9 Hz, 2 H), 6.74 (d, J = 8.9 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, minor-isomer) δ 21.1, 21.9, 32.8, 35.0, 35.2, 42.1, 52.1, 55.8, 62.8, 113.2, 114.2, 114.8, 142.1, 144.3, 151.6; HRMS, calcd for C₁₇H₂₇NO₂: 277.2018. Found m/z (relative intensity): 278.2001 (M⁺+1, 1), 277.2014 (M⁺, 2), 260.1983 (13), 204.1406 (100).

(4S,6S)-4-(4-methoxyphenylamino)-6-methyloct-7-en-1-ol: (4a)
Following General Procedure 1, Purification by flash column chromatography.

(4S,6S)-4-(4-methoxyphenylamino)-6-methyloct-7-en-1-ol (4a): (a mixture of major and minor isomers in a ratio of 5:1): IR (neat) 3310 (s), 3071 (s), 2924 (s), 1643 (m), 1458 (s), 1065 (s), 910 (s), 741 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), major-isomer) \(\delta\) 0.99 (d, \(J = 6.7\) Hz, 3 H), 1.60 – 1.69 (m, 6 H), 2.35 (qm, \(J = 6.7\) Hz, 1 H), 2.52 (br, 1H), 3.32 (m, 1 H), 3.60 (t, \(J = 6.1\) Hz, 2 H), 3.73 (s, 3 H), 4.92 (dm, \(J = 10.7\) Hz, 1 H), 4.93 (dd, \(J = 16.9, 1.0\) Hz, 1 H), 5.65 (ddd, \(J = 16.9, 10.7, 8.0\) Hz, 1 H), 6.54 (dd, \(J = 6.6, 2.2\) Hz, 2 H), 6.75 (m, 2 H); \(^1\)C NMR (100 MHz, CDCl\(_3\), major-isomer) \(\delta\) 21.0, 29.3, 32.0, 35.0, 42.5, 54.0, 55.8, 62.9, 63.0, 113.2, 114.9, 115.0, 115.4, 141.5, 141.8, 144.3; \(^1\)H NMR (400 MHz, CDCl\(_3\), minor-isomer) \(\delta\) 0.99 (d, \(J = 6.7\) Hz, 3 H), 1.60 – 1.69 (m, 6 H), 2.35 (qm, \(J = 6.7\) Hz, 1 H), 2.52 (br, 1H), 3.32 (m, 1 H), 3.60 (t, \(J = 6.1\) Hz, 2 H), 3.73 (s, 3 H), 4.93 (dd, \(J = 16.9, 1.0\) Hz, 1 H), 4.98 (dm, \(J = 17.1\) Hz, 1 H), 5.65 (ddd, \(J = 16.9, 10.7, 8.0\) Hz, 1 H), 6.54 (dd, \(J = 6.6, 2.2\) Hz, 2 H), 6.75 (m, 2 H); \(^1\)C NMR (100 MHz, CDCl\(_3\), minor-isomer) \(\delta\) 20.8, 29.2, 32.0, 35.0, 45.3, 54.0, 55.8, 62.9, 63.0, 113.2, 114.8, 115.0, 115.4, 141.6, 141.8, 144.1; HRMS, calcd for C\(_{16}\)H\(_{25}\)NO\(_2\): 263.1885. Found \(m/z\) (relative intensity): 264.1882 (M\(^{+}\)+1, 18), 263.1850 (M\(^{+}\), 97), 205.1411 (15), 204.1394 (100).

(4S,6S)-4-(4-methoxyphenylamino)-6-methyl-1-(naphthalenyl) octen-7-ol: (4b)

Following General Procedure 1, Purification by flash column chromatography.
(4S,6S)-4-(4-methoxyphenylamino)-6-methyl-1-(naphthalenyl) octen-7-ol (4b): (a mixture of major and minor isomers in a ratio of 2:1): IR (neat) 3366 (s), 2930 (s), 2359 (m), 1506 (s), 1238 (s), 1040 (s), 820 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, major-isomer) $\delta$ 0.95 (d, $J = 6.8$ Hz, 3 H), 1.38 – 1.94 (m, 6 H), 2.29 (qm, $J = 6.8$ Hz, 1 H), 3.11 (br, 1 H), 3.32 (br q, $J = 5.9$ Hz, 1 H), 3.71 (br, 1 H), 3.72 (d, $J = 8.9$ Hz, 2 H), 3.79 – 7.82 (m, 7 H). $^1$H NMR (400 MHz, CDCl$_3$, minor-isomer) $\delta$ 0.92 (d, $J = 6.8$ Hz, 3 H), 1.38 – 1.94 (m, 6 H), 2.29 (qm, $J = 6.8$ Hz, 1 H), 3.11 (br, 1 H), 3.32 (br q, $J = 5.9$ Hz, 1 H), 3.72 (s, 3 H), 4.83 (dm, $J = 18.3$ Hz, 1 H), 4.88 (dd, $J = 18.3$, 1.9 Hz, 1 H), 4.89 (dd, $J = 10.8$, 1.9 Hz, 1 H), 5.58 – 5.66 (m, 1 H), 6.53 (d, $J = 8.9$ Hz, 2 H), 6.70 (dd, $J = 8.9$, 1.0 Hz, 2 H), 7.39 – 7.82 (m, 7 H); $^{13}$C NMR (100 MHz, CDCl$_3$, major-isomer) $\delta$ 20.9, 31.7, 35.0, 35.5, 42.3, 53.0, 55.7, 74.5, 113.2, 114.8, 115.3, 123.9, 124.4, 125.6, 125.7, 125.9, 126.0, 127.5, 128.0, 132.8, 133.1, 141.9, 144.1, 152.2; $^1$H NMR (400 MHz, CDCl$_3$, minor-isomer) $\delta$ 0.92 (d, $J = 6.8$ Hz, 3 H), 1.38 – 1.94 (m, 6 H), 2.29 (qm, $J = 6.8$ Hz, 1 H), 3.11 (br, 1 H), 3.32 (br q, $J = 5.9$ Hz, 1 H), 3.72 (s, 3 H), 4.83 (dm, $J = 18.3$ Hz, 1 H), 4.88 (dd, $J = 18.3$, 1.9 Hz, 1 H), 4.89 (dd, $J = 10.8$, 1.9 Hz, 1 H), 5.58 – 5.66 (m, 1 H), 6.53 (d, $J = 8.9$ Hz, 2 H), 6.70 (dd, $J = 8.9$, 1.0 Hz, 2 H), 7.39 – 7.82 (m, 7 H); $^{13}$C NMR (100 MHz, CDCl$_3$, minor-isomer) $\delta$ 20.9, 31.2, 34.9, 35.7, 42.3, 52.7, 55.7, 74.4, 113.2, 114.8, 115.2, 124.0, 124.4, 125.6, 125.7, 125.9, 126.0, 127.5, 128.1, 132.6, 133.1, 141.3, 144.1, 152.1; HRMS, calcd for C$_{26}$H$_{31}$NO$_2$: 389.2355. Found m/z (relative intensity): 389.2340 (M$^+$, 100).
10-(4-methoxyphenylamino)-7,12-dimethyl-13-tetradecen-7-ol: (4c)

Following General Procedure 1, Purification by flash column chromatography.

10-(4-methoxyphenylamino)-7,12-dimethyl-13-tetradecen-7-ol (4c): (a mixture of major and minor isomers in a ratio of 3:1): IR (neat) 3379 (s), 2932 (s), 2359 (m), 1639 (s), 1514 (s), 1238 (s), 1043 (s), 912 (s), 818 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, major-isomer) $\delta$ 0.88 (t, $J = 6.4$ Hz, 3 H), 0.96 (d, $J = 6.8$ Hz, 3 H), 1.12 –1.26 (m, 8 H), 1.42 (br, 3 H), 1.49 – 1.69 (m, 8 H), 2.29 (qm, $J = 6.8$ Hz, 1 H), 3.25 – 3.33 (m, 1 H), 3.74 (s, 3 H), 4.91 (dd, $J = 10.7$, 1.5 Hz, 1 H), 4.92 (dd, $J = 17.5$, 1.5 Hz, 1 H), 5.63 (ddd, $J = 17.5$, 10.7, 8.0 Hz, 1 H), 6.69 – 6.72 (m, 2 H), 6.75 (d, $J = 9.3$ Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, major-isomer) $\delta$ 14.1, 20.7, 20.9, 22.6, 26.9, 27.6, 29.8, 31.8, 35.0, 37.4, 37.6, 41.9, 55.6, 55.7, 72.6, 113.3, 114.0, 116.8, 143.4, 143.9, 144.0; $^1$H NMR (400 MHz, CDCl$_3$, minor-isomer) $\delta$ 0.88 (t, $J = 6.4$ Hz, 3 H), 0.97 (d, $J = 6.8$ Hz, 3 H), 1.12 –1.26 (m, 8 H), 1.42 (br, 3 H), 1.49 – 1.69 (m, 8 H), 2.29 (qm, $J = 6.8$ Hz, 1 H), 3.25 – 3.33 (m, 1 H), 3.74 (s, 3 H), 4.91 (dd, $J = 10.7$, 1.5 Hz, 1 H), 4.92 (dd, $J = 17.5$, 1.5 Hz, 1 H), 5.63 (ddd, $J = 17.5$, 10.7, 8.0 Hz, 1 H), 6.69 – 6.72 (m, 2 H), 6.75 (d, $J = 9.0$ Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, minor-isomer) $\delta$ 14.1, 20.8, 20.9, 22.6, 26.8, 27.6, 29.8, 31.8, 35.0, 37.4, 37.6, 41.9, 55.6, 55.7, 72.7, 113.4, 114.0, 116.7, 143.5, 143.9, 144.0; HRMS, calcd for C$_{23}$H$_{39}$NO$_2$: 361.2981. Found m/z (relative intensity): 361.2969 (M$^+$, 100).
(5S,7S)-5-(4-methoxyphenylamino)-3,3,7-trimethylnon-8-ol (4e)

Following General Procedure 1, Purification by flash column chromatography.

(5S,7S)-5-(4-methoxyphenylamino)-3,3,7-trimethylnon-8-ol (4e): (a mixture of major and minor isomers in a ratio of 4:1): IR (neat) 3373 (s), 2932 (s), 2359 (m), 1732 (s), 1514 (s), 1234 (s), 1042 (s), 818 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, major-isomer) δ 0.94 (s, 6 H), 0.97 (d, \( J = 6.8 \) Hz, 3 H), 1.21 – 1.70 (m, 6 H), 2.28 (q, \( J = 6.8 \) Hz, 1 H), 3.02 (br, 1 H), 3.34 (m, 1 H), 3.69 (s, 3 H), 3.66 – 3.76 (m, 2 H), 4.98 (dd, \( J = 17.7, 1.8 \) Hz, 1 H), 4.99 (dd, \( J = 10.0, 1.8 \) Hz, 1 H), 5.67 (ddd, \( J = 17.7, 10.0, 8.3 \) Hz, 1 H), 6.55 (br, 2 H), 6.75 (br d, \( J = 8.3 \) Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, major-isomer) δ 20.1, 21.6, 28.4, 28.5, 32.7, 44.5, 47.5, 47.9, 49.3, 55.0, 59.6, 113.6, 114.9, 115.0, 144.1, 144.7, 152.0; ¹H NMR (400 MHz, CDCl₃, minor-isomer) δ 0.95 (s, 6 H), 0.99 (d, \( J = 6.6 \) Hz, 3 H), 1.21 – 1.70 (m, 6 H), 2.28 (q, \( J = 6.8 \) Hz, 1 H), 3.02 (br, 1 H), 3.34 (m, 1 H), 3.67 (s, 3 H), 3.66 – 3.76 (m, 2 H), 4.92 (dd, \( J = 10.2, 0.8 \) Hz, 1 H), 4.95 (dd, \( J = 16.9, 0.8 \) Hz, 1 H), 5.67 (ddd, \( J = 17.7, 10.0, 8.3 \) Hz, 1 H), 6.55 (br, 2 H), 6.75 (br d, \( J = 8.3 \) Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, minor-isomer) δ 20.1, 21.6, 28.4, 28.5, 32.6, 44.3, 47.5, 47.9, 49.3, 55.0, 59.6, 113.6, 114.8, 115.0, 144.1, 144.7, 152.0; HRMS, calcd for C₁₉H₃₁NO₂: 305.2355. Found m/z (relative intensity): 306.2373 (M⁺+1, 9), 305.2337 (M⁺, 44), 237.1655 (18), 236.1608 (100), 235.1535 (19).
2-((3S,5S)-3-(4-methoxyphenylamino)-5-methyl-6-heptenyl)phenol (4f)

Following General Procedure 1, Purification by flash column chromatography.

2-((3S,5S)-3-(4-methoxyphenylamino)-5-methyl-6-heptenyl)phenol (4f): (a mixture of major and minor isomers in a ratio of 7:1): IR (neat) 3308 (s), 2930 (s), 1583 (m), 1506 (s), 1236 (s), 1040 (s), 822 (s), 754 (s) cm\(^{-1}\); \(^1^H\) NMR (400 MHz, CDCl\(_3\), major-isomer) \(\delta\) 0.84 (d, \(J = 6.8\) Hz, 3 H), 1.11 – 1.68 (m, 4 H), 2.20 (qm, \(J = 6.8\) Hz, 1 H), 2.65 – 2.71 (m, 2 H), 2.88 – 2.95 (m, 1 H), 3.13-3.29 (m, 1 H), 3.75 (s, 3 H), 4.86 (dd, \(J = 10.8, 0.8\) Hz, 1 H), 4.87 (dd, \(J = 16.7, 0.8\) Hz, 1 H), 5.57 (ddd, \(J = 16.7, 10.8, 7.8\) Hz, 1 H) , 6.78 (d, \(J = 8.6\) Hz, 2 H), 6.84 (d, \(J = 8.6\) Hz, 2 H), 6.73 – 6.92 (m, 2 H), 7.06 – 7.12 (m, 2 H); \(^1^C\) NMR (100 MHz, CDCl\(_3\), major-isomer) \(\delta\) 20.2, 26.2, 34.8, 35.3, 40.0, 53.3 , 55.6, 55.7, 112.9, 114.8, 116.3, 120.3, 127.2, 127.3, 127.4, 129.9, 130.0, 144.3, 154.8; \(^1^H\) NMR (400 MHz, CDCl\(_3\), minor-isomer) \(\delta\) 0.89 (d, \(J = 6.3\) Hz, 3 H), 1.11 – 1.68 (m, 4 H), 2.20 (qm, \(J = 6.8\) Hz, 1 H), 2.65 – 2.71 (m, 2 H), 2.88 – 2.95 (m, 1 H), 3.13-3.29 (m, 1 H), 3.75 (s, 3 H), 4.86 (dd, \(J = 10.8, 0.8\) Hz, 1 H), 4.87 (dd, \(J = 16.7, 0.8\) Hz, 1 H), 5.57 (ddd, \(J = 16.7, 10.8, 7.8\) Hz, 1 H) , 6.78 (d, \(J = 8.6\) Hz, 2 H), 6.84 (d, \(J = 8.6\) Hz, 2 H), 6.73 – 6.92 (m, 2 H), 7.06 – 7.12 (m, 2 H); \(^1^C\) NMR (100 MHz, CDCl\(_3\), minor-isomer) \(\delta\) 20.2, 26.2, 34.8, 35.3, 40.0, 53.3 , 55.6, 55.7, 112.9, 114.6, 116.3, 120.3, 127.2, 127.3, 127.4, 129.9, 130.1, 144.3, 154.8; HRMS, calcd for C\(_{21}\)H\(_{27}\)NO\(_2\): 325.2042. Found \(m/z\) (relative intensity): 326.2086 (M\(^+\)+1, 18),
325.2045 (M\(^{+}\), 78), 257.1349 (18), 256.1329 (100).

**tert-butyl(5S,7S)-5-(4-methoxyphenylamino)-7-methylnon-8-enylcarbamate (4g)**

Following General Procedure 1, Purification by flash column chromatography.

![Chemical Structure](image)

**tert-butyl(5S,7S)-5-(4-methoxyphenylamino)-7-methylnon-8-enylcarbamate (4g):**

(a mixture of major and minor isomers in a ratio of 3:1): IR (neat) 2864 (s), 2359 (m), 1682 (s), 1539 (s), 1251 (s), 910 (s), 750 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), major-isomer) \(\delta\) 1.01 (d, \(J = 6.8\) Hz, 3 H), 1.34 – 1.51 (m, 8 H), 1.44 (s, 9 H), 2.32 (dm, \(J = 7.4\) Hz, 1 H), 3.11 (br, 2 H), 3.67 (br, 1 H), 4.93 (dd, \(J = 10.2, 1.1\) Hz, 1 H), 5.01 (dd, \(J = 17.4, 1.1\) Hz, 1 H), 5.77 (ddd, \(J = 17.4, 10.2, 7.4\) Hz, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), major-isomer) \(\delta\) 20.2, 22.6, 28.4, 30.1, 35.4, 37.2, 40.4, 44.5, 70.1, 79.0, 112.6, 114.9, 155.9; \(^1\)H NMR (400 MHz, CDCl\(_3\), minor-isomer) \(\delta\) 0.98 (d, \(J = 6.6\) Hz, 3 H), 1.34 – 1.51 (m, 8 H), 1.44 (s, 9 H), 2.32 (dm, \(J = 7.4\) Hz, 1 H), 3.11 (br, 2 H), 3.67 (br, 1 H), 4.88 (dm, \(J = 11.2\) Hz, 1 H), 5.01 (dd, \(J = 17.4, 1.1\) Hz, 1 H), 5.77 (ddd, \(J = 17.4, 10.2, 7.4\) Hz, 1 H), \(\cdot\); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), minor-isomer) \(\delta\) 19.8, 22.6, 28.4, 30.0, 35.4, 37.2, 40.4, 44.3, 69.8, 79.0, 112.0, 114.6, 155.9; HRMS, calcd for C\(_{15}\)H\(_{29}\)NO\(_3\): 271.2147. Found \(m/z\) (relative intensity): 376.2731 (M\(^{+}\), 100).

**(6S,8S)-6-(4-methoxyphenylamino)-8-methyldec-9-en-1-ol (4h)**

Following General Procedure 1, Purification by flash column chromatography.
(6S,8S)-6-(4-methoxyphenylamino)-8-methyldec-9-en-1-ol (4h): (a mixture of major and minor isomers in a ratio of 4:1): IR (neat) 3364 (s), 2934 (s), 1614 (m), 1514 (s), 1238 (s), 1038 (s), 822 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, major-isomer) δ 1.00 (d, J = 6.8 Hz, 3 H), 1.21 – 1.58, (m, 10 H), 2.34 – 2.38 (m, 1 H), 3.27 – 3.32 (m, 1 H), 3.61 (t, J = 6.6 Hz, 2 H), 3.74 (s, 3 H), 4.92 (dd, J = 10.2, 0.9 Hz, 1 H), 4.93 (dd, J = 17.0, 0.9 Hz, 1 H), 5.65 (ddd, J = 17.0, 10.2, 8.1 Hz, 1 H), 6.63 (d, J = 9.1 Hz, 2 H), 6.74 (d, J = 9.1 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, major-isomer) δ 21.2, 25.6, 25.9, 32.8, 35.1, 35.3, 42.4, 55.8, 55.9, 62.9, 113.3, 114.9, 116.4, 139.8, 144.3, 152.8; ¹H NMR (400 MHz, CDCl₃, minor-isomer) δ 0.97 (d, J = 6.8 Hz, 3 H), 1.21 – 1.58, (m, 10 H), 2.34 – 2.38 (m, 1 H), 3.27 – 3.32 (m, 1 H), 3.61 (t, J = 6.4 Hz, 2 H), 3.74 (s, 3 H), 4.92 (dd, J = 10.2, 0.9 Hz, 1 H), 4.93 (dd, J = 17.0, 0.9 Hz, 1 H), 5.65 (ddd, J = 17.0, 10.2, 8.1 Hz, 1 H), 6.63 (d, J = 9.1 Hz, 2 H), 6.74 (d, J = 9.1 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, minor-isomer) δ 21.2, 25.6, 25.9, 32.8, 35.1, 35.3, 42.4, 55.8, 55.9, 63.1, 113.3, 114.8, 116.4, 139.8, 144.3, 152.8; HRMS, calcd for C₁₈H₂₉NO₂: 291.2196. Found m/z (relative intensity): 292.2236 (M⁺+1, 15), 291.2196 (M⁺, 65), 223.1501 (13), 222.1497 (100).

2-(4-methoxyphenylamino)-5-hexenol (6aa)

Following General Procedure 1, Purification by flash column chromatography.
2-(4-methoxyphenylamino)-5-hexenol (6aa): IR (neat) 3375 (s), 3076 (m), 2936 (s), 1639 (s), 1514 (s), 1464 (s), 1238 (s), 1038 (s), 822 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.42 (quin, \(J = 7.5\) Hz, 2 H), 2.14 (br q, \(J = 6.8\) Hz, 1 H), 2.25 (br q, \(J = 6.4\) Hz, 1 H), 2.69 (br, 1 H), 3.40 (m, 2 H), 3.49 (dd, \(J = 10.9, 6.1\) Hz, 1 H), 3.51 (dd, \(J = 10.9, 6.1\) Hz, 1 H), 3.74 (s, 3 H), 4.94 (dm, \(J = 9.7\) Hz, 1 H), 5.00 (dt, \(J = 16.1,1.9\) Hz, 1 H), 5.78 (ddt, \(J = 16.1, 9.7, 6.4\) Hz, 1 H), 6.64 (dd, \(J = 6.6, 2.4\) Hz, 2 H), 6.74 (dd, \(J = 6.6, 2.4\) Hz, 2 H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 28.7, 30.4, 55.8, 56.3, 64.1, 114.8, 115.7, 116.4, 137.8, 139.8, 152.7; HRMS, calcd for C\(_{13}\)H\(_{19}\)NO\(_2\): 221.1416. Found m/z (relative intensity): 222.1449 (M\(^{+1}\), 4), 221.1401 (M\(^+\), 28), 191.1235 (14), 190.1195 (100).

\((E)\)-2-(4-methoxyphenylamino)-4-hexenol (6’aa)

Following General Procedure 1, Purification by flash column chromatography.

\((E)\)-2-(4-methoxyphenylamino)-4-hexenol (6’aa): (a mixture of \(E\)- and \(Z\)- isomers in a ratio of 1 : 2): IR (neat) 3375 (s), 3076 (m), 2936 (s), 1639 (s), 1514 (s), 1464 (s), 1238 (s), 1038 (s), 822 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.64 (dm, \(J = 7.6\) Hz, 3 H), 2.02 (m, 2 H), 3.40 (m, 2 H), 3.49 (dd, \(J = 10.9, 6.1\) Hz, 1 H), 3.51 (dd, \(J = 10.9, 6.1\) Hz, 1 H), 3.74 (s, 3 H), 5.40 (m, 1 H), 5.50 (m, 1 H), 6.64 (dd, \(J = 6.6, 2.4\) Hz, 2 H),
6.74 (dd, $J = 6.6, 2.4$ Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 18.0, 33.3, 55.8, 56.5, 64.4, 114.9, 116.1, 125.7, 133.8, 139.8, 152.8; HRMS, calcd for C$_{13}$H$_{19}$NO$_2$: 221.1416. Found $m/z$ (relative intensity): 222.1449 (M$^+$+1, 4), 221.1401 (M$^+$, 28), 191.1235 (14), 190.1195 (100).

$(2R,4S)$-4-methyl-2-(phenylamino)-5-hexenol (6bb)

Following General Procedure 1, Purification by flash column chromatography.

$(2R,4S)$-4-methyl-2-(phenylamino)-5-hexenol (6bb): (a mixture of major and minor isomers in a ratio of 8:1): IR (neat) 3393 (s), 3078 (m), 2926 (s), 1601 (s), 1506 (s), 1317 (s), 1030 (s), 914 (m), 748 (s), 692 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, major-isomer) δ 1.03 (d, $J = 6.8$ Hz, 3 H), 1.52 (t, $J = 5.7$ Hz, 2 H), 2.32 (ddm, $J = 7.7$, 6.8 Hz, 1 H), 3.49 (dd, $J = 10.5, 5.4$ Hz, 1 H), 3.55 (tdm, $J = 5.4, 4.1$ Hz, 2 H), 3.71 (dd, $J = 10.5, 4.1$ Hz, 1 H), 4.89 (dd, $J = 17.2, 0.9$ Hz, 1 H), 4.92 (dd, $J = 10.4, 0.9$ Hz, 1 H), 5.64 (ddd, $J = 17.2, 10.4, 7.7$ Hz, 1 H), 6.64 (dd, $J = 8.6, 1.2$ Hz, 2 H), 6.70 (t, $J = 7.3$ Hz, 1 H), 7.15 (dd, $J = 8.6, 7.3$ Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, major-isomer) δ 21.1, 35.0, 39.8, 53.5, 65.0, 113.7, 113.8, 117.8, 129.3, 143.7, 147.7; $^1$H NMR (400 MHz, CDCl$_3$, minor-isomer) δ 1.00 (d, $J = 6.8$ Hz, 3 H), 1.50 (t, $J = 5.1$ Hz, 2 H), 2.32 (ddm, $J = 7.7$, 6.8 Hz, 1 H), 3.49 (dd, $J = 10.5, 5.4$ Hz, 1 H), 3.55 (tdm, $J = 5.4, 4.1$ Hz, 2 H), 3.71 (dd, $J = 10.5, 4.1$ Hz, 1 H), 4.89 (dd, $J = 17.2, 0.9$ Hz, 1 H), 4.92 (dd, $J = 10.4, 0.9$ Hz, 1 H), 5.64 (ddd, $J = 17.2, 10.4, 7.7$ Hz, 1 H), 6.64 (dd, $J = 8.6, 1.2$ Hz, 2 H).
(2R,4S)-2-(4-methoxyphenylamino)-4-methyl-5-hexenol (6ba)

Following General Procedure 1, Purification by flash column chromatography.

\[
\text{HN}^\text{PMP} \quad \text{OH}
\]

(2R,4S)-2-(4-methoxyphenylamino)-4-methyl-5-hexenol (6ba): \(\text{IR (neat)} 3383 (s), 3078 (m), 2932 (s), 1618 (s), 1418 (s), 1238 (s), 1040 (m), 820 (s)\) cm\(^{-1}\); \(\text{\(^1\)H NMR (400 MHz, CDCl}_3\) \(\delta 1.01 (d, J = 6.6 \text{ Hz}, 3 \text{ H}), 1.49 (t, J = 6.8 \text{ Hz}, 2 \text{ H}), 2.31 (qtm, J = 6.6, 6.6 \text{ Hz}, 1 \text{ H}), 3.45 (dd, J = 8.4, 3.2 \text{ Hz}, 1 \text{ H}), 3.46 (dd, J = 8.4, 5.5 \text{ Hz}, 1 \text{ H}), 3.71 (dm, J = 6.6 \text{ Hz}, 1 \text{ H}), 3.74 (s, 3 \text{ H}), 4.89 (dd, J = 17.1, 1.2 \text{ Hz}, 1 \text{ H}), 4.92 (dd, J = 10.2, 1.2 \text{ Hz}, 1 \text{ H}), 5.63 (dd, J = 17.1, 8.1 \text{ Hz}, 1 \text{ H}), 6.64 (dd, J = 6.6, 2.2 \text{ Hz}, 2 \text{ H}), 6.76 (dd, J = 6.6, 2.2 \text{ Hz}, 2 \text{ H}); \text{\(^{13}\)C NMR (100 MHz, CDCl}_3\) \(\delta 21.0, 34.9, 39.6, 55.0, 55.7, 64.8, 113.6, 114.8, 115.4, 141.7, 143.7, 152.3\); HRMS, calcld for C\(_{14}\)H\(_{21}\)NO\(_2\): 235.1572. Found \(m/z\) (relative intensity): 236.1583 (M\(^+\) + 1, 5), 235.1562 (M\(^+\), 28), 204.1378 (100).

(2R,4S)-2-(2-methoxyphenylamino)-4-methyl-5-hexenol (6bc)

Following General Procedure 1, Purification by flash column chromatography.
(2R,4S)-2-(2-methoxyphenylamino)-4-methyl-5-hexenol (6bc): (a mixture of major and minor isomers in a ratio of 8:1): IR (neat) 3414 (s), 3070 (m), 2932 (s), 2359 (s), 1601 (s), 1516 (s), 1456 (s), 1223 (s), 1030 (s), 914 (s), 737 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, major-isomer) δ 1.03 (d, J = 6.8 Hz, 3 H), 1.54 (t, J = 6.6 Hz, 2 H), 2.31 (qm, J = 6.8 Hz, 1 H), 3.50 (dd, J = 10.4, 5.8 Hz, 1 H), 3.55 (tdm, J = 6.6, 3.9 Hz, 1 H), 3.72 (dd, J = 10.4, 3.9 Hz, 1 H), 3.85 (s, 3 H), 4.87 (dd, J = 17.8, 1.7 Hz, 1 H), 4.90 (dd, J = 10.1, 1.7 Hz, 1 H), 5.64 (dd, J = 17.8, 10.1, 8.0 Hz, 1 H), 6.68 (d, J = 7.6 Hz, 1 H), 6.69 (dd, J = 7.6, 1.6 Hz, 1 H), 6.77 (dd, J = 7.6, 1.2 Hz, 1 H), 6.83 (dm, J = 7.6 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃, major-isomer) δ 21.1, 34.9, 39.8, 53.4, 55.5, 65.1, 109.8, 111.2, 113.7, 116.9, 121.3, 137.4, 143.7, 147.0; ¹H NMR (400 MHz, CDCl₃, minor-isomer) δ 0.99 (d, J = 6.8 Hz, 3 H), 1.54 (t, J = 6.6 Hz, 2 H), 2.31 (qm, J = 6.8 Hz, 1 H), 3.50 (dd, J = 10.4, 5.8 Hz, 1 H), 3.55 (tdm, J = 6.6, 3.9 Hz, 1 H), 3.72 (dd, J = 10.4, 3.9 Hz, 1 H), 3.85 (s, 3 H), 4.87 (dd, J = 17.8, 1.7 Hz, 1 H), 4.90 (dd, J = 10.1, 1.7 Hz, 1 H), 5.64 (dd, J = 17.8, 10.1, 8.0 Hz, 1 H), 6.68 (d, J = 7.6 Hz, 1 H), 6.69 (dd, J = 7.6, 1.6 Hz, 1 H), 6.77 (dd, J = 7.6, 1.2 Hz, 1 H), 6.83 (dm, J = 7.6 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃, minor-isomer) δ 21.1, 35.0, 39.8, 53.4, 55.6, 65.1, 109.8, 111.2, 113.7, 116.9, 121.3, 137.4, 143.8, 147.0; HRMS, calcd for C₁₄H₂₁NO₂: 235.1572. Found m/z (relative intensity): 235.1568 (M⁺, 29), 205.1415 (19), 204.1378 (100).
(2R,4S)-2-(4-bromophenylamino)-4-methyl-5-hexenol (6bd)

Following General Procedure 1, Purification by flash column chromatography.

(2R,4S)-2-(4-bromophenylamino)-4-methyl-5-hexenol (6bd): IR (neat) 3400 (s), 2927 (s), 2868 (s), 2362 (m), 1593 (s), 1496 (s), 1317 (s), 1074 (s), 916 (m), 812 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.01 (d, J = 6.6 Hz, 3 H), 1.50 (m, 2 H), 2.02 (br, 1 H), 2.30 (m, 1 H), 3.48 (m, 2 H), 3.71 (dd, J = 13.6 Hz, 1 H), 4.88 (dd, J = 23, 1.2 Hz, 1 H), 4.92 (dd, J = 16, 1.2 Hz, 1 H), 5.62 (ddd, J = 17.0, 10.2, 8.1 Hz, 1 H), 6.49 (d, J = 9.0 Hz, 2 H), 7.21 (d, J = 9.0 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ 21.0, 34.9, 38.5, 53.4, 64.8, 109.0, 113.9, 115.0, 131.8, 143.5, 146.7; HRMS, calcd for C₁₃H₁₈BrNO: 283.0572. Found m/z (relative intensity): 283.0562 (M⁺, 25), 254.0476 (100).

(2R,4S)-2-(4-methoxyphenylamino)-8-methyl-4-vinylnon-7-enol (6ca)

Following General Procedure 1, Purification by flash column chromatography.

(2R,4S)-2-(4-methoxyphenylamino)-8-methyl-4-vinylnon-7-enol (6ca): IR (neat) 3368 (s), 3078 (m), 2916 (s), 1607 (m), 1514 (s), 1375 (s), 1240 (s), 1042 (s), 914 (s), 820 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.33 (m, 2 H), 1.46 (dd, J = 10.1, 4.4 Hz,
2 H), 1.56 (s, 3 H), 1.67 (s, 3 H), 1.94 (m, 2 H), 2.15 (dm, $J = 4.4$ Hz, 1 H), 3.44 (dd, $J = 10.0, 7.4$ Hz, 1 H), 3.46 (dd, $J = 10.0, 5.8$ Hz, 1 H), 3.69 (m, 2 H), 3.74 (s, 3 H), 4.84 (dd, $J = 17.0, 2.0$ Hz, 1 H), 4.99 (dd, $J = 10.2, 2.0$ Hz, 1 H), 5.05 (tt, $J = 5.6, 1.4$ Hz, 1 H), 5.49 (ddd, $J = 17.0, 10.2, 9.0$ Hz, 1 H), 6.65 (dd, $J = 6.6, 2.3$ Hz, 2 H), 6.75 (dd, $J = 6.6, 2.3$ Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 17.7, 25.6, 25.7, 35.5, 38.1, 40.5, 55.7, 65.0, 114.8, 115.5, 115.8, 124.1, 131.4, 141.2, 142.2, 152.7; HRMS, calcd for C$_{19}$H$_{29}$NO$_2$: 303.2198. Found $m/z$ (relative intensity): 304.2201 (M$^+$+1, 11), 303.2183 (M$, 48), 273.2022 (19), 272.2000 (100).

3-(4-methoxyphenylamino)-6-hexene-1,2-diol (8aa)

Following General Procedure 1, Purification by flash column chromatography.

3-(4-methoxyphenylamino)-6-hexene-1,2-diol (8aa): (a mixture of major and minor isomers in a ratio of 3:1): IR (neat) 3356 (s), 3074 (m), 2934 (s), 1666 (s), 1441 (s), 1236 (s), 1038 (s), 822 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, major-isomer) $\delta$ 1.62 (td, $J = 8.7, 5.9$ Hz, 2 H), 2.00 – 2.33 (m, 2 H), 2.60 – 3.00 (m, 1 H), 3.35 – 3.47 (m, 1 H), 3.68 – 3.80 (m, 2 H), 3.74 (s, 3 H), 4.95 (dd, $J = 9.9, 1.5$ Hz, 1 H), 4.96 (dd, $J = 17.8, 1.5$ Hz, 1 H), 5.76 (ddt, $J = 17.8, 9.9, 6.7$ Hz, 1 H), 6.65 (dt, $J = 9.3, 2.5$ Hz, 2 H), 6.76 (dt, $J = 9.3, 2.5$ Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, major-isomer) $\delta$ 30.3, 30.8, 55.7, 57.8, 64.0, 72.7, 114.9, 115.2, 115.6, 137.7, 141.1, 152.6; $^1$H NMR (400 MHz,
CDCl$_3$, minor-isomer) $\delta$ 1.62 (td, $J = 8.7, 5.9$ Hz, 2 H), 2.00 – 2.33 (m, 2 H), 2.60 – 3.00 (m, 1 H), 3.35 – 3.47 (m, 1 H), 3.68 – 3.80 (m, 2 H), 3.74 (s, 3 H), 4.95 (dd, $J = 9.9, 1.5$ Hz, 1 H), 4.96 (dd, $J = 17.8, 1.5$ Hz, 1 H), 5.76 (ddt, $J = 17.8, 9.9, 6.7$ Hz, 1 H), 6.65 (dt, $J = 9.3, 2.5$ Hz, 2 H), 6.76 (dt, $J = 9.3, 2.5$ Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, minor-isomer) $\delta$ 30.2, 30.8, 55.7, 57.8, 64.2, 72.6, 114.8, 115.2, 115.6, 137.7, 141.2, 152.6; HRMS, calcd for C$_{14}$H$_{21}$NO$_3$: 251.1521. Found m/z (relative intensity): 252.1614 (M$^{+}$+1, 4), 251.1512 (M$, 30), 220.1334 (6), 191.1258 (14), 190.1187 (100).

(E)-3-(4-methoxyphenylamino)-5-hexene-1,2-diol (8’aa)

Following General Procedure 1, Purification by flash column chromatography.

(E)-3-(4-methoxyphenylamino)-5-hexene-1,2-diol (8’aa): (a mixture of major and minor isomers in a ratio of 3:1): IR (neat) 3356 (s), 3074 (m), 2934 (s), 1666 (s), 1441 (s), 1236 (s), 1038 (s), 822 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, major-isomer) $\delta$ 1.72 (d, $J = 6.8$ Hz, 3 H), 2.00 – 2.33 (m, 2 H), 2.60 – 3.00 (m, 1 H), 3.35 – 3.47 (m, 1 H), 3.68 – 3.80 (m, 2 H), 3.74 (s, 3 H), 5.36 – 5.43 (m, 1 H), 5.48 – 5.55, (m, 1 H), 6.65 (dt, $J = 9.3, 2.5$ Hz, 2 H), 6.76 (dt, $J = 9.3, 2.5$ Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, major-isomer) $\delta$ 18.0, 33.8, 55.7, 57.4, 64.8, 72.2, 114.9, 115.2, 126.5, 128.8, 141.5, 152.8; $^1$H NMR (400 MHz, CDCl$_3$, minor-isomer) $\delta$ 1.72 (d, $J = 6.8$ Hz, 3 H), 2.00 – 2.33 (m, 2 H), 2.60 – 3.00 (m, 1 H), 3.35 – 3.47 (m, 1 H), 3.68 – 3.80 (m, 2 H), 3.74 (s,
3 H), 5.36 – 5.43 (m, 1 H), 5.48 – 5.55, (m, 1 H), 6.65 (dt, J = 9.3, 2.5 Hz, 2 H), 6.76 (dt, J = 9.3, 2.5 Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, minor-isomer) $\delta$ 18.0, 33.8, 55.7, 57.4, 64.7, 72.2, 114.8, 115.2, 126.5, 128.8, 141.5, 152.8; HRMS, calcd for C$_{14}$H$_{21}$NO$_3$: 251.1521. Found $m/z$ (relative intensity): 252.1614 (M$^+$1, 4), 251.1512 (M$^+$, 30), 220.1334 (6), 191.1258 (14), 190.1187 (100).

(3$R$,5$S$)-5-methyl-3-(phenylamino)-6-heptene-1,2-diol (8bb)

Following General Procedure 1, Purification by flash column chromatography.

(3$R$,5$S$)-5-methyl-3-(phenylamino)-6-heptene-1,2-diol (8bb): (a mixture of major and minor isomers in a ratio of 2:1): IR (neat) 3281 (s), 2961 (s), 1603 (s), 1512 (s), 1325 (s), 1024 (s), 748 (s), 692 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, major-isomer) $\delta$ 1.01 (d, J = 6.8 Hz, 3 H), 1.54 – 1.63 (m, 2 H), 2.23 – 2.33 (qm, J = 6.8 Hz, 1 H), 3.54 – 3.77 (m, 4 H), 4.94 (dd, J = 10.3, 1.5 Hz, 1 H), 4.98 (dd, J = 17.1, 1.5 Hz, 1 H), 5.59 (ddd, J = 17.1, 10.3, 8.3 Hz, 1 H), 6.65 (td, J = 8.5, 1.0 Hz, 2 H), 6.70 – 6.74 (m, 1 H), 7.15 (dt, J = 8.5, 7.6 Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, major-isomer) $\delta$ 21.4, 34.9, 39.0, 54.3, 64.0, 73.5, 113.7, 117.8, 118.1, 129.2, 143.4, 147.6; $^1$H NMR (400 MHz, CDCl$_3$, minor-isomer) $\delta$ 0.97 (d, J = 6.6 Hz, 3 H), 1.47 (ddd, J = 14.0, 9.8, 4.2 Hz, 2 H), 2.23 – 2.33 (qm, J = 6.8 Hz, 1 H), 3.54 – 3.77 (m, 4 H), 4.82 (dd, J = 17.3, 1.7 Hz, 1 H), 4.92 (dd, J = 9.9, 1.7 Hz, 1 H), 5.72 (ddd, J = 17.3, 9.9, 7.4 Hz, 1 H), 6.65 (td, $j =$
8.5, 1.0 Hz, 2 H), 6.70 – 6.74 (m, 1 H), 7.15 (dt, \( J = 8.5, 7.6 \) Hz, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), minor-isomer) \( \delta \) 21.2, 34.5, 38.2, 54.6, 63.8, 72.7, 113.8, 117.8, 118.0, 129.3, 143.9, 147.4; HRMS, calcd for C\(_{14}H_{21}NO_2\): 235.1572. Found \( m/z \) (relative intensity): 236.1596 (M\(^{+}+1\), 3), 235.1554 (M\(^{+}\), 12), 175.1262 (13), 174.1240 (100).

\((3R,5S)-3-(4\text{-methoxyphenylamino})-5\text{-methyl-6-heptene-1,2-diol} (8ba)\)

Following General Procedure 1, Purification by flash column chromatography.

\[(3R,5S)-3-(4\text{-methoxyphenylamino})-5\text{-methyl-6-heptene-1,2-diol} (8ba) : (a \text{ mixture of major and minor isomers in a ratio of 2:1): IR (neat) 3366 (s), 3078 (m), 2932 (m), 2835 (m), 1655 (s), 1238 (s), 1036 (s), 822 (s) \text{ cm}^{-1}; ^{1}\text{H NMR (400 MHz, CDCl}_3, \text{ major-isomer}) \delta 1.00 (d, \( J = 6.6 \) Hz, 3 H), 1.48 (ddd, \( J = 14.0, 9.7, 4.2 \) Hz, 1 H), 1.55 (ddd, \( J = 14.0, 9.7, 4.2 \) Hz, 1 H), 2.03 (br, 2 H) 2.25 (m, 1 H), 3.44 – 3.54 (m, 1 H), 3.74 (s, 3 H), 3.66 – 3.8 (m, 4 H), 4.80 (dd, \( J = 17.1, 1.3 \) Hz, 1 H), 4.91 (dd, \( J = 10.5, 1.3 \) Hz, 1 H), 5.57 (ddd, \( J = 17.1, 10.5, 8.3 \) Hz, 1 H), 6.68 (dd, \( j = 6.8, 2.3 \) Hz, 2 H), 6.76 (dd, \( J = 6.8, 2.3 \) Hz, 2 H); ^{13}\text{C NMR (100 MHz, CDCl}_3, \text{ major-isomer}) \delta 21.4, 35.0, 39.0, 55.8, 56.3, 64.1, 73.1, 114.2, 114.9, 115.9, 143.5, 143.7, 152.8; ^{1}\text{H NMR (400 MHz, CDCl}_3, \text{ minor-isomer}) \delta 0.96 (d, \( J = 6.6 \) Hz, 3 H), 1.48 (ddd, \( J = 14.0, 9.7, 4.2 \) Hz, 1 H), 1.55 (ddd, \( J = 14.0, 9.7, 4.2 \) Hz, 1 H), 2.03 (br, 2 H) 2.25 (m, 1 H), 3.44 – 3.54 (m, 1 H), 3.74 (s, 3 H), 3.66 – 3.8 (m, 4 H), 4.80 (dd, \( J = 17.1, 1.3 \) Hz, 1 H), 4.97]
(dd, $J = 17.4, 1.3$ Hz, 1 H), 5.67 (ddd, $J = 17.4, 10.2, 7.6$ Hz, 1 H), 6.68 (dd, $j = 6.8, 2.3$ Hz, 2 H), 6.76 (dd, $J = 6.8, 2.3$ Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, minor-isomer) $\delta$ 20.4, 34.7, 39.0, 55.8, 56.3, 63.8, 73.1, 115.0, 114.9, 116.1, 143.5, 143.7, 152.8; HRMS, calcd for C$_{15}$H$_{23}$NO$_3$: 265.1678. Found $m/z$ (relative intensity): 266.1678 ($M^+1$, 3), 265.1659 (M+, 18), 205.1406 (15), 204.1406 (100).

(3R,5S)-3-(4-methoxyphenylamino)-9-methyl-5-vinyl-8-decene-1,2-diol (8ca)

Following General Procedure 1, Purification by flash column chromatography.

(3R,5S)-3-(4-methoxyphenylamino)-9-methyl-5-vinyl-8-decene-1,2-diol (8ca): (a mixture of major and minor isomers in a ratio of 2:1): IR (neat) 3358 (s), 3074 (s), 2916 (s), 2343 (m), 1666 (s), 1514 (s), 1238 (s), 1040 (s), 822 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, major-isomer) $\delta$ 1.19 – 1.38 (m, 4 H), 1.55 (s, 3 H), 1.67 (s, 3 H), 1.79 – 1.98 (dm, $J = 7.5$ Hz, 1 H), 2.00 – 2.17 (m, 2 H), 3.47 (dd, $J = 12.0, 5.9$ Hz, 1 H), 3.54 (dd, $J = 12.0, 6.9$ Hz, 1 H), 3.69 – 3.80 (m, 3 H), 3.74 (s, 3 H), 4.74 (dd, $J = 18.6, 2.0$ Hz, 1 H), 4.94 – 5.05 (m, 1 H), 4.98 (dd, $J = 10.0, 2.0$ Hz, 1 H), 5.46 (dd, $J = 18.6, 10.0, 7.5$ Hz, 1 H), 6.69 (d, $J = 6.6$ Hz, 2 H), 6.75 – 6.78 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, major-isomer) $\delta$ 17.7, 25.4, 25.6, 35.2, 35.4, 40.5, 55.6, 55.7, 64.0, 73.1, 114.9, 115.3, 116.2, 124.1, 124.3, 131.5, 131.6, 141.9; $^1$H NMR (400 MHz, CDCl$_3$, minor-isomer) $\delta$ 1.19 – 1.38 (m, 4 H), 1.54 (s, 3 H), 1.64 (s, 3 H), 1.79 – 1.98 (dm, $J = 7.5$ Hz, 1 H), 2.00
- 2.17 (m, 2 H), 3.47 (dd, $J = 12.0$, 5.9 Hz, 1 H), 3.54 (dd, $J = 12.0$, 6.9 Hz, 1 H), 3.69 – 3.80 (m, 3 H), 3.75 (s, 3 H), 4.74 (dd, $J = 18.6$, 2.0 Hz, 1 H), 4.94 – 5.05 (m, 1 H), 4.98 (dd, $J = 10.0$, 2.0 Hz, 1 H), 5.46 (ddd, $J = 18.6$, 10.0, 7.5 Hz, 1 H), 6.69 (d, $J = 6.6$ Hz, 2 H), 6.75 – 6.78 (m, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, minor-isomer) $\delta$ 17.7, 25.4, 25.6, 35.2, 35.4, 40.4, 55.6, 55.7, 64.0, 73.1, 114.8, 115.3, 116.3, 124.1, 124.3, 131.4, 131.6, 141.8; HRMS, calecd for C$_{20}$H$_{31}$NO$_3$: 333.2304. Found m/z (relative intensity): 334.2348 (M$^{++}$1, 7), 333.2312 (M$^+$, 33), 302.2102 (4), 273.2012 (20), 272.2004 (100).

$(2S, 3S, 5S)$- 5-(4-methoxyphenylamino)-8-nonen-1,2,3-triol (9aa)

Following General Procedure 1, Purification by flash column chromatography.

$(2S, 3S, 5S)$- 5-(4-methoxyphenylamino)-8-nonen-1,2,3-triol (9aa): (a mixture of major and minor isomers in a ratio of 1:1): IR (neat) 3277 (m), 2932 (s), 2839 (s), 1732 (s), 1514 (s), 1456 (s), 1441 (s), 1238 (s), 1040 (s), 970 (s), 912 (m), 824 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, major-isomer) $\delta$ 1.43 (m, 2 H), 1.87 (dt, $J = 11.5$, 3.2 Hz, 2 H), 2.15- 2.30 (br d, $J = 6.8$ Hz, 2 H), 3.51- 3.62 (m, 4 H), 3.61 (br t, $J = 3.2$ Hz, 1 H), 3.74 (s, 3 H), 3.93- 4.01 (m, 1 H), 4.95 (dd, $J = 11.2$, 1.6 Hz, 1 H), 4.98 (dd, $J = 18.1$, 1.6 Hz, 1 H), 5.78 (ddd, $J = 18.1$, 11.2, 6.8 Hz, 1 H), 6.70 (d, $J = 8.8$ Hz, 2 H), 6.77 (d, $J = 8.8$ Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, major-isomer) $\delta$ 28.7, 32.7, 36.5, 55.7,
56.8, 63.7, 71.3, 74.6, 114.5, 114.8, 118.3, 138.5, 141.1, 153.2; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, minor-isomer) \(\delta\) 1.43 (m, 2 H), 1.87 (dt, \(J = 11.5, 3.2\) Hz, 2 H), 2.15 - 2.30 (br d, \(J = 6.8\) Hz, 2 H), 3.51 - 3.62 (m, 4 H), 3.61 (br t, \(J = 3.2\) Hz, 1 H), 3.74 (s, 3 H), 3.93 - 4.01 (m, 1 H), 4.95 (dd, \(J = 11.2, 1.6\) Hz, 1 H), 4.98 (dd, \(J = 18.1, 1.6\) Hz, 1 H), 5.78 (ddd, \(J = 18.1, 11.2, 6.8\) Hz, 1 H), 6.70 (d, \(J = 8.8\) Hz, 2 H), 6.77 (d, \(J = 8.8\) Hz, 2 H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}, minor-isomer) \(\delta\) 28.7, 32.7, 36.1, 55.7, 56.8, 63.7, 71.3, 74.7, 114.6, 114.8, 118.5, 138.5, 141.1, 153.3; HRMS, calcd for C\textsubscript{16}H\textsubscript{25}NO\textsubscript{4}: 295.1783. Found \(m/z\) (relative intensity): 296.1817 (M\textsuperscript{+}+1, 21), 295.1776 (M\textsuperscript{+}, 100), 294.1700 (5).

(2S, 3S, 5S)- 5-(4-methoxyphenylamino)-7-nonen-1,2,3-triol (9’aa)

Following General Procedure 1, Purification by flash column chromatography.

(2S, 3S, 5S)- 5-(4-methoxyphenylamino)-7-nonen-1,2,3-triol (9’aa): (a mixture of major and minor isomers in a ratio of 3:1): IR (neat) 3277 (m), 2932 (s), 2839 (s), 1732 (s), 1514 (s), 1456 (s), 1441 (s), 1238 (s), 1040 (s), 970 (s), 912 (m), 824 (s) cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, major-isomer) \(\delta\) 1.43 (m, 2 H), 1.87 (dt, \(J = 11.5, 3.2\) Hz, 2 H), 2.15 - 2.30 (m, 2 H), 2.03 (d, \(J = 7.3\) Hz, 3 H), 3.51 - 3.62 (m, 4 H), 3.61 (br t, \(J = 3.2\) Hz, 1 H), 3.74 (s, 3 H), 3.93 - 4.01 (m, 1 H), 5.32 (dq, \(J = 14.6, 7.3\) Hz, 1 H), 5.46 (dt, \(J = 14.6, 6.6\) Hz, 1 H), 6.70 (d, \(J = 8.8\) Hz, 2 H), 6.77 (d, \(J = 8.8\) Hz, 2 H); \textsuperscript{13}C
NMR (100 MHz, CDCl₃, major-isomer) δ 18.0, 32.5, 37.7, 52.7, 55.7, 63.9, 71.1, 74.1, 114.9, 116.9, 125.5, 130.6, 140.8, 154.0; ¹H NMR (400 MHz, CDCl₃, minor-isomer) δ 1.43 (m, 2 H), 1.87 (dt, J = 11.5, 3.2 Hz, 2 H), 2.15- 2.30 (m, 2 H), 2.03 (d, J = 7.3 Hz, 3 H), 3.51- 3.62 (m, 4 H), 3.61 (br t, J = 3.2 Hz, 1 H), 3.74 (s, 3 H), 3.93- 4.01 (m, 1 H), 5.32 (dq, J = 14.6, 7.3 Hz, 1 H), 5.46 (dt, J = 14.6, 6.6 Hz, 1 H), 6.70 (d, J = 8.8 Hz, 2 H), 6.77 (d, J = 8.8 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, minor-isomer) δ 18.0, 32.5, 37.4, 52.7, 55.7, 63.9, 71.1, 74.3, 114.9, 117.0, 125.2, 130.7, 140.8, 154.0; HRMS, calcd for C₁₆H₂₅NO₄: 295.1783. Found m/z (relative intensity): 296.1817 (M⁺+1, 21), 295.1776 (M⁺, 100), 294.1700 (5).

(2S, 3S, 5S, 7S)- 5-(4-methoxyphenylamino)-7-methyl-8-nonen-1,2,3-triol (9ba)

Following General Procedure 1, Purification by flash column chromatography.

(2S, 3S, 5S, 7S)- 5-(4-methoxyphenylamino)-7-methyl-8-nonen-1,2,3-triol (9ba): (a mixture of major and minor isomers in a ratio of 2:1): IR (neat) 3267 (s), 2835 (s), 1639 (m), 1616 (m), 1417 (s), 1238 (s), 1180 (s), 1038 (s), 914 (s), 824 (s), 606 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, major-isomer) δ 1.00 (d, J = 6.6 Hz, 3 H), 1.46- 1.64 (m, 4 H), 1.88 (ddd, J = 14.4, 8.5, 3.4 Hz, 1 H), 2.26- 2.33 (br-d, J = 7.3 Hz, 1 H), 3.48- 3.80 (m, 3 H), 3.75 (s, 3 H), 3.97 (ddd, J = 11.5, 5.6, 2.9 Hz, 1 H), 4.89 (dd, J = 17.2, 1.0 Hz, 1 H), 4.91 (dd, J = 9.7, 1.7 Hz, 1 H), 5.65 (ddd, J = 17.2, 9.7, 7.3 Hz, 1
H), 6.66 (d, J = 9.0 Hz, 2 H), 6.77 (d, J = 9.0 Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, major-isomer) δ 20.7, 35.1, 37.4, 42.6, 51.2, 55.8, 63.9, 71.3, 74.0, 113.5, 114.9, 116.2, 141.0, 144.0, 153.0; $^1$H NMR (400 MHz, CDCl$_3$, minor-isomer) δ 0.94 (d, J = 6.8 Hz, 3 H), 1.46- 1.64 (m, 4 H), 1.91 (ddd, J = 14.4, 8.5, 3.4 Hz, 1 H), 2.26- 2.33 (br-d, J = 7.3 Hz, 1 H), 3.48- 3.80 (m, 3 H), 3.75 (s, 3 H), 3.97 (ddd, J = 11.5, 5.6, 2.9 Hz, 1 H), 4.89 (dd, J = 17.2, 1.0 Hz, 1 H), 4.91 (dd, J = 9.7, 1.7 Hz, 1 H), 5.65 (ddd, J = 17.2, 9.7, 7.3 Hz, 1 H), 6.67 (d, J = 10.5 Hz, 2 H), 6.69 (d, J = 10.2 Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$, minor-isomer) δ 20.7, 34.9, 37.2, 43.2, 51.6, 55.7, 63.8, 71.3, 74.2, 113.5, 114.9, 116.2, 141.0, 144.2, 153.0; HRMS, calcd for C$_{17}$H$_{27}$NO$_4$: 309.1940. Found m/z (relative intensity): 310.1951 (M$^+$+1, 19), 309.1932 (M$^+$, 100), 248.1652 (12), 247.1566 (5).

(2S, 3S, 5S, 7S)- 5-(2-methoxyphenylamino)-7-methyl-8-nonen-1,2,3-triol (9bc)

Following General Procedure 1, Purification by flash column chromatography.

(2S, 3S, 5S, 7S)- 5-(2-methoxyphenylamino)-7-methyl-8-nonen-1,2,3-triol (9bc): (a mixture of major and minor isomers in a ratio of 2:1): IR (neat) 3379 (s), 3071 (s), 2932 (s), 2360 (s), 1596 (s), 1512 (s), 1458 (s), 1227 (s), 1026 (s), 910 (s), 733 (s), 679 (s) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, major-isomer) δ 0.99 (d, J = 6.6 Hz, 3 H), 1.42- 1.52 (br d, J = 6.6 Hz, 4 H), 2.22- 2.27 (br d, J = 6.6 Hz, 1 H), 3.42- 3.43 (m, 1 H),
3.57- 3.58 (m, 2 H), 3.76- 3.78 (m, 3 H), 3.77 (s, 3 H), 4.01 (br, 3 H), 4.83 (d, \( J = 17.3 \) Hz, 1 H), 4.86 (d, \( J = 10.0 \) Hz, 1 H), 5.62 (ddd, \( J = 17.3, 10.0, 7.5 \) Hz, 1 H), 6.56- 6.64 (m, 1 H), 6.70- 6.72 (m, 2 H), 6.78 (t, \( J = 7.6 \) Hz, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), major-isomer) \( \delta \) 20.5, 34.7, 38.4, 43.3, 48.4, 55.3, 63.1, 70.1, 74.5, 109.7, 110.8, 113.1, 116.2, 121.2, 137.6, 143.9, 146.6; \(^1\)H NMR (400 MHz, CDCl\(_3\), minor-isomer) \( \delta \) 0.95 (d, \( J = 6.3 \) Hz, 3 H), 1.65- 1.78 (m, 4 H), 2.22- 2.27 (br d, \( J = 6.6 \) Hz, 1 H), 3.42- 3.43 (m, 1 H), 3.57- 3.58 (m, 2 H), 3.76- 3.78 (m, 3 H), 3.77 (s, 3 H), 4.01 (br, 3 H), 4.83 (d, \( J = 17.3 \) Hz, 1 H), 4.86 (d, \( J = 10.0 \) Hz, 1 H), 5.62 (ddd, \( J = 17.3, 10.0, 7.5 \) Hz, 1 H), 6.56- 6.64 (m, 1 H), 6.70- 6.72 (m, 2 H), 6.78 (t, \( J = 7.6 \) Hz, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), minor-isomer) \( \delta \) 20.7, 34.6, 38.4, 43.3, 48.2, 55.3, 63.1, 70.1, 74.5, 109.7, 110.8, 113.2, 116.4, 121.2, 137.5, 143.9, 146.6; HRMS, calcd for C\(_{17}\)H\(_{27}\)NO\(_4\): 309.1940. Found \( m/z \) (relative intensity): 309.1922 (M\(^+\), 100).

**(2S, 3S, 5S, 7S)- 5-(3,4-dimethoxyphenylamino)-7-methyl-8-nonen-1,2,3-triol (9bf)**

Following General Procedure 1, Purification by flash column chromatography.

![Structure of 5-(3,4-dimethoxyphenylamino)-7-methyl-8-nonen-1,2,3-triol](image)

**(2S, 3S, 5S, 7S)- 5-(3,4-dimethoxyphenylamino)-7-methyl-8-nonen-1,2,3-triol (9bf):** (a mixture of major and minor isomers in a ratio of 2:1):IR (neat) 3379 (s), 3078 (m), 2932 (s), 1705 (m), 1612 (s), 1458 (s), 1234 (s), 1026 (s), 918 (m), 733 (s) cm\(^{-1}\);
\(^1\)H NMR (400 MHz, CDCl\(_3\), major-isomer) \(\delta\) 1.00 (d, \(J = 6.6\) Hz, 3 H), 1.45-1.63 (m, 4 H), 1.86 (ddd, \(J = 14.2, 9.3, 3.2\) Hz, 1 H), 2.20-2.40 (m, 1 H), 3.12 (br, 1 H), 3.56 (br dd, \(J = 9.5, 5.4\) Hz, 1 H), 3.75 (m, 2 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 3.95 (ddd, \(J = 8.8, 5.4, 3.1\) Hz, 1 H), 4.90 (d, \(J = 17.1\) Hz, 1 H), 4.92 (d, \(J = 10.5\) Hz, 1 H), 5.65 (ddd, \(J = 17.1, 10.5, 7.9\) Hz, 1 H), 6.23 (dd, \(J = 8.5, 2.4\) Hz, 1 H), 6.32 (d, \(J = 2.4\) Hz, 1 H), 6.72 (d, \(J = 8.5\) Hz, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), major-isomer) \(\delta\) 20.7, 35.0, 37.7, 42.7, 50.8, 55.8, 56.6, 56.8, 63.6, 70.9, 100.5, 105.7, 113.4, 122.3, 132.3, 141.7, 144.0, 149.9; \(^1\)H NMR (400 MHz, CDCl\(_3\), minor-isomer) \(\delta\) 0.96 (d, \(J = 6.8\) Hz, 3 H), 1.45-1.63 (m, 4 H), 1.95 (ddd, \(J = 14.4, 8.8, 3.2\) Hz, 1 H), 2.20-2.40 (m, 1 H), 3.12 (br, 1 H), 3.56 (br dd, \(J = 9.5, 5.4\) Hz, 1 H), 3.75 (m, 2 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 4.00 (m, 1 H), 4.88 (d, \(J = 18.8\) Hz, 1 H), 4.98 (br d, \(J = 10.8\) Hz, 1 H), 5.58 (ddd, \(J = 18.8, 10.8, 8.0\) Hz, 1 H), 6.29 (dt, \(J = 8.5, 2.4\) Hz, 1 H), 6.34 (d, \(J = 2.4\) Hz, 1 H), 6.74 (d, \(J = 8.5\) Hz, 1 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), minor-isomer) \(\delta\) 20.7, 35.0, 37.7, 42.7, 50.8, 55.8, 56.6, 63.6, 70.9, 100.5, 105.7, 113.4, 122.3, 132.3, 141.7, 144.0, 149.9; HRMS, calcd for C\(_{18}\)H\(_{29}\)NO\(_5\): 339.2046. Found \(m/z\) (relative intensity): 340 (M\(^+\)+1, 24), 339.2039 (M\(^+\), 100), 324 (7), 321 (3).

(2S, 3S, 5S, 7S)-5-phenylamino-7-methyl-8-nonen-1,2,3-triol (9bb)

Following General Procedure 1, Purification by flash column chromatography.
(2S, 3S, 5S, 7S)-5-phenylamino-7-methyl-8-nonen-1,2,3-triol (9bb): (a mixture of major and minor isomers in a ratio of 2:1); IR (neat) 3400 (s), 2870 (s), 1639 (s), 1602 (s), 1502 (s), 1259 (s), 1180 (s), 993 (s), 873 (s), 754 (s), 667 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, major-isomer) δ 1.01 (d, J = 6.8 Hz, 3 H), 1.52-1.58 (m, 4 H), 1.85 (ddd, J = 14.4, 9.3, 3.4 Hz, 2 H), 2.28-2.35 (br d, J = 7.2 Hz, 1 H), 3.55 (br d, J = 9.3 Hz, 1 H), 3.77 (m, 3 H), 3.95 (ddd, J = 9.3, 5.4, 2.7 Hz, 1 H), 4.88 (dt, J = 17.4, 1.0 Hz, 1 H), 4.92 (dt, J = 9.9, 0.9 Hz, 1 H), 5.65 (ddd, J = 17.4, 9.9, 7.5 Hz, 1 H), 6.65 (dd, J = 8.5, 1.0 Hz, 2 H), 6.70 (dd, J = 8.5, 7.3 Hz, 1 H), 7.16 (dd, J = 8.5, 7.3 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, major-isomer) δ 20.9, 35.1, 38.1, 43.1, 49.5, 63.7, 71.0, 74.1, 113.9, 114.5, 129.3, 144.0, 147.5; ¹H NMR (400 MHz, CDCl₃, minor-isomer) δ 0.97 (d, J = 6.8 Hz, 3 H), 1.52-1.58 (m, 4 H), 1.85 (ddd, J = 14.4, 9.3, 3.4 Hz, 2 H), 2.28-2.35 (br d, J = 7.2 Hz, 1 H), 3.55 (br d, J = 9.3 Hz, 1 H), 3.77 (m, 3 H), 3.95 (ddd, J = 9.3, 5.4, 2.7 Hz, 1 H), 4.88 (dt, J = 17.4, 1.0 Hz, 1 H), 4.92 (dt, J = 9.9, 0.9 Hz, 1 H), 5.59 (br dd, J = 9.6, 7.5 Hz, 1 H), 6.65 (dd, J = 8.5, 1.0 Hz, 2 H), 6.70 (dd, J = 7.6, 6.8 Hz, 1 H), 7.16 (dd, J = 8.5, 7.3 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, minor-isomer) δ 20.9, 35.0, 38.1, 43.1, 49.5, 63.7, 71.0, 74.1, 113.6, 115.5, 129.3, 144.0, 147.5; HRMS, calcd for C₁₆H₂₅NO₃: 279.1834. Found m/z (relative intensity): 280.1877 (M⁺+1, 19), 279.1831 (M⁺, 100), 278.1753 (4), 248.1628 (6), 217.1507 (3).

(2S, 3S, 5S, 7S)-4-(4-chlorophenylamino)-7-methyl-8-nonen-1,2,3-triol (9bg)

Following General Procedure 1, Purification by flash column chromatography.
(2S, 3S, 5S, 7S)- 4-(4-chlorophenylamino)-7-methyl-8-nonen-1,2,3-triol (9bg): (a mixture of major and minor isomers in a ratio of 2:1): IR (neat) 3364 (s), 3078 (s), 2924 (s), 2361 (s), 1705 (s), 1597 (s), 1504 (s), 1319 (s), 1258 (s), 1180 (s), 918 (s), 818 (s), 671 (s) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), major-isomer) \(\delta\) 0.91 (d, \(J = 6.6\) Hz, 3 H), 1.38 (t, \(J = 6.6\) Hz, 2 H), 1.18- 1.60 (m, 2 H), 2.18 (br quint, d, \(J = 6.6\) Hz, 1 H), 3.34- 3.39 (m, 1 H), 3.49- 3.57 (m, 3 H), 3.70- 3.72 (m, 2 H), 3.78 (br, 3 H), 4.76 (d, \(J = 17.2\) Hz, 1 H), 4.83 (d, \(J = 10.2\) Hz, 1 H), 5.52 (ddd, \(J = 17.2, 10.2, 7.9\) Hz, 1 H), 6.46 (d, \(J = 8.8\) Hz, 2 H), 6.97 (d, \(J = 8.8\) Hz, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), major-isomer) \(\delta\) 20.0, 34.9, 38.4, 43.1, 49.2, 63.1, 70.2, 74.5, 113.6, 114.5, 121.6, 129.0, 143.9, 146.5; \(^1\)H NMR (400 MHz, CDCl\(_3\), minor-isomer) \(\delta\) 0.88 (d, \(J = 6.8\) Hz, 3 H), 1.38 (t, \(J = 6.6\) Hz, 2 H), 1.18- 1.60 (m, 2 H), 2.18 (br quint, d, \(J = 6.6\) Hz, 1 H), 3.34- 3.39 (m, 1 H), 3.49- 3.57 (m, 3 H), 3.70- 3.72 (m, 2 H), 3.78 (br, 3 H), 4.76 (d, \(J = 17.2\) Hz, 1 H), 4.83 (d, \(J = 10.2\) Hz, 1 H), 5.52 (ddd, \(J = 17.2, 10.2, 7.9\) Hz, 1 H), 6.51 (d, \(J = 8.8\) Hz, 2 H), 7.02 (d, \(J = 8.8\) Hz, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), minor-isomer) \(\delta\) 21.0, 34.8, 38.4, 42.7, 49.2, 63.1, 70.2, 74.4, 113.7, 114.5, 121.6, 129.1, 143.8, 146.5; HRMS, calcd for C\(_{16}\)H\(_{24}\)ClNO\(_3\): 313.1445. Found m/z (relative intensity): 314.1446 (M\(^+\)+1, 6), 313.1418 (M\(^+\), 29), 245.0748 (13), 244.0726 (100).
**Following General Procedure 1, Purification by flash column chromatography.**

(2S, 3S, 5S, 7S)- 5-(4-methoxyphenylamino)-7-vinyl-11-dodecen-1,2,3-triol (9ca):

(a mixture of major and minor isomers in a ratio of 1:1): IR (neat) 3300 (m), 2912 (s), 2835 (s), 1639 (s), 1500 (s), 1456 (s), 1294 (s), 1238 (s), 1180 (s), 1039 (s), 916 (s), 821 (s), 748 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, major-isomer) δ 1.18- 1.36 (m, 2 H), 1.46- 1.71 (m, 2 H), 1.56 (s, 3 H), 1.67 (s, 3 H), 1.82- 2.00 (m, 2 H), 1.91 (ddd, J = 14.1, 9.2, 3.7 Hz, 2 H), 2.04- 2.16 (m, 1 H), 3.53- 3.59 (br dd, J = 9.2, 5.3 Hz, 1 H), 3.62- 3.65 (br d, J = 3.7 Hz, 1 H), 3.71- 3.85 (m, 2 H), 3.75 (s, 3 H), 3.95- 4.00 (m, 1 H), 4.86 (dd, J = 17.1, 1.7 Hz, 1 H), 4.99 (dd, J = 10.1, 1.7 Hz, 1 H), 5.02- 5.06 (t m, J = 7.1 Hz, 1 H), 5.49 (ddd, J = 17.1, 10.1, 7.1 Hz, 1 H), 6.67 (d, J = 8.9 Hz, 2 H), 6.76 (d, J = 8.9 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, major-isomer) δ 17.8, 25.6, 25.8, 35.4, 37.6, 40.7, 41.1, 51.6, 55.8, 63.8, 71.4, 74.1, 114.9, 115.5, 116.5, 124.2, 131.5, 142.6, 142.8, 153.2; ¹H NMR (400 MHz, CDCl₃, minor-isomer) δ 1.18- 1.36 (m, 2 H), 1.46- 1.71 (m, 2 H), 1.56 (s, 3 H), 1.67 (s, 3 H), 1.82- 2.00 (m, 2 H), 1.91 (ddd, J = 14.1, 9.2, 3.7 Hz, 2 H), 2.04- 2.16 (m, 1 H), 3.53- 3.59 (br dd, J = 9.2, 5.3 Hz, 1 H), 3.62- 3.65 (br d, J = 3.7 Hz, 1 H), 3.71- 3.85 (m, 2 H), 3.75 (s, 3 H), 3.95- 4.00 (m, 1 H), 4.80 (dd, J = 17.6, 1.6 Hz, 1 H), 4.97 (dd, J = 10.2, 1.6 Hz, 1 H), 5.02- 5.06 (t m, J
\[\delta 7.1, 1 \text{ H}, 5.49 (\text{ddd, } J = 17.1, 10.1, 7.1 \text{ Hz, } 1 \text{ H}), 6.67 (\text{d, } J = 8.9 \text{ Hz, } 2 \text{ H}), 6.78 (\text{d, } J = 9.0 \text{ Hz, } 2 \text{ H}); ^{13}\text{C NMR (100 MHz, CDCl}_3, \text{ minor-isomer) } \delta 17.8, 25.4, 25.7, 35.4, 37.6, 40.7, 41.1, 51.6, 55.7, 63.8, 71.4, 74.2, 114.8, 115.5, 116.5, 124.2, 131.5, 142.6, 142.8, 153.8; \text{ HRMS, calcd for C}_{22}\text{H}_{35}\text{NO}_4: 377.2566. \text{ Found } m/z (\text{relative intensity}): 377.2561 (M^+, 100).\]

**General procedure 2: for the Nickel-catalyzed homoallylation of N,O-acetals prepared from carbohydrate and primary amines with dienes (entry 8, Table 4)**

An oven-dried, 25 mL, three-necked round-bottomed flask equipped with a dropping funnel, a rubber septum cap, an air condenser (fitted with a three-way stopcock connected into nitrogen balloon), and a Teflon-coated magnetic stir bar was charged. A solution of D-ribose (150 mg, 1 mmol) and \(p\)-anisidine (246 mg, 2 mmol) in dry DMF (5 mL) was refluxed for 120 min under nitrogen. The solvent was removed by distillation under reduced pressure (azeotropic removal of water). A mixture of \(\text{Ni(cod)}_2\) (27.5 mg, 0.1 mmol) and isoprene (800 µL, 8 mmol) dissolved in THF (2 mL) and triethylborane (6.0 mmol, 1.0 M THF solution) were successively added to the \(N,O\)-acetal solution via the dropping funnel over a period of 10 min. The reaction mixture was stirred at 50 °C for 48 h and monitored by TLC. After the reaction was completed, the reaction mixture was cooled to 0 °C, and then poured into ice-water. The resulting solution was diluted with 30 mL of EtOAc and carefully washed with 2 M HCl, with sat. NaHCO\(_3\), and brine. The aqueous layer was
extracted with 30 mL of EtOAc. The combined organic phases were dried (MgSO₄) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (eluent; hexane/EtOAc = 0/100 v/v) to afford 10ba (192 mg, 57%; Rf = 0.30; hexane/EtOAc = 0/100 v/v) in a 2:1 ratio.

5-[(4-Methoxyphenyl)amino]-7-methylnon-8-ene-1,2,3,4-tetraol (10ba)

Following General Procedure 2, Purification by flash column chromatography.

5-[(4-Methoxyphenyl)amino]-7-methylnon-8-ene-1,2,3,4-tetraol (10ba): (a mixture of major and minor isomers in a ratio of 2:1): IR (neat) 3400 (m), 2930 (m), 1653 (s), 1539 (s), 1456 (s), 1231 (s), 1180 (s), 1038 (s), 829 (s), 735 (s), 667 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃, major-isomer) δ 0.98 (d, J = 6.6 Hz, 3 H), 1.48- 1.57 (br d, J = 13.8 Hz, 2 H), 1.74 (ddd, J = 13.8, 10.4, 2.9 Hz, 1 H), 2.27- 2.29 (br d, J = 7.7 Hz, 1 H), 3.61- 3.69 (m, 2 H), 3.74 (s, 3 H), 3.76- 3.90 (m, 3 H), 4.82 (d, J = 17.1 Hz, 1 H), 4.92 (dd, J = 10.2, 1.7 Hz, 1 H), 5.60 (ddd, J = 17.1, 10.2, 7.7 Hz, 1 H), 6.78 (d, J = 10.6 Hz, 2 H), 6.79 (d, J = 10.6 Hz, 2 H); ¹³C NMR (100 MHz, CDCl₃, major-isomer) δ 21.7, 35.2, 37.0, 55.9, 57.5, 63.6, 73.0, 73.4, 73.9, 114.4, 115.0, 117.4, 143.9, 153.9, 162.5; ¹H NMR (400 MHz, CDCl₃, minor-isomer) δ 0.96 (d, J = 6.8 Hz, 3 H), 1.48-1.57 (br d, J = 13.8 Hz, 2 H), 1.74 (ddd, J = 13.8, 10.4, 2.9 Hz, 1 H), 2.27- 2.29 (br d, J = 7.7 Hz, 1 H), 3.61- 3.69 (m, 2 H), 3.75 (s, 3 H), 3.76- 3.90 (m, 3 H), 4.82 (d, J = 17.1 Hz, 1 H).
Hz, 1 H), 4.91 (d, \( J = 11.2 \) Hz, 1 H), 5.60 (ddd, \( J = 17.1, 10.2, 7.7 \) Hz, 1 H), 6.78 (d, \( J = 10.6 \) Hz, 2 H), 6.79 (d, \( J = 10.6 \) Hz, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), minor-isomer) \( \delta \) 21.7, 34.9, 36.6, 55.9, 57.5, 63.6, 73.2, 73.7, 73.9, 114.4, 115.1, 117.8, 144.2, 153.9, 162.5; HRMS, calcd for C\(_{17}\)H\(_{27}\)NO\(_5\): 325.1889. Found \( m/z \) (relative intensity): 326.1940 (M\(^{+}\)1, 20), 325.1873 (M\(^{+}\), 100).

\((2R, 3S, 4R, 6S, 8S)-6-(4-methoxyphenylamino)-8-methyl-9-decen-1,2,3,4-tetraol\) (11ba)

Following General Procedure 2, Purification by flash column chromatography.

\((2R, 3S, 4R, 6S, 8S)-6-(4-methoxyphenylamino)-8-methyl-9-decen-1,2,3,4-tetraol\) (11ba): (a mixture of major and minor isomers in a ratio of 1:1): IR (KBr) 3285 (s), 2937 (m), 2924 (m), 1514 (s), 1412 (m), 1240 (s), 1074 (s), 1040 (s), 822 (w), 640 (w) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), major-isomer) \( \delta \) 1.00 (d, \( J = 6.8 \) Hz, 3 H), 1.44- 1.62 (m, 4 H), 2.04- 2.11 (ddd, \( J = 5.1, 9.3, 12.7 \) Hz, 1 H), 2.26 (br d, \( J = 7.5 \) Hz, 1 H), 3.51- 3.83 (m, 5 H), 3.74 (s, 3 H), 4.16- 4.20 (m, 1 H), 4.89 (d, \( J = 18.0 \) Hz, 1 H), 4.92 (d, \( J = 10.5 \) Hz, 1 H), 5.63 (ddd, \( J = 17.1, 10.2, 7.8 \) Hz, 1 H), 6.73 (d, \( J = 9.0 \) Hz, 2 H), 6.77 (d, \( J = 9.0 \) Hz, 2 H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), major-isomer) \( \delta \) 20.8, 35.2, 37.9, 42.5, 51.7, 55.9, 64.0, 68.9, 72.9, 74.7, 113.7, 115.0, 116.7, 140.8, 144.1, 153.3; \(^1\)H NMR (400 MHz, CDCl\(_3\), minor-isomer) \( \delta \) 0.93 (d, \( J = 6.8 \) Hz, 3 H), 1.44- 1.62 (m, 4 H), 2.04- 2.11 (ddd, \( J = 5.1, 9.3, 12.7 \) Hz, 1 H), 2.26 (br d, \( J = 7.5 \) Hz, 1 H), 3.51- 3.83 (m, 5 H), 3.76
(s, 3 H), 4.16-4.20 (m, 1 H), 4.88 (d, $J = 17.3$ Hz, 1 H), 4.97 (d, $J = 9.3$ Hz, 1 H), 5.63 (ddd, $J = 17.1$, 10.2, 7.8 Hz, 1 H), 6.72 (d, $J = 10.7$ Hz, 2 H), 6.79 (d, $J = 9.0$ Hz, 2 H);

$^{13}$C NMR (100 MHz, CDCl$_3$, minor-isomer) $\delta$ 20.6, 35.0, 37.6, 42.9, 51.7, 55.5, 64.2, 68.9, 73.0, 74.3, 113.5, 115.0, 116.7, 140.8, 144.3, 153.3; HRMS, calcd for C$_{18}$H$_{29}$NO$_5$: 339.2046. Found $m/z$ (relative intensity): 340.2072 (M$^+$+1, 20), 339.2037 (M$^+$, 100).
References


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Chapter 3

Multicomponent Coupling Reaction via Nickelacycle:
Efficient and Selective Formation of Unsaturated Carboxylic Acids and Phenylacetic Acids from Diketene

Summary: Ni-catalyzed multicomponent coupling reaction of alkyne, dimethylzinc, and diketene (as butenoic acid equivalent) to provide 3-methylene-4-hexenoic acids in a single manipulation is described. Under similar catalytic conditions, Et₂Al(OEt) accelerates a formal [2+2+2] cycloaddition reaction with diketene and two equivalents of alkynes to produce phenylacetic acid derivatives. Furthermore, in the presence of ligand, such as PPh₃, symmetrical substituted phenylacetic acids are produced with accompanying cleavage reaction of the C–C double bond of diketene via nickelacyclopentane rearrangement.
Introduction

Diketene is a unique and important key intermediate formed by dimerization of ketene\(^1\), and is often used as an acetoacetylation reagent for versatile nucleophiles, such as alcohols, amines, thiols and carbanions, in organic synthesis (Scheme 1, path a)\(^2\). In the presence of transition metal catalysts, diketene smoothly reacts with organometallic compounds, such as Grignard reagents and organozinc reagents, to cleave the vinyl-oxygen bond to construct 3-substituted 3-butenoic acids (Scheme 1, path b)\(^3\). The 3-butenoic acid skeleton serves as a synthon for the preparation of physiologically active molecules and the fine chemicals\(^4\).

![Scheme 1. Reactivity of Diketene with Nucleophiles](image)

Phenylacetic acid (\(\alpha\)-toluic acid) acts as an active auxin and is a critical constituent of many physiologically active molecules, such as tetraline-based natural products, analgesics, and non-steroidal anti-inflammatory drugs (NSAIDs)\(^5\). Although efficient preparations of phenylacetic acid and its analogues are widely

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demanded for use in medicinal chemistry, most involve some limitations of handling and harsh reaction conditions\textsuperscript{6}. Therefore, straightforward and selective formations of unsaturated carboxylic acids and phenylacetic acids from commercially available diketene promoted by transition metal catalysts with organometallic reagents will be beneficial.

Nickel-catalyzed coupling reactions are an attractive synthetic method for the construction of useful and complicated molecules in modern organic chemistry\textsuperscript{7}. We have previously demonstrated the Ni(0)-catalyzed multicomponent coupling reaction of alkyne, dimethylzinc, and unsaturated hydrocarbons (such as conjugated dienes and vinylcyclopropanes) to accomplish C–C bond formations with high regio- and stereoselectivities\textsuperscript{8}. All of these coupling reactions proceeded via nickelacyle intermediates by oxidative cyclization of unsaturated hydrocarbons and Ni(0) catalyst.

Herein, we would like to disclose the Ni-catalyzed multicomponent coupling reaction of alkyne, dimethylzinc, and diketene (as butenoic acid equivalent) to provide 3-methylene-4-hexenoic acids in a single manipulation (Scheme 2). Under similar catalytic conditions, Et\textsubscript{2}Al(OEt) accelerates a formal [2+2+2] cycloaddition reaction with diketene and two equivalents of alkynes to produce phenylacetic acid derivatives. Furthermore, in the presence of ligand, symmetrically substituted phenylacetic acids are produced with accompanying cleavage of the C–C double bond of diketene. Although Ni-catalyzed cycloaddition reactions with alkynes have been well developed\textsuperscript{9},
efficient syntheses of phenylacetic acids via cycloaddition reaction with alkyne and diketene have not been reported to date.

Scheme 2. Ni-Catalyzed Multicomponent Coupling Reaction of Diketene with Organometals
Results and Discussion

The three-component coupling reaction with alkyne, diketene, and dimethylzinc was conducted in the presence of Ni(acac)$_2$ catalyst (1 mol%) in THF under nitrogen atmosphere. Table 1 summarizes the results obtained from using a wide variety of alkynes, including symmetrical and unsymmetrical substituted alkynes. Symmetrical substituted alkynes, such as 2-butyne, 3-hexyne, and 4-octyne reacted with diketene and dimethylzinc smoothly to give the three-component coupling products 3 in excellent yields as a single isomer (entries 1-3, Table 1).

Bis(trimethylsilyl)acetylene also participated in a similar coupling reaction to afford 3d in reasonable yield (entry 4, Table 1). Diphenylacetylene provided the expected coupling product 3e in modest yield (entry 5, Table 1). An electron-deficient alkyne such as dimethyl acetylenedicarboxylate did not take part in the reaction. The regioselectivity of the unsymmetrical alkynes depended on the type of substituents. 1-Trimethylsilyl-1-propyne coupled with dimethylzinc at the trimethylsilyl-substituted carbon atom and diketene at the methyl-substituted carbon atom to provide 3f in syn addition manner as a single stereoisomer (entry 6, Table 1). 1-Trimethylsilyl-2-phenylethyne and 1-phenyl-1-butyne provided the expected unsaturated carboxylic acids as a mixture of regioisomers of 3g and 3h, respectively (entries 7 and 8, Table 1).
Table 1. Scope of the Nickel-Catalyzed Three-Component Coupling Reaction of Diketene, Alkyne 2, and Me₂Zn

![Reaction diagram](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne R¹</th>
<th>R²</th>
<th>time (h)</th>
<th>yield of 3 (%) [ratio]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Me</td>
<td>(2a)</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>Et</td>
<td>(2b)</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>n-Pr</td>
<td>n-Pr</td>
<td>(2c)</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>TMS</td>
<td>TMS</td>
<td>(2d)</td>
<td>6</td>
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<tr>
<td>5</td>
<td>Ph</td>
<td>Ph</td>
<td>(2e)</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>TMS</td>
<td>Me</td>
<td>(2f)</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>TMS</td>
<td>Ph</td>
<td>(2g)</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>Et</td>
<td>(2h)</td>
<td>24</td>
</tr>
</tbody>
</table>

¹ The reaction was undertaken in the presence of Ni(acac)₂ (0.01 mmol), alkyne (1 mmol), diketene (1.5 mmol), and Me₂Zn (1.2 mmol) in THF at 50 °C under nitrogen atmosphere. Yields were calculated based on alkyne.

² The ratio shows the regioisomeric ratio with respect to olefin geometry. Major isomer is depicted as the structure of compound 3.

³ The substituents of R¹ and R² on major isomer are opposite each other on minor isomer.
A plausible mechanism for the coupling reaction with alkyne, diketene, and dimethylzinc is illustrated in Scheme 3. Ni-catalyzed oxidative cyclization of alkyne and diketene in the presence of dimethylzinc proceeds to form nickelacyclopentene intermediate I, which is followed by C–O bond cleavage to provide 7-membered oxanickelacycles II. The methyl group transfer from dimethylzinc to Ni metal provides unsaturated carboxylic acids 3 via reductive elimination and regeneration of the active Ni(0) catalyst.

Scheme 3. Plausible Reaction Mechanism for Ni-Catalyzed Multicomponent Coupling Reaction of Diketene and Alkyne with Me₂Zn
The features of the coupling reaction with diketene and alkyne promoted by Ni catalyst changed dramatically when organoaluminum reagents were used in place of dimethylzinc (Table 2). For example, in the presence of Ni(cod)$_2$ catalyst in THF solvent, Me$_3$Al, diketene, and 3-hexyne combined in a 1:1:1 ratio to form the three-component coupling product 3b as well as the products shown in Table 1 (entry 1, Table 2). Under similar conditions, complex mixtures were produced using Et$_3$Al, Et$_2$AlCl, and Et$_2$Al(OEt) (entries 2-4, Table 2). Among these investigations using various kinds of solvents, toluene was most effective for the cycloaddition reaction, providing ethyl-substituted phenylacetic acids.

In the presence of Ni catalyst and Me$_3$Al, diketene underwent [2+2+2] cycloaddition with two equivalents of 3-hexyne to afford phenylacetic acid 5b in 34% yield, along with the linear coupling product, trienyl carboxylic acid 4ba, in 24% yield as a byproduct (entry 5, Table 2). Use of Et$_3$Al also produced a similar result to give a mixture of 4bb and 5b in modest yields (entry 6, Table 2). Although Et$_2$AlCl resulted in the formation of a complex mixture, Et$_2$Al(OEt) effectively promoted the [2+2+2] cycloaddition reaction to provide 5b in 98% as a single product (entries 7-8, Table 2).
Table 2. Scope of the Nickel-Catalyzed Three-Component Coupling Reaction of Diketene, Alkyne \(2b\), and Organoaluminum\(^a\)

![Chemical structures](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>organoaluminum</th>
<th>solvent</th>
<th>yield of 3b, 4 and 5b (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Me(_3)Al</td>
<td>THF</td>
<td>3b: 50</td>
</tr>
<tr>
<td>2</td>
<td>Et(_3)Al</td>
<td>THF</td>
<td>complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>Et(_2)AlCl</td>
<td>THF</td>
<td>complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>Et(_2)Al(OEt)</td>
<td>THF</td>
<td>complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>Me(_3)Al</td>
<td>toluene</td>
<td>4ba: 24(R = Me), 5b: 34</td>
</tr>
<tr>
<td>6</td>
<td>Et(_3)Al</td>
<td>toluene</td>
<td>4bb: 34(R = Et), 5b: 10</td>
</tr>
<tr>
<td>7</td>
<td>Et(_2)AlCl</td>
<td>toluene</td>
<td>complex mixture</td>
</tr>
<tr>
<td>8</td>
<td>Et(_2)Al(OEt)</td>
<td>toluene</td>
<td>5b: 98</td>
</tr>
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</table>

\(^a\)The reaction was undertaken in the presence of Ni(cod)_2 (0.1 mmol), alkyne (1 mmol), diketene (3 mmol), and organoaluminum (1.2 mmol) at r.t. under nitrogen atmosphere for 72 h.
As shown in Table 3, the cycloaddition reaction of diketene with alkynes in the presence of Ni catalyst and Et$_2$Al(OEt) was applied to a wide variety of alkynes. Surprisingly, use of phosphine ligands under similar catalytic conditions changed the outcome to provide the regioisomeric phenylacetic acid 6 exclusively. Among the results of utilizing monodentate and bidentate phosphine ligands, PPh$_3$ was the most efficient ligand to furnish phenylacetic acids 6 as the sole products (entries 9-12, Table 3). Symmetrical dialkyl-substituted alkynes underwent the cycloaddition reaction with diketene to provide unsymmetrical phenylacetic acids 5 by means of the Ni catalyst and Et$_2$Al(OEt) system in the absence of PPh$_3$ (entries 1-4, Table 3), diphenylacetylene provided the expected coupling product 5e in modest yield (entry 5, Table 3), whereas the formal [2+2+1+1] cycloaddition reaction product, symmetrically substituted phenylacetic acids 6, were selectively produced in the presence of PPh$_3$ ligand (entries 9, and 13-16, Table 3). The structures of both the unsymmetrical and symmetrical phenylacetic acids 5b and 6b were determined unequivocally by X-ray crystallographic analysis, as shown in Figure 1 and 2$^{10}$. Although cycloaddition reactions involving unsymmetrical disubstituted alkynes often exhibit complicated regioselectivities$^{11}$, the desired coupling products 5f and 6f were produced as a single isomer in the case of using of 1-trimethylsilyl-1-propyn regardless of the presence or absence of phosphine ligand (entries 6 and 17, Table 3). Terminal alkynes possessing t-Bu and TMS groups could participate in the coupling reaction and the distinctive regioselective formations of phenylacetic acids 5 and 6 were accomplished (entries 7 and 8, 18 and 19, Table 3).
Figure 1. ORTEP drawing of 5b with 50% probability ellipsoids.
Figure 2. ORTEP drawing of 6b with 50% probability ellipsoids.
The cycloaddition reaction was applied to the construction of a benzobicyclic ring via coupling reaction of a diyne moiety with diketene. 3,9-Dodecadiyne underwent the cycloaddition reaction with diketene and provided tetrahydronaphthylacetic acid 5i using the Ni-catalyst and Et₂Al(OEt) system (eq 1). Unfortunately, in the presence of PPh₃, an intractable mixture was obtained from 3,9-dodecadiyne under similar reaction condition.

![Chemical structure and reaction equation](image)
Table 3. Scope of the Nickel-Catalyzed Three-Component Coupling Reaction of Diketene, Alkyne 2, and Organoaluminum

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne R¹</th>
<th>R²</th>
<th>ligand</th>
<th>yield of 5 and 6 (%)</th>
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<td>Me</td>
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<td>5a: 80</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>Et</td>
<td>none</td>
<td>5b: 98</td>
</tr>
<tr>
<td>3</td>
<td>n-Pr</td>
<td>n-Pr</td>
<td>none</td>
<td>5c: 76</td>
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<tr>
<td>4</td>
<td>n-Bu</td>
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<td>none</td>
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<tr>
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</tr>
<tr>
<td>6</td>
<td>TMS</td>
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<td>none</td>
<td>5k: 65</td>
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<tr>
<td>9</td>
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<td>Et</td>
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<td>6b: 73</td>
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<tr>
<td>10</td>
<td>Et</td>
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<td>P(c-Hex)₃</td>
<td>6b: 20</td>
</tr>
<tr>
<td>11</td>
<td>Et</td>
<td>Et</td>
<td>P(n-Bu)₃</td>
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(Table 3, continued)

<table>
<thead>
<tr>
<th></th>
<th>Alkyl</th>
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<th>Ligand</th>
<th>%</th>
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<tr>
<td>12</td>
<td>Et</td>
<td>Et</td>
<td>Xantphos</td>
<td>6b</td>
</tr>
<tr>
<td>13</td>
<td>Me</td>
<td>Me</td>
<td>PPh3</td>
<td>6a</td>
</tr>
<tr>
<td>14</td>
<td>n-Pr</td>
<td>n-Pr</td>
<td>PPh3</td>
<td>6c</td>
</tr>
<tr>
<td>15</td>
<td>n-Bu</td>
<td>n-Bu</td>
<td>PPh3</td>
<td>6j</td>
</tr>
<tr>
<td>16</td>
<td>Ph</td>
<td>Ph</td>
<td>PPh3</td>
<td>6e</td>
</tr>
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<td>17</td>
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<td>Me</td>
<td>PPh3</td>
<td>6f</td>
</tr>
<tr>
<td>18</td>
<td>t-Bu</td>
<td>H</td>
<td>PPh3</td>
<td>6k</td>
</tr>
<tr>
<td>19</td>
<td>TMS</td>
<td>H</td>
<td>PPh3</td>
<td>6l</td>
</tr>
</tbody>
</table>

*The reaction was undertaken in the presence of Ni(cod)$_2$ (0.1 mmol), ligand (0.2 mmol), alkyne (1 mmol), diketene (3 mmol), and Et$_2$Al(OEt) (1.2 mmol) in toluene (5 mL) at r.t. under nitrogen atmosphere for 72 h.*

*In entry 6, 5f was obtained as a desilylation product 5f*(R$^1$ = H) in 77%.

The reactions of stoichiometric amount of Ni(cod)$_2$, alkyne, and diketene without Et$_2$Al(OEt) were conducted (Scheme 4). In the absence of phosphine ligand, a mixture of Ni(cod)$_2$ (0.5 mmol), 3-hexyne (1 mmol), and diketene (0.5 mmol) did not provide the expected phenylacetic acid 5b, and instead the intractable mixture was obtained. On the other hand, in the presence of two equivalents of PPh$_3$ based on Ni(0) complex, the reaction mixture of Ni(cod)$_2$ (0.5 mmol), PPh$_3$ (1.0 mmol), 3-hexyne (1 mmol), and diketene (0.5 mmol) stirring for 72 hours followed by
hydrolysis with acidic water provided the symmetrical phenylacetic acid 6b in 54% as a sole product. At the initial stage of the reaction for 1 hour, (3E)-4-ethyl-5-methylene-3-heptenoic acid 7b was obtained in 80% with high stereoselectivity. Furthermore, we would like to argue the cross-coupling reaction of a mixture of stoichiometric amount of diketene, alkyne, PPh₃, and Ni(cod)₂ complex with phenylmagnesium bromide. Addition of PhMgBr solution to the mixture of Ni(cod)₂ (0.5 mmol), PPh₃ (1 mmol), 3-hexyne (0.5 mmol), and diketene (0.5 mmol) provided (3Z)-4-ethyl-5-methylene-3-phenyl-3-heptenoic acid 8b in 26%, along with (3Z)-4-ethyl-5-methylene-3-[(3Z)-4-phenyl-3-hexenyl]-3-heptenoic acid 9b in 39% (eq 2). These results suggest the cleavage reaction of C–C double bond of diketene proceeds via a crucial key intermediate by the synergistic effect of Ni active species and PPh₃ ligand.
Scheme 4. C–C Bond Cleavage Reaction of Diketene Promoted by Stoichiometric Amount of Ni(0) in the Presence or in the Absence of Phosphine Ligand
Although it is premature to provide a complete explanation of the reactivities described here, a plausible mechanism for the cycloaddition reactions of diketene and alkyne promoted by Ni catalyst and Et₂AlX are proposed in Scheme 5 and 6. In the absence of phosphine ligand, oxidative cyclization of alkyne and diketene with Ni(0) catalyst provides nickelacycle I, which undergoes the ring expansion reaction to form oxanickelacycle intermediate II (Scheme 5). Further insertion of an additional alkyne promoted by Et₂AlX to afford vinylnickel intermediate III via transmetalation with Et₂AlX. Intramolecular carbonickelation via 6-endo cyclization of III (X = OEt), and the subsequent β-hydride elimination occurs to afford phenylacetic acid salt 5 with liberation of Ni(0) species¹². For Me₃Al and Et₃Al, reductive elimination might proceed through the intermediate III (X = Me or Et) rather than carbonickelation to afford the linear unsaturated carboxylic acids 4ba and 4bb as a major product¹³.
Scheme 5. Plausible Reaction Mechanism for the Formation of Phenylacetic Acids in the Absence of PPh₃

The similar catalytic system, in the presence of PPh₃ ligand, might promote diketene to undergo the oxidative cyclization with alkyne to form the nickelacyclopentene intermediate I (Scheme 6). On the contrary to the mechanism demonstrated in Scheme 5, the active metallacycle I having PPh₃ ligand invokes C–C bond cleavage reaction via nickel carbene cyclopropane rearrangement to form the nickelacyclopentene IV⁴. [1,2]-Shift of the Ni atom proceeds to avoid the distortion of the spiro-β-lactone ring giving rise to the dienynickelacycle intermediate V, which then
undergoes cycloaddition reaction with alkyne to form vinylnickel intermediate VI\textsuperscript{15}. Intramolecular carbonickelation followed by aromatization (VII, VIII) provides the alternative regioisomer \textit{6} by transmetalation with Et\textsubscript{2}Al(OEt) accompanying the liberation of catalytically active Ni(0) species\textsuperscript{16}.

Sterically controlled oxanickelacycle V would afford (3\textit{E})-4-ethyl-5-methylene-3-heptenoic acid 7\textit{b} with high stereoselectivity by hydrolysis with acid aqueous media. Instead, the addition of PhMgBr to the reaction mixture would provide (3\textit{Z})-4-ethyl-5-methylene-3-phenyl-3-heptenoic acid 8\textit{b} via transmetallation with oxanickelacycle V and (3\textit{Z})-4-ethyl-5-methylene-3-[(3\textit{Z})-4-phenyl-3-hexenyl]-3-heptenoic acid 9\textit{b} from trienynickel intermediate VI. Although intermediates V and VI could not be verified by X-ray crystallographic analysis or NMR spectra, highly stereoselective formations of 7\textit{b}, 8\textit{b}, and 9\textit{b} might prove the formation of nickel intermediates V and VI \textit{in situ}. Thus, a mechanism for the formation of \textit{6} involving the stereodefined nickelacycle V might be conceivable.
Scheme 6. Mechanism for the Formation of Phenylacetic Acids via Ni-Catalyzed Coupling of Diketene, Alkyne, and Organoaluminum in the Presence of PPh₃
In conclusion, the multicomponent coupling reaction of diketene, alkyne, and Me$_2$Zn has been demonstrated to give 3-methylene-4-hexenoic acids in excellent yields. Under similar conditions, the combination of Ni catalyst and Et$_2$Al(OEt) accelerates the dimerization of alkyne followed by a [2+2+2] cycloaddition reaction to furnish phenyl- acetic acid derivatives. In the presence of PPh$_3$, a formal [2+2+1+1] cycloaddition reaction proceeds to afford the alternative regioisomer of phenylacetic acid derivatives accompanying the C–C double bond cleavage reaction of diketene. Synthetic applications involving the cleavage reaction of various C–C double bonds are currently under investigation.
**Experimental Section**

Reactions employed oven-dried glassware unless otherwise noted. Thin layer chromatography (TLC) employed glass 0.25 mm silica gel plates with UV indicator (Merck, Silica gel 60F$^{254}$). Flash chromatography columns were packed with 230-400 mesh silica gel as a slurry in hexane. Gradient flash chromatography was conducted eluting with a continuous gradient from hexane to the indicated solvent. Distillation were carried out in a Kugelrohr apparatus (SIBATA glass tube oven GTO-350RG). Boiling points are meant to refer to the oven temperature (± 1 °C). Microanalyses were performed by the Instrumental Analysis Center of Nagasaki University. Analysis agreed with the calculated values within ± 0.4%. Proton and carbon NMR data were obtained with a JEOL-GX400 with tetramethylsilane as an internal standard. Chemical shift values were given in ppm downfield from the internal standard. Infrared spectra were recorded with a JASCO A-100 FT-IR or SHIMAZU FTIR-8700 spectrophotometer. High resolution mass spectra (HRMS) were measured with a JEOL JMS-DX303.

**Solvents and Reagents**

Tetrahydrofuran was dried and distilled from benzophenone and sodium immediately prior to use under nitrogen atmosphere. Anhydrous toluene was purchased (Aldrich) and used without further purification. Ni(acac)$_2$, Ni(cod)$_2$, PPh$_3$, c-Hex$_3$P, n-Bu$_3$P, Xantphos [4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene],
Me₂Zn (1.0 M hexane solution), Me₃Al (1.0 M hexane solution), Et₃Al (1.0 M hexane solution), Et₂AlCl (1.0 M hexane solution), Et₂Al(OEt) (1.0 M hexane solution), PhMgBr (1.0 M THF solution) (Kanto Kagaku) were purchased and used without further purification. 2-Butyne, 3-hexyne, 4-octyne, 5-decyne, bis(trimethylsilyl)acetylene, diphenylacetylene, 1-phenyl-2-(trimethylsilyl)acetylene, 1-trimethylsilyl-1-propyne, 3,3-dimethyl-1-butyne, trimethylsilylacetylene, and 1-phenyl-1-butyne (Tokyo Kasei Kogyo Co., Ltd) were purchased and distilled prior to use. Diketene (Tokyo Kasei Kogyo Co., Ltd) was purchased and used without further purification.
General procedure 1: Formation of Unsaturated Carboxylic Acids from Diketene Promoted by Ni Catalyst (entry 2, Table 1)

An oven-dried, 25 mL, three-necked round-bottomed flask equipped with a dropp- ing funnel, a rubber septum cap, an air condenser (fitted with a three-way stopcock connected into nitrogen balloon), and a Teflon-coated magnetic stir bar was charged with Ni(acac)$_2$ (2.6 mg, 0.01 mmol). The apparatus was purged with nitrogen and the flask was charged successively via syringe with freshly dry THF (5 mL), diketene (126.1 mg, 1.5 mmol), and 3-hexyne (82.1 mg, 1 mmol). Dimethylzinc (1.2 mmol, 1.0 M hexane solution) was added slowly at room temperature via the dropping funnel over a period of 10 min. The mixture was stirred at 50 °C for 24 h and monitored by TLC. After the reaction was completed, the reaction mixture was cooled to 0 °C, and then poured into ice-water. The resulting solution was diluted with 30 mL of EtOAc and carefully washed with 2 M HCl, with sat. NaHCO$_3$, and brine. The aqueous layer was extracted with 30 mL of EtOAc. The combined organic phases were dried (MgSO$_4$) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (eluent; hexane/EtOAc = 4/1 v/v) to afford 3b as a colorless oil (173.2 mg, 95%; $R_f = 0.33$; hexane/EtOAc = 4/1 v/v).
(E)-4-Ethyl-5-methyl-3-methylenehept-4-enoic acid: (3b)

(E)-4-Ethyl-5-methyl-3-methylenehept-4-enoic acid (3b): IR (neat) 2964 (s), 2934 (s), 2874 (s), 2584 (brs), 1711 (s), 1630 (m), 1406 (m), 1375 (m), 907 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.92 (t, J= 7.6 Hz, 3 H), 0.98 (t, J= 7.6 Hz, 3 H), 1.67 (s, 3 H), 2.06 (q, J= 7.6 Hz, 2 H), 2.10 (q, J= 7.6 Hz, 2 H), 3.10 (s, 2 H), 4.84 (d, J= 1.9 Hz, 1 H), 5.18 (d, J= 1.9 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 13.0, 13.4, 19.0, 23.1, 26.5, 41.4, 116.9, 133.0, 135.6, 141.7, 175.7; High-resolution MS, calcd for C₁₁H₁₈O₂: 182.1307. Found m/z (relative intensity): 183 (M⁺+1, 14), 182.1312 (M⁺, 100), 137 (26).

4,5-Dimethyl-3-methylenehex-4-enoic acid: (3a)

Following General Procedure 1, Purification by flash column chromatography.

4,5-Dimethyl-3-methylenehex-4-enoic acid (3a): IR (neat) 3085 (br), 2976 (s), 2920 (s), 2862 (s), 2679 (m), 2573 (m), 1713 (s), 1636 (m), 1412 (m), 1294 (s), 907 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.68 (s, 3 H), 1.70 (s, 3 H), 1.73 (s, 3 H), 3.14 (s, 2 H), 4.78 (d, J= 1.7 Hz, 1 H), 5.12 (d, J= 1.7 Hz, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 17.9, 20.1, 21.7, 41.1, 115.8, 127.4, 129.0, 143.5, 176.9; High-resolution MS, calcd for
C₁₀H₁₄O₂: 154.0994. Found m/z (relative intensity): 155 (M⁺+1, 45), 154.0989 (M⁺, 100), 140 (68), 139 (100), 137 (24), 125 (32).

(E)-5-Methyl-3-methylene-4-propyloct-4-enoic acid: (3c)

Following General Procedure 1, Purification by flash column chromatography.

(3c)

(E)-5-Methyl-3-methylene-4-propyloct-4-enoic acid (3c): IR (neat) 3074 (br), 2931 (s), 2872 (s), 2682 (br), 2598 (br), 1713 (s), 1632 (m), 1410 (m), 1302 (s), 905 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.87 (t, J = 7.6 Hz, 3 H), 0.89 (t, J = 7.6 Hz, 3 H), 1.32 (sext, J = 7.6 Hz, 2 H), 1.40 (sext, J = 7.6 Hz, 2 H), 1.67 (s, 3 H), 2.03 (t, J = 7.6 Hz, 2 H), 2.07 (t, J = 7.6 Hz, 2 H), 3.10 (s, 2 H), 4.83 (d, J = 2.0 Hz, 1 H), 5.17 (d, J = 2.0 Hz, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 13.9, 14.0, 19.5, 21.4, 21.7, 32.2, 35.6, 41.4, 116.8, 132.0, 134.8, 141.9, 177.3; High-resolution MS, calcd for C₁₃H₂₂O₂: 210.1620. Found m/z (relative intensity): 211 (M⁺+1, 2), 210.1612 (M⁺, 10), 167 (9), 135 (22), 121 (100).

(Z)-3-Methylene-4,5-bis(trimethylsilyl)hex-4-enoic acid: (3d)

Following General Procedure 1, Purification by flash column chromatography.

(3d)
(Z)-3-Methylene-4,5-bis(trimethylsilyl)hex-4-enoic acid (3d): IR (neat) 2952 (s), 2900 (s), 2580 (brs), 2343 (s), 1712 (s), 1624 (m), 1406 (m), 1249 (s), 893 (m), 839 (s), 756 (s) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.18 (s, 9 H), 0.19 (s, 9 H), 1.84 (s, 3 H), 2.99 (s, 2 H), 4.58 (d, \(J = 3.1\) Hz, 1 H), 5.09 (d, \(J = 3.1\) Hz, 1 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 1.25, 1.85, 22.0, 42.3, 111.4, 145.4, 150.0, 155.6, 175.6; High-resolution MS, calcd for C\(_{13}\)H\(_{26}\)O\(_2\)Si\(_2\): 270.1471. Found m/z (relative intensity): 271 (M\(^{+}\)+1, 13), 270.1477 (M\(^{+}\), 58), 255 (100), 241 (2).

(Z)-3-methylene-4,5-diphenylhex-4-enoic acid: (3e)

Following General Procedure 1, Purification by flash column chromatography.

(Z)-3-methylene-4,5-diphenylhex-4-enoic acid (3e): IR (neat) 3020 (br), 2914 (m), 2856 (w), 1709 (s), 1599 (m), 1489 (m), 1443 (s), 1265 (m), 762 (s), 698 (s) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 2.28 (s, 3 H), 3.00 (s, 2H), 5.36 (d, \(J = 1.7\) Hz, 1 H), 5.44 (d, \(J = 1.7\) Hz, 1 H), 6.94-7.19 (m, 10 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 23.1, 40.9, 118.9, 126.0, 126.2, 127.5, 127.5, 129.0, 130.2, 136.3, 138.7, 139.5, 141.8, 143.4, 176.8; High-resolution MS, calcd for C\(_{19}\)H\(_{18}\)O\(_2\): 278.1307 Found m/z (relative intensity): 279 (M\(^{+}\)+1, 8), 278.1312 (M\(^{+}\), 33.7), 219 (100), 204 (26).

(E)-4-Methyl-3-methylene-5-(trimethylsilyl)hex-4-enoic acid: (3f)

Following General Procedure 1, Purification by flash column chromatography.
*(E)-4-Methyl-3-methylene-5-(trimethylsilyl)hex-4-enoic acid* (3f): IR (neat) 3091 (br), 2957 (br), 2916 (br), 2862 (m), 1713 (s), 1638 (m), 1603 (s), 1408 (s), 1250 (s), 907 (m), 837 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.15 (s, 9 H), 1.68 (s, 3 H), 1.89 (s, 3 H), 3.14 (s, 2 H), 4.86 (d, J = 1.5 Hz, 1 H), 5.14 (d, J = 1.5 Hz, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 0.26, 19.7, 22.8, 41.3, 115.4, 130.6, 144.2, 145.8, 177.3; High-resolution MS, calcd for C₁₁H₂₀O₂Si: 212.1233. Found m/z (relative intensity): 212.1215 (M⁺, 14), 198 (16), 197 (100).

*(Z)-3-Methylene-5-(trimethylsilyl)-4-phenylhex-4-enoic acid:* (3g)

Following General Procedure 1, Purification by flash column chromatography.

*(Z)-3-Methylene-5-(trimethylsilyl)-4-phenylhex-4-enoic acid* (3g): (a mixture of regioisomers in a 3 : 1 ratio): IR (neat) 3061 (br), 2960 (br), 2899 (br), 2862 (br), 2677 (m), 1638 (m), 1711 (s), 1408 (m), 1248 (s), 908 (m), 837 (s), 762 (m), 702 (s), 633 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, major isomer) δ -0.21 (s, 9 H), 1.92 (s, 3 H), 2.93 (s, 2 H), 5.12 (d, J = 1.7 Hz, 1 H), 5.26 (d, J = 1.7 Hz, 1 H), 7.12-7.16 (m, 2 H), 7.22-7.26 (m, 2 H), 7.26 (m, 1 H); ¹³C NMR (CDCl₃, 100 MHz, major isomer) δ 0.77, 20.6, 41.2, 117.6, 127.8, 128.5, 129.5, 136.5, 142.0, 149.9, 151.4, 177.0; ¹H NMR (CDCl₃, 400 MHz, minor isomer) δ -0.21 (s, 9 H), 2.02 (s, 3 H), 3.15 (s, 2 H), 4.83 (d,
\( J = 1.5 \text{ Hz, 1 H}, \) 5.21 (d, \( J = 1.5 \text{ Hz, 1 H}, \) 7.12-7.16 (m, 2 H), 7.26-7.31 (m, 2 H), 7.26 (m, 1 H); \(^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz, minor isomer}) \delta 0.77, 24.4, 43.3, 113.9, 127.8, 128.1, 128.5, 129.5, 135.1, 145.5, 149.9, 177.0; \) High-resolution MS, calcld for \( \text{C}_{16}\text{H}_{22}\text{O}_2\text{Si}: 274.1389. \) Found \( m/z \) (relative intensity): 275 (M\(^+\), 9), 274.1377 (M\(^+\), 37), 260 (21), 259 (100), 241 (10).

\((E)\)-4-Ethyl-3-methylene-5-phenylhex-4-enoic acid: (3h)

Following General Procedure 1, Purification by flash column chromatography.

\begin{center}
\includegraphics[width=0.5\textwidth]{structure}
\end{center}

\((E)\)-4-Ethyl-3-methylene-5-phenylhex-4-enoic acid (3h): (a mixture of regioisomers in a 10 : 1 ratio): IR (neat) 2968 (s), 2931 (s), 2594 (brs), 1708 (s), 1629 (m), 1598 (m), 1490 (m), 1438 (m), 1407 (m), 1296 (s), 910 (s), 765 (s), 702 (s) cm\(^{-1}\); \(^{1}\text{H NMR (CDCl}_3, 400 \text{ MHz, major isomer}) \delta 0.84 (t, \( J = 7.3 \text{ Hz, 3 H}, \) 1.98 (q, \( J = 7.3 \text{ Hz, 2 H}, \) 1.98 (s, 3 H), 3.21 (s, 2 H), 5.05 (d, \( J = 1.6 \text{ Hz, 1 H}, \) 5.34 (d, \( J = 1.6 \text{ Hz, 1 H}, \) 7.12 (dd, \( J = 7.4, 1.4 \text{ Hz, 2 H}, \) 7.23 (td, \( J = 7.4, 1.4 \text{ Hz, 1 H}, \) 7.32 (t, \( J = 7.4 \text{ Hz, 2 H}, \) \(^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz, major isomer}) \delta 13.2, 22.5, 24.4, 40.9, 117.9, 126.1, 127.7, 128.0, 129.2, 133.4, 138.4, 140.5, 144.0, 175.7; \(^{1}\text{H NMR (CDCl}_3, 400 \text{ MHz, minor isomer}) \delta 0.94 (t, \( J = 7.3 \text{ Hz, 3 H}, \) 1.98 (q, \( J = 7.3 \text{ Hz, 2 H}, \) 2.17 (s, 3 H), 2.92 (s, 2 H), 5.15 (d, \( J = 1.6 \text{ Hz, 1 H}, \) 5.27 (d, \( J = 1.6 \text{ Hz, 1 H}, \) 7.10-7.32 (m, 5 H); \(^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz, minor isomer}) \delta 13.0, 18.8, 28.0, 30.9, 117.9, 126.4, 127.7, 127.9, 129.2, 133.4, 138.4, 140.5, 144.0, 175.7; \) High-resolution MS, calcld for \( \text{C}_{15}\text{H}_{18}\text{O}_2: \)
230.1307. Found m/z (relative intensity): 231 (M^{+}+1, 10), 230.1304 (M^{+}, 61), 215 (8), 201 (100).

**General procedure 2: Formation of Unsaturated Carboxylic Acids from Diketene with Organoaluminum Promoted by Ni Catalyst (entry 5, Table 2)**

An oven-dried, 25 mL, three-necked round-bottomed flask equipped with a dropping funnel, a rubber septum cap, an air condenser (fitted with a three-way stopcock connected into nitrogen balloon), and a Teflon-coated magnetic stir bar was charged with Ni(cod)$_2$ (27.5 mg, 0.1 mmol). The apparatus was purged with nitrogen and the flask was charged successively via syringe with freshly dry toluene (3 mL), diketene (252.2 mg, 3.0 mmol), and 3-hexyne (82.1 mg, 1 mmol). Organoaluminum (1.2 mmol, 1.0 M hexane solution) was added slowly at room temperature via the dropping funnel over a period of 10 min (the reaction temperature should not be exceeded 50 °C). The mixture was stirred at room temperature for 72 h and monitored by TLC. After the reaction was completed, the reaction mixture was cooled to 0 °C, and then poured into ice-water. The resulting solution was diluted with 30 mL of EtOAc and carefully washed with 2 M HCl, and brine. The aqueous layer was extracted with 30 mL of EtOAc. The combined organic phases were dried (MgSO$_4$) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (eluent; hexane/EtOAc = 10/1 v/v) to afford 4ba as a colorless oil (63.5 mg, 24%; $R_f = 0.40$; hexane/EtOAc = 4/1 v/v).
(4Z,6E)-4,5,6-Triethyl-7-methyl-3-methylenenona-4,6-dienoic acid: (4ba)

![Chemical structure](image)

(4Z,6E)-4,5,6-Triethyl-7-methyl-3-methylenenona-4,6-dienoic acid (4ba) : IR (neat) 2966 (s), 2933 (s), 2874 (s), 2675 (br), 1711 (s), 1410 (m), 1296 (m), 905 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.91 (t, J = 7.3 Hz, 6 H), 0.97 (t, J = 7.3 Hz, 6 H), 1.67 (s, 3 H), 2.05 (q, J = 7.3 Hz, 4 H), 2.10 (q, J = 7.3 Hz, 4 H), 3.10 (s, 2 H), 4.85 (d, J = 1.9 Hz, 1 H), 5.18 (d, J = 1.9 Hz, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 13.0, 13.4, 19.0, 23.1, 26.5, 41.2, 116.9, 130.1, 132.0, 133.0, 135.6, 141.7, 176.4; High-resolution MS, calcd for C₁₇H₂₈O₂: 264.2089. Found m/z (relative intensity): 265 (M⁺+1, 9), 264.2076 (M⁺, 58), 249 (21), 235 (100), 221 (30).

(Z)-4,5,6,7-Tetraethyl-3-methylenenona-4,6-dienoic acid: (4bb)

Following General Procedure 2, Purification by flash column chromatography.

![Chemical structure](image)

(Z)-4,5,6,7-Tetraethyl-3-methylenenona-4,6-dienoic acid (4bb) : IR (neat) 2964 (s), 2873 (s), 2677 (br), 2347 (br), 1709 (s), 1630 (m), 1410 (m), 1296 (m), 905 (m), 864
(m) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.83-1.10 (m, 15 H), 1.99-2.14 (m, 10 H), 3.09 (dd, \(J = 1.2, 0.7\) Hz, 2 H), 4.85 (dt, \(J = 2.0, 0.7\) Hz, 1 H), 5.14 (dt, \(J = 2.0, 1.2\) Hz, 1 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 13.2, 13.5, 14.0, 20.0, 22.8, 23.0, 25.3, 41.6, 116.2, 135.7, 138.2, 138.8, 141.4, 176.6; High-resolution MS, calcd for C\(_{18}\)H\(_{30}\)O\(_2\): 278.2246. Found \(m/z\) (relative intensity): 279 (M\(^{+}+1\), 11), 278.2220 (M\(^+\), 56), 250 (53), 249 (100), 235 (44).

**General procedure 3: Formation of Phenylacetic acids from Diketene with Promoted by Ni Catalyst (entry 8, Table 2)**

An oven-dried, 25 mL, three-necked round-bottomed flask equipped with a dropping funnel, a rubber septum cap, an air condenser (fitted with a three-way stopcock connected into nitrogen balloon), and a Teflon-coated magnetic stir bar was charged with Ni(cod)\(_2\) (27.5 mg, 0.1 mmol). The apparatus was purged with nitrogen and the flask was charged successively via syringe with freshly dry toluene (3 mL), diketene (252.2 mg, 3.0 mmol), and 3-hexyne (82.1 mg, 1 mmol). Oganoaluminum (1.2 mmol, 1.0 M hexane solution) was added slowly at room temperature via the dropping funnel over a period of 10 min (the reaction temperature should not be exceeded 50 °C). The mixture was stirred at room temperature for 72 h and monitored by TLC. After the reaction was completed, the reaction mixture was cooled to 0 °C, and then poured into ice-water. The resulting solution was diluted with 30 mL of EtOAc and carefully washed with 2 M HCl, and brine. The aqueous
layer was extracted with 30 mL of EtOAc. The combined organic phases were dried (MgSO₄) and concentrated in vacuo, and the residual oil was subjected to column chromatography over silica gel (eluent; hexane/EtOAc = 4/1 v/v) to afford 5b as a colorless oil (121.8 mg, 98%; R_f = 0.67; hexane/EtOAc = 4/1 v/v).

2-(2,3,4,5-Tetraethylphenyl)acetic acid: (5b)

Following General Procedure 3, Purification by flash column chromatography.

\[
\text{2-(2,3,4,5-Tetraethylphenyl)acetic acid (5b)}: \text{IR (KBr)} \ 3086 \text{ (br), 2970 (s), 2933 (s), 2862 (s), 2674 (s), 2675 (m), 1709 (s), 1628 (m), 1377 (m), 1034 (m), 874 (m), 835 (m) cm}^{-1}; \ \text{^1H NMR (CDCl}_3, 400 MHz) \ \delta 1.12-1.28 \text{ (m, 12 H), 2.59-2.70 (m, 8 H), 3.65 (s, 2 H), 6.92 (s, 1 H); ^13C NMR (CDCl}_3, 100 MHz) \ \delta 15.2, 15.39, 15.42, 15.8, 21.8, 22.1, 22.3, 25.5, 38.3, 128.6, 129.1, 138.1, 139.4, 139.7, 140.2, 175.6; \ \text{High-resolution MS, calcd for C}_{16}H_{24}O_2: 248.1776. Found m/z (relative intensity): 249 (M}^+{1, 17), 248.1770 (M^+, 100), 233 (43).}
\]

2-(2,3,4,5-Tetramethylphenyl)acetic acid: (5a)

Following General Procedure 3, Purification by flash column chromatography.
2-(2,3,4,5-Tetramethylphenyl)acetic acid (5a) : IR (KBr) 3086 (s), 2931 (s), 2871 (s), 2725 (br), 2534 (m), 1717 (s), 1693 (s), 1628 (m), 1460 (m), 1408 (s), 935 (s), 814 (m), 750 (m), 679 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 2.18 (s, 3 H), 2.20 (s, 3 H), 2.21 (s, 3 H), 2.25 (s, 3 H), 3.64 (s, 2H), 6.86 (s, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 16.1, 16.2, 16.4, 20.6, 39.3, 128.8, 129.4, 132.6, 133.7, 134.4, 135.5, 175.7; High-resolution MS, calcd for C₁₂H₁₆O₂: 192.1150. Found m/z (relative intensity): 193 (M⁺+1, 3), 192.1147 (M⁺, 22), 147 (100), 132 (16).

2-(2,3,4,5-Tetrapropylphenyl)acetic acid: (5c)

Following General Procedure 3, Purification by flash column chromatography.

2-(2,3,4,5-Tetrapropylphenyl)acetic acid (5c) : IR (KBr) 3086 (br), 2959 (s), 2930 (s), 2872 (s), 2662 (br), 2561 (m), 1713 (s), 1651 (m), 1456 (s), 883 (m), 739 (m), 610 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.96-1.06 (m, 12 H), 1.39-1.65 (m, 8 H), 2.53 (m, 8 H), 3.61 (s, 2H), 6.88 (s, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 14.8, 14.9, 15.0, 24.3, 24.5, 24.6, 24.9, 31.6, 31.9, 32.0, 35.0, 38.6, 129.0, 136.8, 138.1, 138.2, 139.1,
177.0; High-resolution MS, calcd for C_{20}H_{32}O_{2}: 304.2402. Found m/z (relative intensity): 305 (M^{+}+1, 22), 304.2409 (M^{+}, 100), 275 (40), 259 (3).

2-(2,3,4,5-tetra-butylphenyl)acetic acid: (5j)

Following General Procedure 3, Purification by flash column chromatography.

\[
\begin{align*}
\text{n-Bu} & \text{n-Bu} \\
\text{n-Bu} & \text{n-Bu} \\
\text{O} & \\
\text{C} & \text{O} \\
\text{C} & \text{H}
\end{align*}
\]

2-(2,3,4,5-tetra-butylphenyl)acetic acid (5j) : IR (KBr) 2953 (s), 2858 (d), 2667 (brs), 2341 (d), 1712 (s), 1651 (s), 1463 (s), 1409 (s), 1377 (s), 1240 (s), 1103 (s), 1047 (s), 948 (brs), 846 (s), 802 (s), 729 (s) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.96 (m, 12 H), 1.45 (m, 16 H), 2.55 (m, 8 H), 3.61 (s, 2 H), 6.87 (s, 1 H); \(^13\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 13.8, 14.0, 23.0, 23.4, 23.5, 23.6, 28.9, 29.2, 29.3, 32.6, 33.2, 33.5, 33.7, 33.8, 38.5, 128.9, 129.2, 137.0, 138.3, 138.5, 139.3, 176.4; High-resolution MS, calcd for C\(_{24}\)H\(_{40}\)O\(_2\): 360.3028 Found m/z (relative intensity): 361 (M^{+}+1, 26), 360.3014 (M^{+}, 100), 275 (11).

2-{(2,3,4,5-tetrahenyl)phenyl}acetic acid: (5e)

Following General Procedure 3, Purification by flash column chromatography.
2-[(2,3,4,5-tetrahenyl)phenyl]acetic acid (5e): IR (neat) 3051 (br), 2932 (m), 2874 (m), 2500 (m), 1709 (s), 1601 (m), 1560 (m), 1493 (m), 1443 (m), 1265 (s), 1157 (m), 739 (s), 770 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 3.60 (s, 2 H), 6.74-7.14 (m, 20 H), 7.46 (s, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 39.1, 125.2, 125.4, 126.0, 126.1, 126.4, 126.4, 126.7, 127.4, 127.4, 129.8, 130.2, 131.0, 131.0, 131.3, 139.2, 139.3, 139.6, 140.0, 140.4, 141.1, 141.4, 141.8, 176.7; High-resolution MS, calcd for C₃₂H₂₄O₂: 440.1776. Found m/z (relative intensity): 441 (M⁺+1, 61), 440.1779 (M⁺, 66.7), 395 (100).

2-(2,4-dimethyl-5-(trimethylsilyl)phenyl)acetic acid: (5f')

Following General Procedure 3, Purification by flash column chromatography.

2-(2,4-dimethyl-5-(trimethylsilyl)phenyl)acetic acid (5f'): IR (neat) 3415 (br), 2932 (s), 2578 (brs), 2363 (s), 1712 (s), 1635 (d), 1448 (s), 1409 (s), 1375 (s), 1249 (s), 1209 (s), 1151 (s), 1031 (s), 839 (s), 758 (s), 690 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.30 (s, 9 H), 2.28 (s, 3 H), 2.40 (s, 3 H), 3.64 (s, 2 H), 6.99 (s, 1 H), 7.23 (s, 1 H).
H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ -0.1, 19.3, 22.5, 38.4, 128.4, 131.0, 135.8, 136.4, 137.7, 142.9, 176.5; High-resolution MS, calcd for C$_{13}$H$_{20}$O$_2$Si: 236.1233 Found $m/z$ (relative intensity): 237 (M$^{+}$+1, 10), 236.1218 (M$^+$, 65), 222 (19), 221 (100).

2-(3,5-di-tert-butylphenyl)acetic acid: (5k)

Following General Procedure 3, Purification by flash column chromatography.

2-(3,5-di-tert-butylphenyl)acetic acid (5k) : IR (neat) 3203 (br), 2964 (s), 2870 (s), 2360 (s), 2341 (s), 1710 (s), 1599 (s), 1409 (s), 1363 (s), 1265 (s), 894 (s), 738 (s) cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.32 (s, 18 H), 3.64 (s, 2 H), 7.12 (d, $J = 1.71$ Hz, 2 H), 7.34 (t, $J = 1.71$ Hz, 1 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 31.4, 34.8, 41.3, 121.2, 123.4, 132.2, 150.9, 176.2; High-resolution MS, calcd for C$_{16}$H$_{24}$O$_2$: 248.1776 Found $m/z$ (relative intensity): 249 (M$^{+}$+1, 4), 248.1776 (M$^+$, 23), 234 (29), 233 (100).

2-(3,5-bis(trimethylsilyl)phenyl)acetic acid: (5l)

Following General Procedure 3, Purification by flash column chromatography.

2-(3,5-bis(trimethylsilyl)phenyl)acetic acid (5l) : IR (neat) 3203 (br), 2964 (s), 2870 (s), 2360 (s), 2341 (s), 1710 (s), 1599 (s), 1409 (s), 1363 (s), 1265 (s), 894 (s), 738 (s) cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.32 (s, 18 H), 3.64 (s, 2 H), 7.12 (d, $J = 1.71$ Hz, 2 H), 7.34 (t, $J = 1.71$ Hz, 1 H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 31.4, 34.8, 41.3, 121.2, 123.4, 132.2, 150.9, 176.2; High-resolution MS, calcd for C$_{16}$H$_{24}$O$_2$: 248.1776 Found $m/z$ (relative intensity): 249 (M$^{+}$+1, 4), 248.1776 (M$^+$, 23), 234 (29), 233 (100).
2-(3,5-bis(trimethylsilyl)phenyl)acetic acid (5i) : IR (neat) 2956 (s), 2570 (brs), 1712 (s), 1645 (d), 1408 (s), 1377 (s), 1303 (s), 1249 (s), 1209 (s), 1151 (s), 1032 (s), 860 (s), 837 (s), 756 (s), 694 (s) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.27 (s, 18 H), 3.65 (s, 2 H), 7.41 (d, \(J = 0.97\) Hz, 2 H), 7.57 (d, \(J = 0.97\) Hz, 1 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) -1.1, 41.1, 113.9, 134.7, 137.4, 139.9, 176.6; High-resolution MS, calcd for C\(_{14}\)H\(_{24}\)O\(_2\)Si\(_2\): 280.1315 Found m/z (relative intensity): 281 (M\(^+\)+1, 8), 280.1313 (M\(^+\), 33), 265 (100), 237 (55).

2-(5,8-diethyl-1,2,3,4-tetrahydronaphthalen-6-yl)acetic acid: (5i)

Following General Procedure 3, Purification by flash column chromatography.

\[\text{Et} \quad \text{Et}\]

\[\text{OH}\]

2-(5,8-diethyl-1,2,3,4-tetrahydronaphthalen-6-yl)acetic acid (5i) : IR (KBr) 3312-2542 (br), 1692 (s), 1454 (s), 1420 (s), 1227 (s), 939 (m), 912 (m), 877 (m) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.03 (t, \(J = 7.56\) Hz, 3 H), 1.19 (t, \(J = 7.56\) Hz, 3 H), 1.77-1.78 (m, 4 H), 2.54 (q, \(J = 7.56\) Hz, 2 H), 2.62 (q, \(J = 7.56\) Hz, 2 H), 2.68 (t, \(J = 6.10\) Hz, 2 H), 2.75 (t, \(J = 6.10\) Hz, 2 H) 3.65 (s, 2 H), 7.24 (s, 1 H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 13.9, 14.1, 21.8, 22.7, 23.1, 25.4, 26.6, 26.9, 38.4, 127.5, 128.3, 134.7, 135.4, 138.2, 139.7, 177.8; High-resolution MS, calcd for C\(_{18}\)H\(_{22}\)O\(_2\) : 246.1620. Found m/z (relative intensity): 247 (M\(^+\)+1, 36), 246.1538 (M\(^+\), 100), 231 (41), 217 (75), 201
2-(2,3,5,6-Tetramethylphenyl)acetic acid: (6a)

Following General Procedure 3, Purification by flash column chromatography.

2-(2,3,5,6-Tetramethylphenyl)acetic acid (6a) : IR (KBr) 3086 (br), 3002 (s), 2924 (s), 2874 (s), 2732 (br), 2332 (s), 2100 (m), 1695 (s), 1607 (m), 1408 (m), 1381 (m), 1213 (s), 1010 (m), 935 (m), 868 (m), 681 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 2.20 (s, 6 H), 2.23 (s, 3 H), 2.24 (s, 3 H), 3.79 (s, 2 H), 6.91 (s, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 16.1, 20.6, 35.5, 128.8, 129.4, 132.9, 133.7, 175.7; High-resolution MS, calcd for C₁₂H₁₆O₂: 192.1150. Found m/z (relative intensity): 193 (M⁺+1, 13), 192.1144 (M⁺, 76), 147 (100).

2-(2,3,5,6-Tetraethylphenyl)acetic acid: (6b)

Following General Procedure 3, Purification by flash column chromatography.

2-(2,3,5,6-Tetraethylphenyl)acetic acid (6b) : IR (KBr) 3103 (br), 2968 (s), 2936 (s),
2876 (s), 2719 (br), 2363 (m), 1699 (s), 1483 (m), 1416 (s), 1231 (s), 939 (m), 887 (s), 802 (m), 656 (m) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.12 (t, \(J = 7.6\) Hz, 6 H), 1.23 (t, \(J = 7.6\) Hz, 6 H), 2.63 (q, \(J = 7.6\) Hz, 4 H), 2.64 (q, \(J = 7.6\) Hz, 4 H), 3.79 (s, 2 H), 6.98 (s, 1 H); \(^13\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 14.8, 15.5, 22.3, 25.7, 34.4, 128.1, 129.4, 138.2, 139.3, 177.8; High-resolution MS, calcd for C\(_{16}\)H\(_{24}\)O\(_2\): 248.1776. Found \(m/z\) (relative intensity): 249 (M\(^+\)1, 14), 248.1770 (M\(^+\), 77), 233 (16), 203 (17), 189 (100).

**2-(2,3,5,6-Tetrapropylphenyl)acetic acid: (6c)**

Following General Procedure 3, Purification by flash column chromatography.

**2-(2,3,5,6-Tetrapropylphenyl)acetic acid (6c) :** IR (KBr) 3103 (br), 2957 (s), 2932 (s), 2870 (s), 2711 (br), 2354 (m), 1703 (s), 1562 (m), 1454 (s), 1414 (m), 1018 (m), 912 (m), 791 (m) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 0.99 (t, \(J = 7.6\) Hz, 6 H), 1.01 (t, \(J = 7.6\) Hz, 6 H), 1.45 (sext, \(J = 7.6\) Hz, 4 H), 1.59 (sext, \(J = 7.6\) Hz, 4 H), 2.50 (t, \(J = 7.6\) Hz, 4 H), 2.54 (t, \(J = 7.6\) Hz, 4 H), 3.75 (s, 2 H), 6.91 (s, 1 H); \(^13\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 14.4, 14.8, 24.0, 24.5, 31.9, 34.8, 35.2, 129.7, 130.0, 137.3, 138.0, 177.7; High-resolution MS, calcd for C\(_{20}\)H\(_{32}\)O\(_2\): 304.2402. Found \(m/z\) (relative intensity): 304.2392 (M\(^+\), 100), 275 (56), 245 (57).
2-(2,3,5,6-tetrabutylphenyl)acetic acid: (6j)

Following General Procedure 3, Purification by flash column chromatography.

\[
\begin{array}{c}
\text{n-Bu} \\
\text{n-Bu} \\
\text{n-Bu} \\
\text{n-Bu}
\end{array}
\]

IR (neat) 3075 (br), 2957(s), 2930 (s), 2860 (s), 2669 (m), 2343 (m), 1709 (s), 1464 (m), 1410 (m), 1379 (m), 1292 (m), 1227 (m), 930 (m), 899 (m) cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \textit{\delta} 0.95 (m, 12 H), 1.38-1.46 (m, 16 H), 2.52-2.58 (m, 8 H), 3.75 (s, 1 H), 6.91. (s, 2 H) ; \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \textit{\delta} 13.8, 13.9, 14.0, 23.0, 23.4, 29.4, 32.8, 32.9, 33.8, 34.9, 124.6, 129.7, 129.9, 137.3, 138.2, 140.1, 178.6 ; High-resolution MS, calcd for C\textsubscript{24}H\textsubscript{40}O\textsubscript{2}: 360.3028. Found \textit{m/z} (relative intensity): 361 (M\textsuperscript{+}+1, 26), 360.3055 (M\textsuperscript{+}, 100), 316 (9).

2-{(2,3,5,6-tetrahenyl)phenyl}acetic acid: (6e)

Following General Procedure 3, Purification by flash column chromatography.

\[
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph}
\end{array}
\]

IR (neat) 3024 (br), 2866 (s), 2835 (s), 2500 (m), 1717 (s), 1653 (s), 1578 (m), 1420 (s), 1232 (s), 918 (m), 692 (s) cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \textit{\delta} 3.66 (s, 2 H), 7.34-7.69 (m, 21 H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100
MHz) δ 37.0, 127.4, 127.5, 128.3, 128.4, 128.5, 128.7, 131.9, 132.0, 171.1;
High-resolution MS, calcd for C\textsubscript{32}H\textsubscript{24}O\textsubscript{2}: 440.1776. Found \textit{m/z} (relative intensity): 441
(M\textsuperscript{+}+1, 29), 440.1769 (M\textsuperscript{+}, 43.8), 395 (100).

\textbf{2-(2,5-dimethyl-3,6-bis(trimethylsilyl)phenyl)acetic acid: (6f)}

Following General Procedure 3, Purification by flash column chromatography.

\begin{center}
\includegraphics[width=0.5\textwidth]{image}
\end{center}

\textbf{2-(2,5-dimethyl-3,6-bis(trimethylsilyl)phenyl)acetic acid (6f) :} IR(neat) 2959 (s),
2903 (s), 2667 (w), 1705 (s), 1636 (m), 1410 (m), 1252 (s), 1211 (m), 1150 (m), 1032
(m), 837 (s), 760 (s), 691 (m), 635 (m) cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ 0.31 (s, 9 H),
0.41 (s, 9 H), 2.32 (s, 3 H), 2.45 (s, 3 H), 3.93 (s, 2 H), 7.19 (s, 1 H); \textsuperscript{13}C NMR (CDCl\textsubscript{3},
100 MHz) δ 0.0, 0.8, 14.0, 20.1, 38.8, 136.2, 137.2, 139.3, 139.6, 140.0, 140.5, 176.4;
High-resolution MS, calcd for C\textsubscript{16}H\textsubscript{28}O\textsubscript{2}Si\textsubscript{2}: 308.1628. Found \textit{m/z} (relative intensity):
308.1634 (M\textsuperscript{+}, 11.1), 293 (100).

\textbf{2-(2,5-di-tert-butylphenyl)acetic acid: (6k)}

Following General Procedure 3, Purification by flash column chromatography.
2-(2,5-di-tert-butylphenyl)acetic acid (6k): IR(neat) 2868 (s), 2550 (s), 2341 (m), 1699 (s), 1464 (s), 1416 (s), 1362 (s), 1231 (s), 1204 (s), 910 (s), 824 (s), 741 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.29 (s, 9 H), 1.39 (s, 9 H), 3.95 (s, 2 H), 7.21 (s, 1 H), 7.33 (d, J = 8.5 Hz, 1 H), 7.38 (d, J = 8.5 Hz, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ 31.2, 31.6, 34.0, 36.5, 40.2, 124.0, 126.0, 130.0, 130.8, 148.4, 149.6, 177.8; High-resolution MS, calcd for C₁₆H₂₄O₂: 248.1776. Found m/z (relative intensity): 248.1768 (M⁺, 49.5), 233 (100), 216 (2.5), 203 (1.6).

2-(2,5-bis(trimethylsilyl)phenyl)acetic acid: (6l)

Following General Procedure 3, Purification by flash column chromatography.

2-(2,5-bis(trimethylsilyl)phenyl)acetic acid (6l): IR(neat) 2955 (s), 2899 (s), 2856 (m), 1713 (s), 1410 (m), 1373 (m), 1250 (s), 839 (s), 752 (s), 691 (m), 637 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 0.26 (s, 9 H), 0.33 (s, 9 H), 3.81 (s, 2 H), 7.40 (d, J = 1.0 Hz, 1 H), 7.42 (dd, J = 7.8, 1.0 Hz, 1 H), 7.51 (d, J = 7.3 Hz, 1 H); ¹³C NMR (CDCl₃, 100 MHz) δ -0.9, 0.6, 41.5, 131.8, 134.3, 135.5, 138.0, 140.0, 142.0, 177.8; High-resolution
General procedure for the C–C bond cleavage reaction of diketene promoted by stoichiometric amount of Ni(0) (Scheme 4)

To a solution of Ni(cod)$_2$ (137.5 mg, 0.5 mmol), and PPh$_3$ (262.3 mg, 1.0 mmol) in dry toluene (5 mL) were successively added diketene (42.0 mg, 0.5 mmol), 3-hexyne (41.1 mg, 0.5 mmol) via syringe under nitrogen atmosphere. The mixture was stirred at room temperature for 1 h. After the reaction, added 2 N HCl and stirred for overnight at room temperature. The mixture was diluted with 30 mL of EtOAc and washed with brine. The extract was dried (MgSO$_4$) and concentrated in vacuo and the residual oil was subjected to column chromatography over silica gel (hexane/EtOAc = 4/1 v/v) to give 7b (67.3 mg, 80%, $R_f$ = 0.33; hexane/EtOAc = 4/1 v/v).

(3E)-4-ethyl-5-methylene-3-heptenoic acid: (7b)

(3E)-4-ethyl-5-methylene-3-heptenoic acid (7b) : IR(neat) 2970 (s), 2936 (s), 2878 (s), 1713 (s), 1607 (m), 1413 (s), 1288 (s), 1219 (s), 893 (s) cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.98 (t, $J$ = 7.5 Hz, 3 H), 1.05 (t, $J$ = 7.5 Hz, 3 H), 2.25 (qd, $J$ = 7.5, 1.3 Hz, 2 H), 2.25 (q, $J$ = 7.5 Hz, 2 H), 3.21 (d, $J$ = 7.1 Hz, 2 H), 4.92 (d, $J$ = 1.3 Hz, 1 H), 5.03
(s, 1 H), 5.64 (t, J = 7.1 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 13.2, 13.4, 21.5, 26.9, 33.5, 110.1, 116.1, 144.5, 149.2, 177.7; High-resolution MS, calcd for C$_{19}$H$_{16}$O$_2$: 168.1150. Found m/z (relative intensity): 169 (M$^+$+1, 83.7), 168.1143 (M$, 51.1), 153 (100).

General procedure for the C–C bond cleavage reaction of diketene promoted by stoichiometric amount of Ni(0) with PhMgBr (eq 2)

To a solution of Ni(cod)$_2$ (137.5 mg, 0.5 mmol), and PPh$_3$ (262.3 mg, 1.0 mmol) in dry toluene (5 mL) were successively added diketene (42.0 mg, 0.5 mmol), 3-hexyne (41.1 mg, 0.5 mmol) via syringe under nitrogen atmosphere. The mixture was stirred at room temperature for 1 h. Then, added the PhMgBr (0.6 mmol, 1M THF solution) and stirred for overnight at room temperature. After the reaction, added 2 N HCl and stirred for 24 h at room temperature. The mixture was diluted with 30 mL of EtOAc and washed with brine. The extract was dried (MgSO$_4$) and concentrated in vacuo and the residual oil was subjected to column chromatography over silica gel (hexane/EtOAc = 4/1 v/v) to give the mixture of 8b and 9b (8b: 63.5 mg, 26%, 9b: 127.2 mg, 39%, $R_f$ = 0.33; hexane/EtOAc = 4/1 v/v).
A mixture of (3Z)-4-ethyl-5-methylene-3-phenyl-3-heptenoic acid (8b) and (3Z)-4-ethyl-5-methylene-3-[(3Z)-4-phenyl-3-hexenyl]-3-heptenoic acid (9b) in a 1:2 ratio: IR(neat) 3402 (br), 3084 (s), 3028 (s), 2966 (s), 2934 (s), 1705 (s), 1636 (s), 1441 (m), 1410 (m), 1286 (m), 943 (s), 897 (s), 766 (s), 700 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz, (8)) δ 0.90 (t, J = 7.5 Hz, 3 H), 1.05 (t, J = 7.5 Hz, 3 H), 2.31 (q, J = 7.5 Hz, 2 H), 2.33 (q, J = 7.5 Hz, 2 H), 2.78 (s, 2 H), 4.89 (s, 1 H), 5.01 (s, 1 H), 7.08-7.32 (m, 5 H); ¹³C NMR (CDCl₃, 100 MHz, (8b)) δ 11.9, 12.5, 26.0, 28.5, 41.7, 118.4, 126.0, 127.6, 128.9, 139.1, 141.8, 143.0, 145.7, 176.2; High-resolution MS (8b), calcd for C₁₆H₂₀O₂: 244.1463. Found m/z (relative intensity): 245 (M⁺+1, 19.0), 244.1458 (M⁺, 100), 242 (2.9).

¹H NMR (CDCl₃, 400 MHz, (9b)) δ 0.86 (t, J = 7.5 Hz, 3 H), 0.87 (t, J = 7.5 Hz, 3 H), 1.02 (t, J = 7.5 Hz, 3 H), 1.06 (t, J = 7.5 Hz, 3 H), 1.85 (q, J = 7.5 Hz, 2 H), 2.31 (q, J = 7.5 Hz, 2 H), 2.33 (q, J = 7.5 Hz, 2 H), 2.40 (q, J = 7.5 Hz, 2 H), 3.47 (s, 2 H), 4.65 (d, J = 1.5 Hz, 1 H), 4.80 (d, J = 1.5 Hz, 1 H), 7.08-7.32 (m, 5 H); ¹³C NMR (CDCl₃, 100 MHz, (9)) δ 11.9, 12.5, 13.1, 13.2, 25.3, 25.9, 27.4, 28.4, 39.5, 113.2, 126.1, 126.3, 127.0, 127.5, 127.9, 128.7, 138.4, 142.9, 150.2, 176.2; High-resolution MS (9b), calcd for C₂₂H₃₀O₂: 326.2246. Found m/z (relative intensity): 327 (M⁺+1, 42.6), 326.2242 (M⁺, 72.7), 297 (100), 282 (60.3).
**X-ray Crystal Structure Determinations.** X-ray quality single crystals were grown from solvent combinations of ethyl acetate/hexane for both of 5b and 6b. All measurements were made on a Rigaku Saturn724 diffractometer using multi-layer mirror monochromated Mo-Ka radiation. Data were collected and processed using CrystalClear (Rigaku) at a temperature of -179±1 °C to a maximum 2θ value of 55°. The structures were solved by direct methods (SHELXL-97) and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using the riding model. All calculations were performed using the CrystalStructure 4.0 (Crystal Structure Analysis Package, Rigaku Corporation) except for refinement, which was performed using SHELXL-97. Crystal data and refinement parameters for the structurally characterized compounds 5b and 6b are summarized in Tables 4 and 5, respectively. An ORTEP drawing of 5b and 6b are shown in Figure 1 and 2, respectively. CCDC 832667 contains the supplementary crystallographic data for 5b and CCDC 828924 for 6b. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Table 4. Crystallographic data for compound 5b

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<td>GOF[^{d}]</td>
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[^{a}] R1 = Σ ||Fo| - |Fc||/Σ |Fo|.
[^{b}] R = Σ |Fo² - Fc²|/Σ Fo².
[^{c}] Rw = \{Σw(Fo² - Fc²)²/Σw (Fo²)²\}^{1/2}.
[^{d}] GOF = \{Σw(Fo² - Fc²)²/(No - Np)\}^{1/2}, where No and Np denote the number of observations and parameters.
**Table 5.** Crystal data and data refinement for 6b

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<td>GOF $^d$</td>
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</table>

$^a$ $R_1 = \Sigma |F_o| - |F_c|/\Sigma |F_o|$.  
$^b$ $R = \Sigma |F_o^2 - F_c^2|/\Sigma F_o^2$.  
$^c$ $R_w = \{\Sigma w(F_o^2 - F_c^2)^2/\Sigma w (F_o^2)^2\}^{1/2}$.  
$^d$ GOF = $[\{\Sigma w(F_o^2 - F_c^2)^2\}/(No - Np)]^{1/2}$, where No and Np denote the number of observations and parameters.
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Reviews: (c) S. Saito, Y. Yamamoto, Chem. Rev. 2000, 100, 2901-2916.


(h) F.-S. Han, Chem. Soc. Rev. 2013, 42, 5270-5298.


Ni-Catalyzed [2+2] cycloaddition reaction of alkyne with activated alkenes:


CCDC 832667 contains the supplementary crystallographic data for **5b** and CCDC 828924 for **6b**.

These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via, [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).


(12) Intramolecular carbonickelations of alkenylnickel species on sp² framework via 6-endo-trig cyclization have been reported:


(14) Palladacyclopentene rearrangements involving Pd carbene complex have been reported by B. M. Trost et al:


(15) Ni-catalyzed β-carbon elimination, see:


Publication List

Chapter 1

“Stereoselective Coupling Reaction of Dimethylzinc and Alkyne toward Nickelacycles”

Takamichi Mori, Toshiyuki Nakamura, Masanari Kimura,


“Regio- and Stereoselective Multicomponent Coupling Reaction of Alkynes and Dimethylzinc Involving Allylnickelacycles”

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Chapter 2

“Ni-Catalyzed Homoallylation of Polyhydroxy N,O-Acetals with Conjugated Dienes Promoted by Triethylborane”

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Chapter 3

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Other related publications

“Decarboxylative C–C Bond Cleavage Reactions via Oxapalladacycles”
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