Advances in Electrophilic, Nucleophilic, and Amphiphilic Allylation Promoted by Synergy Effect of Palladium and Lewis Acids

パラジウム触媒とルイス酸の協働作用を活用した親電子的、求核的、双極的アリル化反応に関する研究

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Dedication

This dissertation is dedicated to my wonderful wife, Mayumi Hirata. Without her love, support, and encouragement I would not have made it this far.
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General Introduction

Environmental pollution is a rising problem on a global scale that will have serious consequences for the next generation, unless we act today to prevent this problem. Burning of fossil fuels to supply the energy that all humankind require to sustain all human activities. However, it is the main causes for the environmental pollution, climate change and generally to expend the natural reserves. As such, the excessive use of fossil-based carbon feedstocks should be reduced. Additionally, the diminishing petroleum reserves will be a major problem in the future anyways and therefore humankind needs to find alternatives to sustain our demand for energy, and economic growth. To realize sustainable society, organic chemists need to develop new catalytic methodology that enable sustainable, green and clean synthetic methods with high efficiency, thus leading to less wastes.

Tsuji-Trost Reaction

Tsuji-Trost reaction is one of the most reliable method in organic synthesis. Tsuji and his co-workers reported the first example of the reaction of $\pi$-allylpalladium chloride complex with acetoacetate and malonate in 1965.\textsuperscript{1} In this reaction, $\pi$-allylpalladium complexes are electrophilic and can be attacked by nucleophiles to
afford allylic products. In 1977, Trost and his co-workers reported asymmetric catalytic allylic alkylation reaction of cyclic allylacetate by using (+)-DIOP chiral phosphine ligand. Since the pioneering work on π-allylpalladium chemistry by Tsuji and Trost, many efficient catalyst systems have been developed and are widely applied to natural and unnatural compounds synthesis.

**Transition-Metal-Catalyzed Allylic Substitution**

Other transition metals such as Mo, W, Fe, Ru, Co, Rh, Ir, Ni, Pt and Cu are also known to catalyze the allylic substitution reactions. In 1979, Roustan and his co-workers reported a Fe- and Co-catalyzed allylic alkylation with active methylene compounds. Generally, the regioselectivity of Pd- and Ni-catalyzed allylic substitutions tend to lead to preferential formation at the less substituted allylic terminus. In contrast, Mo-, W-, Ru- and Ir-catalyzed allylic substitutions tend to lead to construction of branch product via attack at the more substituted terminus.

**Transition-Metal-Catalyzed Direct Allylic Substitution of Allyl alcohol**

One of the most useful routes for generating π-allylmetal complex is the oxidative addition of allylic substrate in the presence of a low valent metal complex. Various allyl substrates such as allylic halides, esters and carbonates have been used in this oxidative addition step. However, the formation of π-allylmetal complex with
underivatized allyl alcohol is very rare owing to the poor leaving ability of hydroxyl group, although development of a direct catalytic allylic substitution reaction is the most straightforward and desirable (Scheme 1). Initial attempts to break through the poor leaving ability of hydroxyl group either required severe reaction conditions such as high temperature or the addition of stoichiometric or catalytic amounts of an activator such as Ti(O\text{Pr})_4, As_2O_3, SnCl_2, BF_3\cdot Et_2O, BPh_3, BEt_3, CO_2, and Brønsted acid. In 1999, Nomura and his co-workers reported the Pd-catalyzed allylic alkylation of allyl alcohol with zinc enolates in the presence of a catalytic amount of Ti(O\text{Pr})_4 and LiCl. In this reaction, Ti(O\text{Pr})_4 works as an activator to enhance the reactivity of allyl alcohol toward oxidative addition to Pd(0) species. Tamaru and Kimura already disclosed that palladium catalyst and triethylborane system provided the direct method for electrophilic alkylation of various nucleophiles with allyl alcohols.
Scheme 1. Direct Allylic Substitution of Allyl Alcohol

In this system, Et₃B activates allyl alcohols toward oxidative addition to palladium catalyst by coordinating of hydroxyl group to form π-allylpalladium. This π-allylpalladium species serves as an allyl cation equivalent. In the absence of nucleophiles, π-allylpalladium undergoes an allyl-ethyl exchange reaction to provide allyldiethylborane served as an allyl anion equivalent (Scheme 2).

Scheme 2. Pd-catalyzed, Et₃B-promoted generation of an allyl cation and an allyl anion species.
The author planned to develop novel and synthetically useful catalytic reactions via allyl anion equivalents by use of a palladium and triethylborane system or palladium and diethylzinc system to give heterocyclic compounds and also to obtain insights into the reaction mechanism of these reactions.

**Abstract of This Thesis**

This thesis is composed of three chapters. Chapter 1 deals with palladium catalyst and diethylzinc system-promoted nucleophilic allylation of aldehydes and aldimes with vinylcyclopropane. In chapter 2, consecutive double amphiphilic allylation of nitriles with 2-methylenepropane-1,3-diol catalyzed by cooperative palladium/triethylborane system is described. In chapter 3, the amphiphilic allylation of aldimes with 2,3-bismethylenebutane-1,4-diol derivatives to serve as bis-allylic zwitterion species promoted by the combination of palladium catalyst and diethylzinc to preparing 3,4-bismethylenepiperidines is summarized. Chapter 4 deals with the palladium-catalyzed direct electrophilic allylation of amines by using of phosphine-borane compound as an efficient ligand.
References and Notes


(15) (a) Masuyama, Y.; in: Advances in Metal-Organic Chemistry; (Ed.: L. S. Liebeskind), JAI Press, 1994, vol. 3, p. 255; (b) Tamaru, Y.; in Handbook of


(20) Yang, S.-C.; Hsu, Y.-C.; Gan, K.-H. Tetrahedron, 2006, 62, 3949.
Chapter 1

Synthesis of Lactones and Lactams from Vinylcyclopropane by Palladium-Catalyzed Nucleophilic Allylation

1.1 Abstract

A palladium-catalyzed nucleophilic allylation of aldehydes with vinylcyclopropane in the presence of diethylzinc proceeded to provide homoallyl alcohols with \textit{anti} stereoselectivity. Aldimines prepared from aldehyde and primary amines in situ underwent a similar nucleophilic allylation to give homoallylamines with \textit{syn} stereoselectivity. The resulting homoallyl alcohols and homoallylamines could be converted by treatment with a tetranuclear zinc cluster into $\gamma$-vinyl-$\delta$-valerolactones and $\gamma$-vinyl-$\delta$-valerolactams, respectively.
1.2 Introduction

Activated cyclopropanes are important and efficient key intermediates in modern organic synthesis. In particular, cycloaddition and ring expansion reactions of vinylcyclopropanes are powerful tools for the construction of highly functionalized heterocycles and unsaturated hydrocarbons. Recently, Tamaru, Kimura and their co-workers developed a multicomponent coupling reaction of alkynes and dimethylzinc with vinylcyclopropane promoted by a Ni catalyst (Scheme 1). In this case, vinylcyclopropane served as an allylnickel species, undergoing insertion of alkynes followed by transmetalation with dimethylzinc to construct octadiene frameworks with high regio- and stereoselectivity.

**Scheme 1** Ni-catalyzed multicomponent coupling of vinylcyclopropane, alkyne, and Me₂Zn

Furthermore, vinylcyclopropane is known to form π-allylpalladium complex to serve as an allyl cation equivalent by oxidative addition. Pd-catalyzed allylation is one of the most useful and convenient methods for the synthesis of important complex molecules containing physiologically active scaffolds. Recently, Tamaru and Kimura
developed a method for direct formation of \( \pi \)-allylpalladium from allylic alcohol, promoted by a Pd catalyst and triethylborane or diethylzinc.\(^5\) An example is the activation of allylic alcohol promoted by triethylborane as a Lewis acid, which facilitates oxidative addition toward the Pd(0) catalyst to form a \( \pi \)-allylpalladium species serving as an allylic cation equivalent (Scheme 2). Under the reaction system

**Scheme 2 Umpolung of \( \pi \)-allylpalladium with triethylborane**

\[
\begin{align*}
\text{OH} & \quad \text{Pd} \quad \text{Et}_3\text{B} \\
\overset{-\text{OH}}{\text{Pd}} \quad \text{B} \quad \text{Et}_3 \\
\overset{\text{Et}}{\text{B}} \quad \text{Et}_2 \\
\overset{-\text{Pd}}{\text{Pd}} \\
\overset{\text{Et}}{\text{B}} \quad \text{Et}_2
\end{align*}
\]

involving a Pd catalyst and triethylborane, soft nucleophiles, such as malonates, amines, and indoles undergo electrophilic allylations with allylic alcohols, affording allylation products by direct Tsuji–Trost allylation. Interestingly, moreover, in the presence of

**Scheme 3 Pd-catalyzed nucleophilic allylation of aldehydes or aldimes with allyl alcohols**

\[
\begin{align*}
\text{R}^1 & \quad \text{O} \\
\text{Pd catalyst} & \quad \text{Et}_3\text{B or Et}_2\text{Zn} \\
\text{OH} & \quad \text{R}^2
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{N} \quad \text{R}^1 \\
\text{Pd catalyst} & \quad \text{Et}_3\text{B} \\
\text{NHR}^1 & \quad \text{R}^2
\end{align*}
\]
electrophiles, a similar catalytic system consisting of a Pd catalyst and triethylborane also promoted nucleophilic allylation of carbonyl groups, such as aldehydes and aldimes to afford homoallylic alcohols and homoallylamines, respectively (Scheme 3). In these cases, umpolung of $\pi$-allylpalladium with triethylborane proceeded to afford an allyldiethylborane as an allyl anion equivalent for nucleophilic allylation of electrophiles involving an allyl–ethyl exchange reaction. The combination of Pd(0)

**Scheme 4** Pd-catalyzed nucleophilic allylation of aldehydes or aldimes with vinylcyclopropane

![Scheme 4](image)

catalyst and diethylzinc and triethylborane accelerates amphiphilic allylations with allyl alcohols as an allyl cation and allyl anion equivalents, depending on the nucleophiles and electrophiles in situ. In this chapter, the author demonstrate a successful extension of the Pd(0) catalyst and diethylzine system to nucleophilic allylation of aldehydes and aldimes with vinylcyclopropane derived from dimethyl malonate and 1,4-dichloro-2-butene to form homoallyl alcohols and homoallyl amines (Scheme 4).
Furthermore, these products can be converted into $\gamma$-vinyl-$\delta$-valerolactones and $\gamma$-vinyl-$\delta$-valerolactams by treatment with a tetranuclear zinc cluster.
1.3 Results and Discussion

First, the author investigated the nucleophilic allylation of benzaldehyde with vinylcyclopropane. Treatment of benzaldehyde with vinylcyclopropane in THF in the presence of Pd(OAc)$_2$ (10 mol%), $n$-Bu$_3$P (20 mol%) and Et$_3$B (240 mol%) at 50 °C for 48 hours afforded homoallyl alcohol 1a in 37% isolated yield as a single isomer with anti stereoselectivity (Table 1, entry 1). Interestingly, when diethylzinc was used in place of triethylborane, 1a was obtained in 25% yield along with the cyclized product 2a in 22% yield as a by-product in a 2:1 ratio (Table 1, entry 2). Use of PdCl$_2$ decreased the yield of 1a (Table 1, entry 3). Pd(0) complex such as Pd(PPh$_3$)$_4$ promoted the formation of 1a in 65% yield (Table 1, entry 4). The use of Pd(acac)$_2$ resulted in formation of 1a in 56% yield (Table 1, entry 5). As a result, the author found that the nucleophilic allylation of benzaldehyde (1 mmol) with vinylcyclopropane (1.2 mmol) afforded 1a in 72% yield in the presence of Pd(acac)$_2$ (5 mol%), PPh$_3$ (10 mol%), diethylzinc (2.4 mmol), under concomitant formation of small amount of 2a (Table 1, entry 6).

Table 2 shows the results of allylation of various aldehydes, such as aromatic, α,β-unsaturated, and aliphatic aldehydes. $p$-Chlorobenzaldehyde participated in nucleophilic allylation to afford the homoallyl alcohol 1b in excellent yield with high
stereoselectivity (Table 2, entry 1). \(p\)-Tolualdehyde and 2-naphthylaldehyde showed similar results and gave the desired products in good to reasonable yields (Table 2, entries 2 and 3). Dihydrocinnamaldehyde gave the desired product 1e in 39% yield.

Table 1. Nucleophilic Allylation of Benzaldehyde with vinylcyclopropane

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd cat.</th>
<th>ligand</th>
<th>Et(_2)M</th>
<th>temp. (°C)</th>
<th>yield (%)</th>
<th>total yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)(_2)</td>
<td>(n)-Bu(_3)P</td>
<td>Et(_3)B</td>
<td>50</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)(_2)</td>
<td>(n)-Bu(_3)P</td>
<td>Et(_2)Zn</td>
<td>rt</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>PdCl(_2)</td>
<td>(n)-Bu(_3)P</td>
<td>Et(_2)Zn</td>
<td>rt</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh(_3))(_4)</td>
<td>-</td>
<td>Et(_2)Zn</td>
<td>rt</td>
<td>65</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Pd(acac)(_2)</td>
<td>(n)-Bu(_3)P</td>
<td>Et(_2)Zn</td>
<td>rt</td>
<td>56</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>Pd(acac)(_2)</td>
<td>PPh(_3)</td>
<td>Et(_2)Zn</td>
<td>rt</td>
<td>72</td>
<td>21</td>
</tr>
</tbody>
</table>

\(\text{a}\) The reaction was carried out in the presence of aldehyde (1 mmol), vinylcyclopropane (1.2 mmol), Pd(acac)\(_2\) (0.05 mmol), Ph\(_3\)P (0.1 mmol), and Et\(_2\)Zn (2.4 mmol; 1 M hexane solution) in anhyd THF (1 mL) at r.t. for 48 h under nitrogen. All of the homoallyl alcohols 1a were obtained as a single isomer, whereas lactones 2a were obtained as diastereomeric mixture in 1:1 ratios.

but lactone 2e was obtained in 60% yield as a major product. \(\text{sec}\)-Alkylaldehyde participated in the similar nucleophilic allylation to afford homoallyl alcohol 1f in 54%
yield along with lactone 2f in 36% yield (Table 2, entry 5). Pivalaldehyde provided a trace amount of homoallyl alcohol 1g, instead, lactone 2g was obtained in 62%, exclusively (Table 2, entry 6). The nucleophilicity of the alkoxides of homoallyl alcohols derived from aliphatic aldehydes seems to enhance the intramolecular esterification leading to γ-vinyl-δ-lactones 2.

A similar nucleophilic allylation reaction could be used for the synthesis of homoallylamines and δ-lactames. The result of reactions using various kinds of aromatic and aliphatic aldimines prepared from aldehydes and primary amines are summarized in Table 3. The reaction was conducted as follows: in situ formation of aldimines from primary amines and aldehydes by two azeotropic distillations of a mixture of THFwater (30 min reflux in 1 mL of THF), exposure of the aldimines to a mixture of Pd(acac)₂, PPh₃, and vinylcyclopropane, and addition of diethylzinc with stirring at room temperature. As was the case for aldimines prepared from benzaldehyde and aromatic amines, the reaction was compatible with both electron-donating and electoron-withdrawing aromatic ring of primary amines.

Homoallylamines 3a–3c were produced with syn stereoselectivity along with lactams 4a–4c in a 2:1 ratio (entries 1–3, Table 3). Aldimines from aliphatic amines
Table 2. Pd/Et₂Zn-Promoted Nucleophilic Allylation of Aldehyde with Vinylcyclopropane

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>time (h)</th>
<th>yield (%) [ratio]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-ClC₆H₄</td>
<td>18</td>
<td>1b:78, 2b:21 [1:1]</td>
</tr>
<tr>
<td>2</td>
<td>p-MeC₆H₄</td>
<td>3</td>
<td>1c:71, 2c:28 [1:1]</td>
</tr>
<tr>
<td>3</td>
<td>2-naphthyl</td>
<td>48</td>
<td>1d:69, 2d:17 [1:1]</td>
</tr>
<tr>
<td>4</td>
<td>PhCH₂CH₂</td>
<td>48</td>
<td>1e:39, 2e:60 [2:1]</td>
</tr>
<tr>
<td>5</td>
<td>c-C₆H₁₁</td>
<td>48</td>
<td>1f:54, 2f:36 [1:1]</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td>24</td>
<td>1g:trace, 2g:62 [1:1]</td>
</tr>
</tbody>
</table>

The reaction was carried out in the presence of aldehyde (1 mmol), vinylcyclopropane (1.2 mmol), Pd(acac)₂ (0.05 mmol), Ph₃P (0.1 mmol), and Et₂Zn (2.4 mmol; 1 M hexane solution) in anhyd THF (1 mL) at r.t. for 48 h under nitrogen. All of the homoallyl alcohols 1 were obtained as a single isomer, whereas lactones 2 were obtained as diastereomeric mixture in 1:1 to 2:1 ratios.

such as benzylamine and n-hexylamine could be used as substrates for a similar nucleophilic allylation reaction. However homoallylamines 3 were not obtained at all; instead, lactams 4d and 4e were produced exclusively (entries 4 and 5, Table 3).

Homoallylamines derived from aliphatic amines could be readily converted into lactams 4 by intramolecular lactamization under the reaction conditions owing to the greater nucleophilicity of the amino groups. Although p-chlorobenzaldehyde and aliphatic aldehyde could be also used as aldehydes for nucleophilic allylation, aldime prepared
Table 3. Pd/Et$_2$Zn-Promoted Nucleophilic Allylation of Aldimines with Vinylcyclopropane$^a$

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde $R^1$</th>
<th>amine $R^2$</th>
<th>yield (%) [ratio]</th>
<th>3 [syn/anti]</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>PMP</td>
<td>3a: 42 [4:1]</td>
<td>4a: 47</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph</td>
<td>3b: 44 [3:1]</td>
<td>4b: 27</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>$p$-ClC$_6$H$_4$</td>
<td>3c: 36 [2:1]</td>
<td>4c: 21</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Bn</td>
<td>none</td>
<td>4d: 62</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>$n$-C$<em>6$H$</em>{13}$</td>
<td>none</td>
<td>4e: 50</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>$p$-ClC$_6$H$_4$</td>
<td>PMP</td>
<td>3f: 27 [3:1]</td>
<td>4f: 51</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>$n$-C$<em>5$H$</em>{11}$</td>
<td>PMP</td>
<td>3g: 32 [single]</td>
<td>none</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ The reaction was carried out in the presence of aldimine which was prepared from aldehyde (1 mmol) and amine (1.05 mmol) in THF (1 mL) at reflux (removal of H$_2$O by azeotropic distillation), 2-vinylcyclopropane (1.2 mmol), Pd(acac)$_2$ (0.05 mmol), Ph$_3$P (0.1 mmol), and Et$_2$Zn (2.4 mmol; 1 M hexane solution) in anhyd THF (1 mL) at r.t. for 48 h under nitrogen. All of the lactams 4 were obtained as a diastereoisomeric mixture in a 2:1 ratio.

from $n$-hexanal and $p$-anisidine selectively afforded homoallylamine 3g as a sole product (entries 6 and 7, Table 3).

The homoallyl alcohols 1 and homoallylamines 3 resulting from Pd-catalyzed nucleophilic allylation with vinylcyclopropane could be converted into lactones and lactams (Table 4).$^8$ Mashima and Ohshima reported excellent conversion of esters from a mixture of alcohols and carboxylic acids promoted by a tetrannuclear zinc.
Table 4. Decarboxylative Lactonization and Lactamization of Homoallylic Alcohols and Homoallylamines by Tetranuclear Zinc Cluster

<table>
<thead>
<tr>
<th>entry</th>
<th>1 or 3 [ratio]</th>
<th>yield (%) of 5 or 6 [ratio]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>5a: 75</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>5b: 70</td>
</tr>
<tr>
<td>3</td>
<td>3a [4:1]</td>
<td>6a: 80 [4:1]</td>
</tr>
<tr>
<td>4</td>
<td>3b [3:1]</td>
<td>6b: 76 [4:1]</td>
</tr>
<tr>
<td>5</td>
<td>3b [single]</td>
<td>6g: 89 [single]</td>
</tr>
</tbody>
</table>

a The reaction was carried out in the presence of homoallyl alcohol 1 or homoallylamine 3 (0.3 mmol), and Zn₄(OCOCF₃)₆O (0.0038 mmol) in xylene (1 mL) at reflux under nitrogen for 24 h.

Under similar conditions for esterification by a zinc cluster, homoallyl alcohols and homoallylamines isolated from the reactions detailed in Tables 1 and 2 could be cyclized to afford lactones and lactams under xylene reflux conditions accompanied by decarboxylation. Homoallyl alcohols as single isomers of 1a and 1b led to γ-vinyl-δ- lactones 5a and 5b as single isomers (entries 1 and 2, Table 4). Homoallylamines 3a, 3b, and 3g also underwent the intramolecular cyclization to construct lactams 6a, 6b, and 6g in reasonable ways (entries 3–5, Table 4). The structures of the products were determined based on coupling constants from ¹H NMR.
spectral data and NOE experiments. Selected data for the NOE observed by the irradiation at the protons indicated in bold face are illustrated in Figure 1. The configurations of the lactones $5a$ and lactams $6g$ were complementary to each other; that is, the nucleophilic allylation of aldehydes and aldimines with vinylcyclopropane showed the opposite stereoselectivity, providing anti-homoallyl alcohols and syn-homoallylamines.

![Figure 1](image_url) Structure determination for NOE data of lactone $5a$ and lactam $6g$

A plausible reaction mechanism for Pd-catalyzed nucleophilic allylation of aldehydes and aldimines with vinylcyclopropane is illustrated in Scheme 5. An allyl anion equivalent generated from vinylcyclopropane and diethylzinc via umpolung of $\pi$-allylpalladium intermediate reacts with the aldehyde via the six-membered transition state $I$ to avoid steric repulsion between the aldehyde substituents and the Et group or
Scherme 5 Plausible reaction mechanism for Pd/Et$_2$Zn-promoted nucleophilic allylation of aldehyde and aldime with vinylcyclopropane

ligands on the Zn atom. Thus, homoallyl alcohols 1 are obtained with anti stereoselectivity. In contrast to the results obtained for aldehydes, aldimes undergo nucleophilic allylation through the intermediate II to avoid steric repulsion between substituents on the nitrogen atom and the Et group or the ligands on the zinc atom,
resulting predominantly in the selective formation of syn-isomer 3. An alternative structural feature associated with the six-membered allylzinc species which affects its interaction with aldehydes and aldimines is likely to rationalize the opposite stereoselectivity as well as the nucleophilic allylation of aldehydes and aldimines with allylmetal species.\textsuperscript{9}

In summary, the author have demonstrated the Pd-catalyzed nucleophilic allylation of aldehydes and aldimines with dimethyl 2-ethenylcyclopropane-1,1-dicarboxylate promoted by diethylzinc to form homoallyl alcohols and homoallylamines, respectively.\textsuperscript{10} Furthermore, these products were converted into γ-vinyl-δ-valerolactones and γ-vinyl-δ-valerolactams, accelerated by condensation with a tetratomic zinc cluster as a Lewis acid. This transformation is useful for efficient medicinal synthesis of physiologically active molecules such as hydroxy acids, amino acids, δ-valerolactones, and δ-valerolactams.
1.4 Experimental

**General experimental**  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. 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 spectrophotometer. High resolution mass spectra (HRMS) were measured with a JEOL JMS-DX303.

**Solvents and Reagents**

Tetrahydrofuran were dried and distilled from benzophenone and sodium immediately prior to use under nitrogen atmosphere. Pd(acac)\textsubscript{2}, PPh\textsubscript{3}, Et\textsubscript{2}Zn (1.0 M hexane solution), aniline, \textit{p}-chloroaniline, benzylamine, \textit{n}-hexylamine, 2-naphthylaldehyde were purchased and used without further purification. Benzaldehyde, \textit{p}-chlorobenzaldehyde, \textit{p}-tolualdehyde, \textit{c}-hexanecarbaldehyde, \textit{p}-methoxaldehyde were purchased and distilled prior to use. Oxo[hexa(trifluoroacetato)]tetrazinc trifluoroacetic acid adduct (STREM) was purchased and used without further purification. Vinylcyclopropane was prepared from dimethyl malonate and 1,4-dihalo-2-butene according to the literature.\textsuperscript{11}
General procedure for nucleophilic allylation of aldehyde with vinylcyclopropane (entry 1, Table 1): To a solution of Pd(acac)$_2$ (15.2 mg, 0.05 mmol), and triphenylphosphine (26.2 mg, 0.1 mmol) in dry THF (2 mL) were successively added vinylcyclopropane (221.0 mg, 1.2 mmol), benzaldehyde (106.1 mg, 1 mmol), and diethylzinc (2.4 mmol, 1.0 M hexane solution) via syringe under nitrogen atmosphere. The mixture was stirred at room temperature for 48 h. The mixture was diluted with 30 mL of EtOAc and washed with 2 N HCl, and then 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 = 2/1 v/v) to give 1a (210.5 mg, 72%, $R_f$ = 0.63; hexane/EtOAc = 2/1 v/v) and 2a (54.8 mg, 21%, $R_f$ = 0.5; hexane/EtOAc = 2/1 v/v).

**Dimethyl 2-[2-(hydroxyphenylmethyl)but-3-en-1-yl]malonate (1a):** IR (neat) 3524 (br), 3064 (m), 3030 (m), 1750 (s), 1732 (s), 1640 (m), 765 (m) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.80 (ddd, $J$ = 14.3, 11.8, 5.0 Hz, 1 H), 1.94 (ddd, $J$ = 14.3, 10.0, 3.7 Hz, 1 H), 2.11 (d, $J$ = 2.5 Hz, 1 H), 2.38 (dddd, $J$ = 11.8, 9.3, 7.1, 3.7 Hz, 1 H), 3.38 (dd, $J$ = 10.0, 5.0 Hz, 1 H), 3.67 (s, 6 H), 4.50 (d, $J$ = 7.1 Hz, 1 H), 5.13 (dd, $J$ = 17.5, 1.7 Hz, 1 H), 5.26 (dd, $J$ = 10.2, 1.7 Hz, 1 H), 5.63 (dd, $J$ = 17.5, 10.2, 9.3 Hz, 1 H), 7.27-7.34 (m, 5 H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 29.7, 30.9, 49.6, 50.3, 52.4, 52.5, 120.0, 126.8, 127.9, 128.4, 137.2, 141.7, 169.4, 169.9; High-resolution MS, calcd for C$_{16}$H$_{20}$O$_5$: 292.1311, Found :m/z 292.1311 (M$^+$).

**Dimethyl 2-[2-[(4-chlorophenyl)(hydroxy)methyl]but-3-enyl]malonate (1b):** IR (neat) 3510, 1750, 1732, 1491, 1437, 1244, 1090, 923, 833, 756 cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.79 (ddd, $J$ = 14.0, 11.0, 4.8 Hz, 1 H), 1.94 (ddd, $J$ = 14.0, 10.0, 3.7
Hz, 1 H), 2.14 (d, J = 2.7 Hz, 1H), 2.33 (dddd, J = 11.0, 9.5, 6.6, 3.7 Hz, 1 H), 3.38 (dd, J = 10.0, 4.8 Hz, 1 H), 3.68 (s, 6 H), 4.50 (dd, J = 6.6, 2.7 Hz 1 H), 5.11 (dd, J = 17.3, 1.3 Hz, 1 H), 5.26 (dd, J = 10.1, 1.3 Hz, 1 H), 5.60 (dddd, J = 17.3, 10.1, 9.5 Hz, 1 H), 7.24 (d, J = 8.1 Hz, 2 H), 7.31 (d, J = 8.1 Hz, 2 H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 29.5, 49.5, 50.3, 52.4, 52.5, 75.8, 120.4, 128.2, 128.5, 133.5, 136.7, 140.3, 169.5, 169.9; High-resolution MS, calcd for C$_{16}$H$_{19}$ClO$_5$: 326.0921. Found: m/z 327.0942 (M$^+$+H), 326.0915 (M$^+$).

**Dimethyl 2-{2-[hydroxy($p$-tolyl)methyl]but-3-enyl}malonate (1c):** IR (neat) 3530 (br), 3000 (m), 1750 (s), 1732 (s), 1514 (m), 1434 (m), 1050 (m), 921 (m), 819 (m) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) δ 1.77 (ddd, J = 13.8, 11.0, 4.9 Hz, 1 H), 1.93 (ddd, J = 13.8, 10.0, 3.7 Hz, 1 H), 2.19 (br, 1 H), 2.30-2.39 (m, 4 H), 3.38 (ddd, J = 10.0, 4.9 Hz, 1 H), 3.67 (s, 6 H), 4.45 (d, J = 7.1 Hz, 1 H), 5.14 (ddd, J = 17.2, 1.7 Hz, 1 H), 5.26 (ddd, J = 10.1, 1.7 Hz, 1 H), 5.63 (ddd, J = 17.2, 10.1, 10.0 Hz, 1 H), 7.13 (ddd, J = 8.1 Hz, 2 H), 7.18 (dd, J = 8.1 Hz, 2 H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 21.0, 29.6, 49.6, 52.3, 52.4, 76.4, 119.8, 126.8, 129.1, 137.4, 137.6, 138.8, 169.5, 170.0; High-resolution MS, calcd for C$_{17}$H$_{22}$O$_5$: 306.1467. Found m/z (relative intensity): 307.1519 (M$^+$+H), 306.1470 (M$^+$).

**Dimethyl 2-{2-[hydroxy(naphthalen-7-yl)methyl]but-3-enyl}malonate (1d):** IR (neat) 3447 (br), 3070 (w), 1717 (s), 1638 (m), 1508 (m), 1435 (s), 1159 (m), 860 (s), 824 (s), 760 (s) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) δ 1.85 (ddd, J = 13.9, 10.9, 4.9 Hz, 1 H), 1.97 (ddd, J = 13.9, 10.0, 3.7 Hz, 1 H), 2.49 (ddddd, J = 10.9, 9.3, 7.1, 3.7 Hz, 1 H), 3.39 (dd, J = 10.0, 4.9 Hz, 1 H), 3.63 (s, 3 H), 3.64 (s, 3 H), 4.66 (d, J = 7.1 Hz, 1 H), 5.13 (dd, J = 17.3, 1.5 Hz, 1 H), 5.24 (dd, J = 10.2, 1.5 Hz, 1 H), 5.66 (ddd, J = 17.3,
10.2, 9.3 Hz, 1 H), 7.42-7.48 (m, 3 H), 7.74 (s, 1 H), 7.80-7.83 (m, 3 H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 29.7, 49.6, 50.1, 52.3, 52.4, 76.7, 120.1, 120.2, 124.5, 126.0, 126.1, 126.2, 127.7, 128.0, 128.3, 133.2, 137.1, 139.2, 169.5, 170.0; High-resolution MS, calcd for C$_{20}$H$_{22}$O$_5$: 342.1467. Found: m/z 342.1454 (M$^+$).

**Dimethyl 2-{2-[(dihydrocinnam)(hydroxy)methyl]but-3-enyl}malonate (1e):** IR (neat) 3026 (m), 1734 (s), 1437 (m), 1198 (m), 1159 (m), 1005 (m), 924 (m), 750 (m) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.59 (d, $J$ = 4.6 Hz, 1 H), 1.68-1.85 (m, 2 H), 1.92 (ddd, $J$ = 13.5, 10.6, 4.6 Hz, 1 H), 2.08 (ddddd, $J$ = 10.6, 9.3, 8.5, 3.9 Hz, 1 H), 2.15 (ddd, $J$ = 13.5, 10.0, 3.9 Hz, 1 H), 2.65 (ddd, $J$ = 13.7, 9.6, 6.7 Hz, 1 H), 2.80 (ddd, $J$ = 13.7, 9.8, 5.6 Hz, 1 H), 3.42 (dd, $J$ = 10.0, 4.6 Hz, 1 H), 3.53 (td, $J$ = 8.5, 4.6 Hz, 1 H), 3.70 (s, 3 H), 3.73 (s, 3 H), 5.10 (dd, $J$ = 17.3, 1.7 Hz, 1 H), 5.23 (dd, $J$ = 10.2, 1.7 Hz, 1 H), 5.63 (ddd, $J$ = 17.3, 10.2, 9.3 Hz, 1 H), 7.16-7.29 (m, 5 H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 30.1, 32.0, 36.5, 48.4, 49.6, 52.4, 52.5, 72.8, 119.3, 125.7, 128.2, 128.3, 136.4, 141.8, 169.5, 169.7; High-resolution MS, calcd for C$_{18}$H$_{24}$O$_5$: 320.1624. Found: m/z 321.1707 (M$^+$+H), 320.1633 (M$^+$).

**Dimethyl 2-{2-[(cyclohexyl)(hydroxy)methyl]but-3-enyl}malonate (1f):** IR (neat) 2926 (s), 2853 (m), 1736 (s), 1437 (m), 1240 (m), 1198 (m), 1159 (m), 920 (m) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 0.96-1.27 (m, 6 H), 1.34-1.43 (m, 1 H), 1.55-1.80 (m, 4 H), 1.82-1.90 (m, 1 H), 1.95 (ddd, $J$ = 13.9, 10.7, 5.0 Hz, 1 H), 2.11 (ddd, $J$ = 13.9, 10.0, 4.4 Hz, 1 H), 2.24 (tt, $J$ = 9.5, 4.4 Hz, 1 H), 3.20 (dd, $J$ = 11.5, 6.6 Hz, 1 H), 3.44 (dd, $J$ = 10.0, 5.0 Hz, 1 H), 3.71 (s, 3 H), 3.74 (s, 3 H), 5.07 (dd, $J$ = 17.3, 1.4 Hz, 1 H), 5.22 (dd, $J$ = 10.1, 1.4 Hz, 1 H), 5.66 (ddd, $J$ = 17.3, 10.1, 9.5 Hz, 1 H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 26.0, 26.2, 26.4, 27.7, 29.4, 30.6, 30.9, 40.6, 44.8, 49.6, 52.5, 77.7, 118.9,
Methyl tetrahydro-2-oxo-6-phenyl-5-vinyl-2H-pyran-3-carboxylate (2a): IR (neat) 3035 (w), 2954 (m), 1732 (s), 1643 (m), 1263 (m), 1070 (m), 1002 (m), 925 (m), 702 (s) cm⁻¹; ¹H-NMR (400 MHz, CDCl₃, one isomer) δ 2.15 (ddd, J = 13.9, 9.8, 7.3 Hz, 1 H), 2.44 (ddd, J = 13.9, 11.3, 5.9 Hz, 1 H), 2.80-2.89 (m, 1 H), 3.80 (dd, J = 7.3, 5.9 Hz, 1 H), 3.83 (s, 3 H), 4.99 (d, J = 17.2 Hz, 1 H), 5.08 (d, J = 10.5 Hz, 1 H), 5.09 (d, J = 3.7 Hz, 1 H), 5.56 (ddd, J = 17.2, 10.5, 7.0 Hz, 1 H) 7.26-7.36 (m, 5 H); ¹H-NMR (400 MHz, CDCl₃, the other isomer) δ 2.23-2.29 (m, 1 H), 2.33 (td, J = 13.0, 5.1 Hz, 1 H), 3.72 (dd, J = 7.7, 5.1 Hz, 1 H), 3.82 (s, 3 H), 4.97 (d, J = 17.1 Hz, 1 H), 5.06 (d, J = 3.2 Hz, 1 H), 5.07 (d, J = 10.1 Hz, 1 H), 5.51 (ddd, J = 17.1, 10.1, 7.0 Hz, 1 H), 7.26-7.36 (m, 5 H); ¹³C-NMR (100 MHz, CDCl₃, one isomer) δ 28.2, 41.7, 45.8, 52.9, 86.4, 118.1, 127.1, 128.3, 128.7, 134.9, 137.6, 166.2, 169.7; ¹³C-NMR (100 MHz, CDCl₃, the other isomer) δ 29.4, 43.6 (2C), 47.8, 86.4, 118.3, 127.1, 128.7, 135.1, 137.5, 166.7, 169.3; High-resolution MS, calcd for C₁₅H₁₆O₄: 260.1049. Found m/z: 260.1047 (M⁺).

Methyl 6-(4-chlorophenyl)-tetrahydro-2-oxo-5-vinyl-2H-pyran-3-carboxylate (2b): IR (neat) 1750 (s), 1722 (s), 1495 (m), 1367 (m), 1222 (m), 1167 (m), 1015 (m), 923 (m), 825 (m), 692 (s) cm⁻¹; ¹H-NMR (400 MHz, CDCl₃, one isomer) δ 2.16 (ddd, J = 14.1, 10.2, 7.3 Hz, 1 H), 2.43 (ddd, J = 14.1, 11.1, 5.6 Hz, 1 H), 2.75-2.83 (m, 1 H), 3.79 (dd, J = 7.2, 5.6 Hz, 1 H), 3.84 (s, 3 H), 4.99 (d, J = 17.3 Hz, 1 H), 5.09 (d, J = 10.2 Hz, 2 H), 5.53 (ddd, J = 17.3, 10.2, 7.3 Hz, 1 H), 7.24 (dd, J = 8.5, 2.0 Hz, 2 H), 7.34 (dd, J = 8.5, 2.0 Hz, 2 H); ¹H-NMR (400 MHz, CDCl₃, the other isomer) δ 2.11-2.20 (m, 1 H), 2.33 (td, J = 12.4, 5.4 Hz, 1 H), 2.57-2.67 (m, 1 H), 3.68 (dd, J = 7.3,
5.4 Hz, 1 H), 3.83 (s, 3 H), 4.97 (d, J = 17.1 Hz, 1 H), 5.05 (d, J = 10.5 Hz, 2 H), 5.51 (ddd, J = 17.1, 10.5, 7.3 Hz, 1 H), 7.21-7.36 (m, 4 H); $^{13}$C-NMR (100 MHz, CDCl$_3$, one isomer) $\delta$ 28.3, 41.8, 45.8, 53.0, 85.1, 118.7, 128.4, 128.6, 134.4, 135.7, 165.8, 169.1; $^{13}$C-NMR (100 MHz, CDCl$_3$, the other isomer) $\delta$ 29.5, 43.9 (2C), 47.7, 85.5, 118.7, 128.5, 128.7, 134.6, 136.0, 166.2, 169.2; High-resolution MS, calcd for C$_{15}$H$_{15}$ClO$_4$: 294.0659. Found: m/z 294.0658 (M$^+$).

Methyl tetrahydro-2-oxo-6-p-tolyl-5-vinyl-2$H$-pyran-3-carboxylate (2c): IR (neat) 3010 (m), 1750 (s), 1732 (s), 1643 (m), 1165 (s), 1030 (s), 925 (s) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$, one isomer) $\delta$ 2.14 (ddd, J = 13.9, 9.8, 7.3 Hz, 1 H), 2.34 (s, 3 H), 2.44 (ddd, J = 13.9, 11.5, 5.9 Hz, 1 H), 2.80-2.88 (m, 1 H), 3.78 (dd, J = 7.3, 5.9 Hz, 1 H), 3.83 (s, 3 H), 5.00 (d, J = 17.2 Hz, 1 H), 5.06 (d, J = 3.2 Hz, 1 H), 5.07 (d, J = 10.4 Hz, 1 H), 5.55 (ddd, J = 17.2, 10.4, 6.8 Hz, 1 H), 7.16-7.28 (m, 4 H); $^1$H-NMR (400 MHz, CDCl$_3$, the other isomer) $\delta$ 2.09-2.18 (m, 1 H), 2.34 (s, 3 H), 2.31-2.73 (m, 2 H), 3.72 (dd, J = 10.1, 7.7 Hz, 1 H), 3.82 (s, 3 H), 4.98 (d, J = 17.5 Hz, 1 H), 5.03 (d, J = 3.2 Hz, 1 H), 5.04 (d, J = 10.4 Hz, 1 H), 5.51 (ddd, J = 17.5, 10.4, 7.3 Hz, 1 H), 7.16-7.28 (m, 4 H); $^{13}$C-NMR (100 MHz, CDCl$_3$, one isomer) $\delta$ 21.2, 28.2, 41.5, 45.8, 52.9, 85.8, 118.1, 127.1, 129.0, 134.2, 135.0, 138.5, 166.1, 169.3; $^{13}$C-NMR (100 MHz, CDCl$_3$, the other isomer) $\delta$ 21.2, 29.4, 43.4, 47.8, 52.9 86.4, 118.1, 127.1, 129.1, 134.5, 135.2, 138.6, 166.6, 169.3; High-resolution MS, calcd for C$_{16}$H$_{18}$O$_4$: 274.1205. Found: m/z 275.1263(M$^+$+H), 274.1206 (M$^+$).

Methyl tetrahydro-6-(naphthalen-3-yl)-2-oxo-5-vinyl-2$H$-pyran-3-carboxylate (2d): IR (neat) 3059 (w), 1732 (s), 1641 (m), 1508 (m), 1437 (m), 1165 (m), 860 (s), 822 (s), 737 (s) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$, one isomer) $\delta$ 2.18 (ddd, J = 14.1, 10.0, 7.3
Hz, 1 H), 2.46 (ddd, J = 14.1, 11.2, 5.9 Hz, 1 H), 2.90-2.98 (m, 1 H), 3.66 (dd, J = 7.3, 5.9 Hz, 1 H), 3.85 (s, 3 H), 4.97 (dt, J = 17.3, 0.98 Hz, 1 H), 5.04 (dt, J = 10.5, 0.98 Hz, 1 H), 5.25 (d, J = 5.9 Hz, 1 H), 5.57 (ddd, J = 17.3, 10.5, 7.1 Hz, 1 H), 7.43 (dd, J = 8.5, 1.7 Hz, 1 H), 7.49 (dd, J = 6.3, 3.2 Hz, 2 H) 7.73 (dd, J = 6.6, 3.2 Hz, 1 H), 7.81-7.85 (m, 3 H); "H-NMR (400 MHz, CDCl 3, the other isomer) δ 2.15-2.22 (m, 1 H), 2.32-2.50 (m, 1H), 2.75-2.84 (m, 1 H), 3.76-3.80 (m, 1 H), 3.84 (s, 3 H), 4.95 (dt, J = 17.2, 0.98 Hz, 1 H), 5.00 (dt, J = 10.7, 0.98 Hz, 1 H), 5.22 (d, J = 5.1 Hz, 1 H), 5.53 (ddd, J = 17.2, 10.7, 7.1 Hz, 1 H), 7.39 (dd, J = 8.5, 2.0 Hz, 1 H), 7.49-7.86 (m, 6H); 13C-NMR (100 MHz, CDCl3, one isomer) δ 29.5, 43.5, 47.8, 52.9, 86.0, 118.3, 124.1, 126.3, 126.4, 127.0, 127.6, 128.1, 128.4, 132.7, 133.3, 134.7, 135.0, 166.6, 169.2; 13C-NMR (100 MHz, CDCl3, the other isomer) δ 28.0, 41.6, 45.8, 52.9, 86.6, 118.2, 124.1, 126.3, 126.4, 126.7, 128.1, 128.5, 133.3, 134.5, 134.8, 135.0, 166.1, 169.3; High-resolution MS, calcd for C19H18O4: 310.1205. Found: m/z 311.1238 (M^++H), 310.1205 (M^+).

Methyl tetrahydro-2-oxo-6-phenethyl-5-vinyl-2H-pyran-3-carboxylate (2e): IR (neat) 3026 (w), 2950 (m), 1732 (s), 1456 (m), 1435 (m), 1196 (m), 928 (m), 752 (m), 702 (m) cm⁻¹; 1H-NMR (400 MHz, CDCl3, major isomer) δ 1.80-2.09 (m, 2 H), 2.35 (dt, J = 14.1, 6.3 Hz, 1 H), 2.52 (dt, J = 14.1, 8.8 Hz, 1 H), 2.65-2.75 (m, 2 H), 2.86-2.97 (m, 1 H), 3.57 (t, J = 8.8 Hz, 1 H), 3.77 (s, 3 H), 4.06-4.16 (m, 1 H), 5.17 (d, J = 17.1 Hz, 1 H), 5.19 (d, J = 10.0 Hz, 1 H), 5.56 (ddd, J = 17.1, 10.0, 8.4 Hz, 1 H), 7.16-7.29 (m, 5 H); 1H-NMR (400 MHz, CDCl3, minor isomer) δ1.80-2.09 (m, 2 H), 2.35 (dt, J = 14.1, 6.3 Hz, 1 H), 2.52 (dt, J = 14.1, 8.8 Hz, 1 H), 2.65-2.75 (m, 2 H), 2.86-2.97 (m, 1 H), 3.63 (t, J = 7.1 Hz, 1 H), 3.79 (s, 3 H), 4.06-4.16 (m, 1 H), 5.17 (d, J = 17.1 Hz, 1 H), 5.19 (d, J = 10.0 Hz, 1 H), 5.56 (ddd, J = 17.1, 10.0, 8.4 Hz, 1 H), 7.16-7.29 (m, 5 H);
$^{13}$C-NMR (100 MHz, CDCl$_3$, major isomer) $\delta$ 28.7, 30.5, 30.6, 35.2, 40.6, 45.5, 52.8, 82.1, 118.3, 125.9, 128.4, 128.4, 135.8, 140.9, 166.4, 169.1; $^{13}$C-NMR (100 MHz, CDCl$_3$, minor isomer) $\delta$ 29.8, 30.6, 30.8, 35.3, 42.7, 47.6, 52.8, 82.6, 118.5, 128.4, 128.5, 136.0, 140.9, 167.3, 169.1; High-resolution MS, calcd for C$_{17}$H$_{20}$O$_4$: 288.1362. Found: m/z 288.1343 (M$^+$).

**Methyl 6-cyclohexyl-tetrahydro-2-oxo-5-vinyl-2H-pyran-3-carboxylate (2f):** IR (neat) 2928 (s), 2855 (m), 1732 (s), 1456 (m), 1434 (m), 1362 (m), 1195 (m), 1164 (m) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$, one isomer) $\delta$ 1.14-1.29 (m, 3 H), 1.49-1.78 (m, 7 H), 1.97 (ddd, $J = 14.0$, 9.5, 7.5 Hz, 1 H), 2.09-2.23 (m, 1 H), 2.31 (dt, $J = 13.9$, 6.1 Hz, 1 H), 2.40-2.58 (m, 1 H), 3.52 (t, $J = 8.9$ Hz, 1 H), 3.78 (s, 3 H), 4.04 (d, $J = 10.5$ Hz, 1 H), 5.20 (d, $J = 17.1$ Hz, 1 H), 5.26 (d, $J = 9.3$ Hz, 1 H), 5.82 (ddddd, $J = 17.1$, 12.7, 10.1, 9.1 Hz, 1 H); $^1$H-NMR (400 MHz, CDCl$_3$, the other isomer) $\delta$ 1.14-1.29 (m, 3 H), 1.49-1.78 (m, 7 H), 1.97-2.23 (m, 3 H), 2.66-2.83 (m, 1 H), 3.62 (t, $J = 7.1$ Hz, 1 H), 3.79 (s, 3 H), 3.97 (dd, $J = 9.9$, 2.3 Hz, 1 H), 5.19 (d, $J = 16.8$ Hz, 1 H), 5.21 (d, $J = 11.9$ Hz, 1 H), 5.62 (ddd, $J = 17.9$, 9.8, 8.1 Hz, 1 H); $^{13}$C-NMR (100 MHz, CDCl$_3$, one isomer) $\delta$ 24.5, 26.0, 26.1, 26.4, 28.8, 30.0, 30.2, 39.5, 47.7, 52.8, 87.3, 118.0, 136.1, 166.7, 169.3; $^{13}$C-NMR (100 MHz, CDCl$_3$, the other isomer) $\delta$ 24.9, 25.3, 26.0, 26.1, 26.4, 29.8, 37.1, 39.4, 45.5, 52.7, 87.9, 117.8, 136.4, 167.5, 169.3; High-resolution MS, calcd for C$_{15}$H$_{22}$O$_4$: 266.1518. Found: m/z 266.1497 (M$^+$).

**Methyl 6-tert-butyl-tetrahydro-2-oxo-5-vinyl-2H-pyran-3-carboxylate: (2g):** IR (neat) 2925 (s), 2910(m), 2875(m), 1737(s), 1456(m), 1435(m), 1364(m), 1165 (m), 1076(s) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$, one isomer) $\delta$ 1.00 (s, 9H), 2.03 (ddd, $J = 10.4$, 7.6, 3.1 Hz, 1H), 2.87-2.93 (m, 1H), 3.60-3.75 (m, 1H), 3.79 (s, 3H), 4.08 (d, $J =
2.1 Hz, 1H), 5.08-5.25 (m, 2H), 5.96 (ddd, J = 17.1, 9.6, 9.6 Hz, 1H); $^1$H-NMR (400 MHz, CDCl$_3$, the other isomer) $\delta$1.02(s, 9H), 2.07 (ddd, $J = 8.1, 6.7, 3.2$ Hz, 1H), 2.87-2.93 (m, 1H), 3.60-3.75 (m, 1H), 3.81 (s, 3H), 3.89 (d, $J = 2.1$ Hz, 1H), 5.08-5.25 (m, 2H), 5.93 (ddd, $J = 16.9, 9.7, 9.7$ Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$, one isomer) $\delta$ 26.18, 33.4, 38.2, 44.5, 52.7, 89.6, 116.2, 137.2, 169.2, 170.1; $^{13}$C-NMR (100 MHz, CDCl$_3$, the other isomer) $\delta$ 26.2, 26.5, 29.7, 34.7, 38.4, 44.9, 52.9, 87.5, 117.8, 135.0, 167.1, 169.4; High-resolution MS, calcd for C$_{13}$H$_{20}$O$_4$: 240.1362. Found: m/z 240.1365 (M$^+$).

**General procedure for nucleophilic allylation of aldimine with vinylcyclopropane**

(entry 1, Table 2): A solution of benzaldehyde (106.1 mg, 1 mmol) and $p$-anisidine (129.3 mg, 1.05 mmol) in dry THF (1 mL) was refluxed for 30 min under nitrogen. The solvent was removed by distillation under atmospheric pressure of nitrogen (azeotropic removal of water). The azeotropic distillation of THF (1 mL)/water was repeated two times. A mixture of Pd(acac)$_2$ (15.2 mg, 0.05 mmol) and triphenylphosphine (26.2 mg, 0.1 mmol) in dry THF (2 mL) and vinylcyclopropane (221.0 mg, 1.2 mmol) dissolved in THF (1 mL) and diethylzinc (2.4 mmol, 1.0 M hexane solution) were successively added to the aldimine residue. The mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with 30 mL of EtOAc and washed with sat. NaHCO$_3$, and brine. The organic phase was dried (MgSO$_4$) and concentrated in vacuo to give a brown oil, which was subjected to column chromatography over silica gel (hexane/EtOAc = 70/30 v/v) to give 3a (167 mg, 42%, R$_{f}$ = 0.5; hexane/ethyl acetate = 2/1v/v) and 4a (172 mg, 47%, R$_{f}$ = 0.27; hexane/EtOAc = 2/1 v/v).
Dimethyl 2-[(p-methoxyphenylamino)phenylmethyl-but-3-en-1-yl]malonate (3a):
IR (neat) 3404 (m), 3001 (m), 2933 (m), 1750 (s), 1601 (s), 1435 (s),
1159 (br), 1038 (s), 925 (m), 704 (s) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$, major isomer) δ
1.69 (ddd, $J = 13.7$, 11.3, 4.4 Hz, 1 H), 2.32 (ddd, $J = 13.7$, 10.5, 2.9 Hz, 1 H),
2.42-2.49 (m, 1 H), 3.37 (dd, $J = 10.5$, 4.4 Hz, 1 H), 3.67 (s, 6 H), 3.72 (s, 3 H), 4.30 (d, $J = 5.1$ Hz, 1 H), 5.09 (ddd, $J = 17.1$, 1.5 Hz, 1 H), 5.17 (dd, $J = 10.2$, 1.5 Hz, 1 H), 5.46 (ddd, $J = 17.1$, 10.2, 9.8 Hz, 1 H), 6.45 (d, $J = 8.9$ Hz, 2 H), 6.65 (d, $J = 8.9$ Hz, 2 H),
7.18-7.31 (m, 5 H); $^1$H-NMR (400 MHz, CDCl$_3$, minor isomer) δ 1.69 (ddd, $J = 13.7$,
11.3, 4.4 Hz, 1 H), 2.32 (ddd, $J = 13.7$, 10.5, 2.9 Hz, 1 H), 2.42-2.49 (m, 1 H), 3.37 (dd, $J = 10.5$, 4.4 Hz, 1 H), 3.67 (s, 6 H), 3.68 (s, 3H), 4.30 (d, $J = 5.1$ Hz, 1 H), 5.09 (dd, $J = 17.1$, 1.5 Hz, 1 H), 5.26 (dd, $J = 10.2$, 1.5 Hz, 1 H), 5.46 (ddd, $J = 17.1$, 10.2, 9.8 Hz, 1 H), 6.45 (d, $J = 8.9$ Hz, 2 H), 6.65 (d, $J = 8.9$ Hz, 2 H), 7.18-7.31 (m, 5 H); $^{13}$C-NMR
(100 MHz, CDCl$_3$, major isomer) δ 30.9, 48.5, 49.6, 52.5, 55.7, 60.3, 114.6 (2C), 114.7
(2C), 119.1, 127.1, 127.6 (2C), 128.1 (2C), 136.6, 137.4, 140.2, 151.9, 169.4, 169.6;
$^{13}$C-NMR (100 MHz, CDCl$_3$, minor isomer) δ 30.9, 49.7, 52.4, 55.7, 61.7, 114.6, 114.7
(2C), 119.1, 127.1, 127.3, 128.3, 128.4, 136.6, 137.4, 140.2, 151.9, 169.4, 169.6
High-resolution MS, calcd for C$_{23}$H$_{27}$NO$_5$: 397.1889. Found: m/z 397.1899 (M$^+$).

Dimethyl 2-[[2-phenylamino(phenyl)methyl-but-3-en-1-yl]malonate (3b): IR (neat)
3406 (m), 3026 (m), 2953 (m), 2849 (m), 1732 (s), 1601 (s), 1435 (s), 1155 (m), 750
(m), 694 (m) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$, major isomer) δ 1.69 (ddd, $J = 15.6$,
11.3, 4.4 Hz, 1 H), 2.33 (ddd, $J = 13.7$, 10.5, 3.0 Hz, 1 H), 2.38-2.49 (m, 1 H), 3.37 (dd, $J = 10.5$, 4.4 Hz, 1 H), 3.66 (s, 3 H), 3.71 (s, 3 H), 4.31-4.40 (brs, 2 H), 5.08 (dd, $J = 17.1$, 1.7 Hz, 1 H), 5.17 (dd, $J = 10.1$, 1.7 Hz, 1 H), 5.46 (ddd, $J = 17.1$, 10.1, 9.8 Hz, 1 H), 6.48 (d, $J = 8.5$ Hz, 2 H), 6.59 (t, $J = 7.3$ Hz, 1 H), 7.04 (dd, $J = 8.5$, 7.3 Hz, 2 H).
7.17-7.35 (m, 5 H); $^1$H-NMR (400 MHz, CDCl$_3$, minor isomer) $\delta$ 1.84 (ddd, $J = 15.6$, 10.5, 4.9 Hz, 1 H), 2.09 (ddd, $J = 13.9$, 10.0, 3.9 Hz, 1 H), 2.38-2.49 (m, 1 H), 3.39 (ddd, $J = 10.0$, 4.9 Hz, 1 H), 3.63 (s, 3 H), 3.67 (s, 3 H), 4.20 (d, $J = 6.6$ Hz, 1 H), 5.15 (d, $J = 17.1$ Hz, 1 H), 5.25 (d, $J = 10.2$ Hz, 1 H), 5.58 (ddd, $J = 17.1$, 10.2, 8.8 Hz, 1 H), 6.48 (d, $J = 8.5$ Hz, 2 H), 6.59 (t, $J = 7.3$ Hz, 1 H), 7.04 (dd, $J = 8.5$, 7.3 Hz, 2 H), 7.17-7.35 (m, 5 H); $^{13}$C-NMR (100 MHz, CDCl$_3$, major isomer) $\delta$ 30.6, 48.5, 49.6, 52.5 (2C), 60.7, 113.2, 117.2, 119.2, 127.1, 127.5, 128.1, 128.9, 136.5, 140.1, 146.6, 169.4, 169.5; $^{13}$C-NMR (100 MHz, CDCl$_3$, minor isomer) $\delta$ 29.7, 49.1, 49.7, 52.3 (2C), 61.1, 113.3, 117.3, 119.0, 127.1, 127.2, 128.3, 128.9, 137.3, 141.4, 147.0, 169.2, 169.6. High-resolution MS, calcd for C$_{22}$H$_{25}$NO$_4$: 367.1784. Found: $m/z$ 368.1882 (M$^+$$+$H), 367.1789 (M$^+$).

**Dimethyl 2-[2-(4-chlorophenylamino)(phenyl)methyl-but-3-en-1-yl]malonate (3c):**

IR (neat) 3400 (m), 3028 (m), 2951 (m), 1749 (m), 1732 (s), 1601 (m), 1506 (m), 1456 (m), 1159 (m), 817 (m), 704 (m) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$, major isomer) $\delta$ 1.82 (ddd, $J = 14.0$, 10.2, 4.4 Hz, 1 H), 2.08 (ddd, $J = 14.0$, 10.3, 4.0 Hz, 1 H), 2.38-2.47 (m, 1 H), 3.37 (dd, $J = 10.7$, 4.2 Hz, 1 H), 3.65 (s, 3 H), 3.69 (s, 3 H), 4.15 (d, $J = 6.8$ Hz, 1 H), 4.35 (br s, 1 H), 5.16 (dd, $J = 17.3$, 1.5 Hz, 1 H), 5.27 (dd, $J = 10.3$, 1.5 Hz, 1 H), 5.57 (ddd, $J = 17.3$, 10.3, 9.0 Hz, 1 H), 6.39 (d, $J = 8.9$ Hz, 2 H), 6.98 (d, $J = 8.9$ Hz, 2 H), 7.19-7.33 (m, 5 H); $^1$H-NMR (400 MHz, CDCl$_3$, minor isomer) $\delta$ 1.67 (ddd, $J = 13.8$, 9.2, 4.2 Hz, 1 H), 2.33 (ddd, $J = 13.8$, 10.7, 3.0 Hz, 1 H), 2.38-2.47 (m, 1 H), 3.37 (dd, $J = 10.7$, 4.2 Hz, 1 H), 3.68 (s, 3 H), 3.70 (d, $J = 6.1$ Hz, 1 H), 3.73 (s, 3 H), 4.35 (br s, 1 H), 5.08 (dd, $J = 17.1$, 1.5 Hz, 1 H), 5.18 (dd, $J = 10.1$, 1.5 Hz, 1 H), 5.44 (ddd, $J = 17.1$, 10.1, 9.9 Hz, 1 H), 6.39 (d, $J = 8.9$ Hz, 2 H), 6.98 (d, $J = 8.9$ Hz, 2 H), 7.19-7.33 (m, 5 H); $^{13}$C-NMR (100 MHz, CDCl$_3$, major isomer) $\delta$ 30.6, 48.4, 49.5,
52.5 (2C), 60.8, 114.3, 119.4, 121.8, 127.1, 127.5, 128.2, 128.7, 136.3, 139.6, 145.1, 169.4, 169.5; \( ^{13} \)C-NMR (100 MHz, CDCl\(_3\), minor isomer) \( \delta \) 29.6, 49.0, 49.6, 52.4, 56.8, 61.2, 114.4, 119.2, 122.0, 127.2, 127.3, 128.4, 128.7, 137.2, 140.8, 145.5, 169.2, 169.5. High-resolution MS, calcd for C\(_{22}\)H\(_{24}\)ClNO\(_4\): 401.1394. Found: \( m/z \) 401.1376 (M\(^+\)).

**Dimethyl**

2-[2-(4-methoxyphenylamino)(4-chlorophenyl)methyl-but-3-en-1-yl]malonate (3f):

IR (neat) 3398 (m), 3014 (m), 2951 (m), 2931 (m), 1716 (s), 1508 (m), 1435 (m), 1157 (s), 818 (m) cm\(^{-1}\); \( ^{1} \)H-NMR (400 MHz, CDCl\(_3\), major isomer) \( \delta \) 1.67 (ddd, \( J = 13.7, 11.7, 4.2 \) Hz, 1 H), 2.31 (ddd, \( J = 13.7, 10.5, 2.9 \) Hz, 1 H), 2.37-2.45 (m, 1 H), 3.38 (dd, \( J = 10.5, 4.2 \) Hz, 1 H), 3.68 (s, 3 H), 3.69 (s, 3 H), 3.74 (s, 3 H), 3.98-4.15 (brs, 1 H), 4.26 (d, \( J = 5.4 \) Hz, 1 H), 5.10 (dd, \( J = 17.1, 1.6 \) Hz, 1 H), 5.19 (dd, \( J = 10.1, 1.6 \) Hz, 1 H), 5.42 (ddd, \( J = 17.1, 10.1, 9.8 \) Hz, 1 H), 6.41 (d, \( J = 8.9 \) Hz, 2 H), 6.66 (d, \( J = 8.9 \) Hz, 2 H), 7.19 (d, \( J = 8.5 \) Hz, 2 H), 7.26 (d, \( J = 8.5 \) Hz, 2 H); \( ^{1} \)H-NMR (400 MHz, CDCl\(_3\), minor isomer) \( \delta \) 1.81 (ddd, \( J = 13.9, 11.0, 4.7 \) Hz, 1 H), 2.05 (ddd, \( J = 13.9, 10.0, 3.7 \) Hz, 1 H), 2.37-2.45 (m, 1 H), 3.39 (dd, \( J = 10.0, 4.7 \) Hz, 1 H), 3.66 (s, 3 H), 3.68 (s, 3 H), 3.69 (s, 3 H), 4.10 (d, 1 H), 5.10 (dd, \( J = 17.1, 1.6 \) Hz, 1 H), 5.28 (d, \( J = 10.3 \) Hz, 1 H), 5.56 (ddd, \( J = 17.1, 10.3, 9.0 \) Hz, 1 H), 6.40 (d, \( J = 9.2 \) Hz, 2 H), 6.65 (d, \( J = 9.2 \) Hz, 2 H), 7.19 (d, \( J = 8.5 \) Hz, 2 H), 7.26 (d, \( J = 8.5 \) Hz, 2 H); \( ^{13} \)C-NMR (100 MHz, CDCl\(_3\), major isomer) \( \delta \) 30.6, 48.5, 49.5, 52.5 (2C), 55.7, 61.1, 114.5, 114.7, 119.4, 128.3, 128.9, 132.7, 136.2, 139.1, 140.5, 151.9, 169.3, 169.5; \( ^{13} \)C-NMR (100 MHz, CDCl\(_3\), minor isomer) \( \delta \) 29.7, 49.2, 49.6, 52.4, 52.5, 55.7, 61.5, 114.4, 114.6, 128.5, 128.7, 128.8, 132.7, 137.1, 140.3, 141.0, 152.1, 169.1, 169.5. High-resolution MS, calcd for C\(_{23}\)H\(_{26}\)ClNO\(_5\): 431.1500. Found: \( m/z \) 431.1450 (M\(^+\)).
**Dimethyl 2-[3-(4-methoxyphenylamino)-2-vinloctyl]malonate (3g):** IR (neat) 3384 (w), 2955 (m), 2851 (w), 1732 (s), 1514 (s), 1437 (m), 1238 (s), 1040 (m), 820 (m) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 0.86 (t, $J = 6.7$ Hz, 3 H), 1.22-1.32 (m, 6 H), 1.44-1.49 (m, 2 H), 1.87 (ddd, $J = 13.5, 11.1, 4.9$ Hz, 1 H), 2.13-2.27 (m, 2 H), 3.24 (dt, $J = 8.8, 4.4$ Hz, 1 H), 3.38 (dd, $J = 9.9, 4.9$ Hz, 1 H), 3.69 (s, 3 H), 3.71 (s, 3 H), 3.73 (s, 3 H), 4.96 (dd, $J = 17.1, 1.8$ Hz, 1 H), 5.13 (dd, $J = 10.2, 1.8$ Hz, 1 H), 5.56 (ddd, $J = 17.1, 10.2, 9.5$ Hz, 1 H), 6.52 (d, $J = 8.8$ Hz, 2 H), 6.75 (d, $J = 8.8$ Hz, 2 H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 13.9, 22.5, 26.0, 30.5, 31.3, 31.9, 45.9, 50.0, 52.4, 52.5, 55.8, 57.8, 114.8, 115.0, 118.8, 137.6, 142.2, 151.9, 169.8, 170.1; High-resolution MS, calcd for C$_{21}$H$_{29}$NO$_4$: 391.2359. Found: $m/z$ 391.2354 (M$^+$).

**Methyl 1-(p-methoxyphenyl)-2-oxo-6-phenyl-5-vinylpiperidine-3-carboxylate (4a):**
IR (neat) 2955 (m), 2839 (m), 1738 (s), 1693 (s), 1514 (s), 1250 (s), 1033 (m), 833 (m) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$, major isomer) $\delta$ 2.09 (dt, $J = 13.9, 7.0$ Hz, 1 H), 2.40-2.47 (m, 1 H), 2.74-2.84 (m, 1 H), 3.70 (s, 3 H), 3.76-3.81 (m, 1 H), 3.84 (s, 3 H), 4.69 (d, $J = 5.6$ Hz, 1 H), 5.18 (dt, $J = 17.3, 1.2$ Hz, 1 H), 5.21 (dd, $J = 10.5, 1.2$ Hz, 1 H), 5.92 (ddd, $J = 17.3, 10.5, 6.6$ Hz, 1 H), 6.72 (d, $J = 9.0$ Hz, 2 H), 6.97 (d, $J = 9.0$ Hz, 2 H), 7.16-7.35 (m, 5 H); $^1$H-NMR (400 MHz, CDCl$_3$, minor isomer) $\delta$ 2.27 (ddd, $J = 13.2, 9.3, 5.6$ Hz, 1 H), 2.40-2.47 (m, 1 H), 2.74-2.84 (m, 1 H), 3.67 (s, 3 H), 3.76-3.81 (m, 1 H), 3.78 (s, 3 H), 4.55 (d, $J = 9.2$ Hz, 1 H), 4.96 (d, $J = 17.3$ Hz, 1 H), 5.03 (d, $J = 10.5$ Hz, 1 H), 5.71 (ddd, $J = 17.3, 10.5, 7.0$ Hz, 1 H), 6.67 (d, $J = 9.0$ Hz, 2 H), 6.88 (d, $J = 9.0$ Hz, 2 H), 7.16-7.35 (m, 5 H); $^{13}$C-NMR (100 MHz, CDCl$_3$, major isomer) $\delta$ 27.0, 42.8, 47.3, 52.6, 55.2, 70.1, 114.0, 117.1, 127.5, 127.8, 128.2, 128.3, 134.3, 137.2, 140.0, 158.0, 166.0, 171.5; $^{13}$C-NMR (100 MHz, CDCl$_3$, minor isomer) $\delta$ 29.2, 45.4, 49.6, 52.3, 55.2, 70.6, 113.9, 117.2, 127.6, 127.8, 128.4, 128.6, 133.4, 137.0, 139.4,
Methyl 2-oxo-1,6-diphenyl-5-vinylpiperidine-3-carboxylate (4b): IR (neat) 3061 (m), 2947 (m), 1734 (s), 1651 (m), 1597 (m), 1416 (m), 1273 (m), 729 (m), 698 (m) cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\), major isomer) \(\delta\) 2.10 (dt, \(J = 13.8, 7.0\) Hz, 1 H), 2.44 (ddd, \(J = 13.8, 8.2, 3.8\) Hz, 1 H), 2.79-2.86 (m, 1 H), 3.77-3.81 (m, 1 H), 3.84 (s, 3 H), 4.76 (d, \(J = 5.4\) Hz, 1 H), 5.20 (dt, \(J = 17.2, 1.2\) Hz, 1 H), 5.22 (dd, \(J = 10.5, 1.2\) Hz, 1 H), 5.93 (ddd, \(J = 17.2, 10.5, 6.6\) Hz, 1 H), 7.06-7.31 (m, 10 H); \(^1\)H-NMR (400 MHz, CDCl\(_3\), minor isomer) \(\delta\) 2.27-2.31 (m, 1 H), 2.44 (ddd, \(J = 13.8, 8.2, 3.8\) Hz, 1 H), 2.79-2.86 (m, 1 H), 3.77-3.81 (m, 1 H), 3.79 (s, 3 H), 4.62 (d, \(J = 9.0\) Hz, 1 H), 4.98 (d, \(J = 17.2\) Hz, 1 H), 5.04 (d, \(J = 10.5\) Hz, 1 H), 5.72 (ddd, \(J = 17.2, 10.5, 7.1\) Hz, 1 H), 7.06-7.31 (m, 10 H); \(^13\)C-NMR (100 MHz, CDCl\(_3\), major isomer) \(\delta\) 27.0, 42.8, 47.3, 52.6, 69.8, 117.2, 127.2, 127.5, 127.6, 127.7, 128.3, 128.7, 137.2, 139.9, 141.5, 165.9, 171.5; \(^13\)C-NMR (100 MHz, CDCl\(_3\), major isomer) \(\delta\) 29.2, 45.3, 49.5, 52.4, 70.3, 117.0, 126.7, 126.8, 127.6, 127.7, 128.2, 128.5, 137.0, 139.2, 140.6, 166.7, 170.4. High-resolution MS, calcd for C\(_{21}\)H\(_{21}\)NO\(_3\): 355.1521. Found: \(m/z\): 355.1515 (M\(^+\)).

Methyl 1-(4-chlorophenyl)-2-oxo-6-phenyl-5-vinylpiperidine-3-carboxylate (4c): IR (neat) 2953 (m), 1736 (s), 1653 (s), 1493 (m), 1171 (m), 754 (m), 705 (m) cm\(^{-1}\); \(^1\)H-NMR (400 MHz, CDCl\(_3\), major isomer) \(\delta\) 2.12 (dt, \(J = 13.9, 7.2\) Hz, 1 H), 2.40-2.46 (m, 1 H), 2.76-2.84 (m, 1 H), 3.77-3.79 (m, 1 H), 3.78 (s, 3 H), 4.58 (d, \(J = 9.3\) Hz, 1 H), 4.96 (d, \(J = 17.1\) Hz, 1 H), 5.03 (d, \(J = 10.5\) Hz, 1 H), 5.69 (ddd, \(J = 17.1, 10.5, 7.0\) Hz, 1 H), 6.91-6.94 (m, 2 H), 6.99-7.25 (m, 7 H); \(^1\)H-NMR (400 MHz, CDCl\(_3\), minor isomer) \(\delta\) 2.28 (ddd, \(J = 13.4, 9.5, 5.9\) Hz, 1 H), 2.40-2.46 (m, 1 H), 2.76-2.84 (m, 1 H),
3.77-3.79 (m, 1 H), 3.84 (s, 3 H), 4.69 (d, $J = 5.9$ Hz, 1 H), 5.16 (d, $J = 17.1$ Hz, 1H), 5.20 (d, $J = 10.5$ Hz, 1 H), 5.88 (ddd, $J = 17.1, 10.5, 6.6$ Hz, 1 H), 6.91-6.94 (m, 2 H), 6.99-7.25 (m, 7 H); $^{13}$C-NMR (100 MHz, CDCl$_3$, major isomer) $\delta$ 27.2, 42.7, 47.4, 52.6, 69.8, 117.3, 127.5, 127.8, 128.5, 128.6, 128.9, 132.4, 136.9, 138.8, 139.5, 166.0, 171.3; $^{13}$C-NMR (100 MHz, CDCl$_3$, minor isomer) $\delta$ 29.2, 45.3, 49.6, 52.4, 70.3, 117.2, 127.7, 127.9, 128.4, 128.7, 129.0, 132.4, 136.7, 139.0, 139.8, 166.8, 170.3. High-resolution MS, calcd for C$_{21}$H$_{20}$ClNO$_3$: 369.1132. Found: m/z 369.1123 (M$^+$).

**Methyl 1-benzyl-2-oxo-6-phenyl-5-vinylpiperidine-3-carboxylate (4d):** IR (neat) 3060 (w), 3032 (m), 2953 (m), 1742 (s), 1645(s), 1495 (m), 1165 (m), 739 (m), 702 (s) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$, major isomer) $\delta$ 1.89 (dt, $J = 13.4, 6.3$ Hz, 1 H), 2.32 (ddd, $J = 13.4, 8.8, 4.2$ Hz, 1 H), 2.58-2.65 (m, 1 H), 3.36 (d, $J = 14.6$ Hz, 1 H), 3.70 (dd, $J = 8.8, 6.3$ Hz, 1 H), 3.82 (s, 3 H), 4.29 (d, $J = 4.9$ Hz, 1 H), 4.81 (d, $J = 17.1$ Hz, 1 H), 4.99 (d, $J = 10.7$ Hz, 1 H), 5.57 (d, $J = 14.6$ Hz, 1 H), 5.61 (ddd, $J = 17.1, 10.7, 6.3$ Hz, 1 H), 7.24-7.40 (m, 10 H); $^1$H-NMR (400 MHz, CDCl$_3$, minor isomer) $\delta$ 2.11-2.19 (m, 2H), 2.48-2.58 (m, 1 H), 3.36 (d, $J = 14.6$ Hz, 1 H) 3.69 (dd, $J = 9.6, 6.4$ Hz, 1H), 3.83 (s, 3 H), 4.01 (d, $J = 9.3$ Hz, 1 H), 4.77 (d, $J = 17.2$ Hz, 1 H), 4.89 (d, $J = 10.2$ Hz, 1 H), 5.45 (d, $J = 14.6$ Hz, 1 H), 5.50 (ddd, $J = 17.2, 10.2, 7.1$ Hz, 1 H), 7.24-7.40 (m, 10 H); $^{13}$C-NMR (100 MHz, CDCl$_3$, major isomer) $\delta$ 26.3, 42.2, 46.7, 47.9, 52.5, 64.0, 116.7, 127.2, 127.4, 127.8, 128.4, 128.7 (2C), 136.5, 137.0, 139.7, 166.0, 171.4; $^{13}$C-NMR (100 MHz, CDCl$_3$, minor isomer) $\delta$ 29.2, 45.6, 47.0, 49.4, 52.4, 65.8, 116.9, 127.5, 128.0, 128.1, 128.6, 128.7(2C), 136.4, 136.9, 139.3, 166.9, 170.8. High-resolution MS, calcd for C$_{22}$H$_{23}$NO$_3$: 349.1678. Found: m/z 349.1677 (M$^+$).
Methyl 1-hexyl-2-oxo-6-phenyl-5-vinylpiperidine-3-carboxylate (4e): IR (neat) 2930 (m), 2858 (m), 1747 (s), 1651 (s), 1456 (m), 1163 (m), 704 (m) cm^−1; ^1H-NMR (400 MHz, CDCl3, major isomer) δ 0.84 (t, J = 6.8 Hz, 3 H), 1.14-1.25 (m, 6 H), 1.44-1.51 (m, 2 H), 1.88 (dt, J = 13.2, 6.6 Hz, 1 H), 2.27 (ddd, J = 13.2, 9.0, 3.8 Hz, 1 H), 2.42-2.56 (m, 2 H), 2.64-2.68 (m, 1 H), 3.60 (dd, J = 9.0, 6.6 Hz, 1 H), 3.79 (s, 3 H), 4.42 (d, J = 4.4 Hz, 1 H), 5.15 (dt, J = 17.2, 1.2 Hz, 1 H), 5.18 (dd, J = 10.5, 1.2 Hz, 1 H), 5.86 (ddd, J = 17.2, 10.5, 6.6 Hz, 1 H), 7.27-7.39 (m, 5 H); ^1H-NMR (400 MHz, CDCl3, minor isomer) δ 0.84 (t, J = 6.8 Hz, 3 H), 1.14-1.25 (m, 6 H), 1.44-1.51 (m, 2 H), 1.88 (dt, J = 13.2, 6.6 Hz, 1 H), 2.11 (ddd, J = 13.2, 9.8, 5.9 Hz, 1 H), 2.42-2.56 (m, 2 H), 2.64-2.68 (m, 1 H), 3.60 (dd, J = 9.0, 6.6 Hz, 1 H), 3.79 (s, 3 H), 4.19 (d, J = 9.3 Hz, 1 H), 4.88 (d, J = 17.1 Hz, 1 H), 5.00 (d, J = 10.2 Hz, 1 H), 5.66 (ddd, J = 17.1, 10.2, 7.1 Hz, 1 H), 7.27-7.39 (m, 5 H); ^13C-NMR (100 MHz, CDCl3, major isomer): δ 13.8, 26.1, 26.4, 26.6, 29.1, 31.3, 42.5, 46.1, 46.5, 52.4, 65.6, 117.0, 127.2, 127.8, 128.7, 137.6, 140.0, 165.9, 171.9; ^13C-NMR (100 MHz, CDCl3, minor isomer) δ 13.8, 26.3, 26.4, 26.5, 29.2, 31.2, 42.3, 45.0, 45.6, 49.2, 66.9, 117.0, 127.5, 128.2, 128.7, 137.4, 139.9, 166.7, 171.2; High-resolution MS, calcd for C21H29NO3: 343.2147. Found: m/z 343.2156 (M⁺).

Methyl 6-(4-chlorophenyl)-1-(4-methoxyphenyl)-2-oxo-5-vinylpiperidine-3-carboxylate (4f): IR (neat) 3065 (m), 2951 (m), 2839 (m), 1734 (s), 1647 (s), 1512 (s), 1246 (m), 831 (m), 721 (m) cm^−1; ^1H-NMR (400 MHz, CDCl3, major isomer) δ 2.14 (dt, J = 14.0, 6.6 Hz, 1 H), 2.39 (ddd, J = 14.0, 7.1, 3.7 Hz, 1 H), 2.70-2.81 (m, 1 H), 3.71 (s, 3 H), 3.76-3.79 (m, 1 H), 3.83 (s, 3 H), 4.65 (d, J = 6.1 Hz, 1 H), 5.14 (d, J = 17.3 Hz, 1 H), 7.19-7.28 (m, 1 H).
5.20 (d, $J = 10.5$ Hz, 1 H), 5.86 (ddd, $J = 17.3, 10.5, 6.6$ Hz, 1 H), 6.73 (d, $J = 9.0$ Hz, 2 H), 6.94 (d, $J = 9.0$ Hz, 2 H), 7.00 (d, $J = 8.3$ Hz, 2 H), 7.18 (d, $J = 8.3$ Hz, 2 H); $^1$H-NMR (400 MHz, CDCl$_3$, minor isomer) $\delta$ 2.26 (ddd, $J = 13.2, 5.6, 3.7$ Hz, 1 H), 2.40-2.48 (m, 1 H), 2.70-2.81 (m, 1 H), 3.69 (s, 3 H), 3.76-3.79 (m, 1 H), 3.78 (s, 3 H), 4.54 (d, $J = 9.5$ Hz, 1 H), 4.94 (d, $J = 17.2$ Hz, 1 H), 5.03 (d, $J = 10.4$ Hz, 1 H), 5.79 (ddd, $J = 17.2, 10.4, 7.1$ Hz, 1 H), 6.68 (d, $J = 9.0$ Hz, 2 H), 6.86 (d, $J = 9.0$ Hz, 2 H), 7.00 (d, $J = 8.3$ Hz, 2 H), 7.18 (d, $J = 8.3$ Hz, 2 H); $^{13}$C-NMR (100 MHz, CDCl$_3$, major isomer): $\delta$ 27.2, 42.8, 47.4, 52.7, 55.2, 69.5, 114.2, 117.7, 128.4 (2C), 128.7 (2C), 133.6, 137.0, 138.7, 151.8; $^{13}$C-NMR (100 MHz, CDCl$_3$, minor isomer) $\delta$ 29.3, 45.6, 49.6, 52.4, 55.2, 69.9, 114.1, 117.7, 128.7 (2C), 128.8, 129.3 (2C), 134.0, 136.7, 138.1, 158.2, 166.2. High-resolution MS, calcd for C$_{22}$H$_{22}$ClNO$_4$: 399.1237. Found: m/z 399.1248 (M$^+$).

Tetrahydro-6-phenyl-5-vinylpyran-2-one (5a): IR (neat) 2950 (w), 1715 (s), 1643 (m), 1495 (m), 1454 (m), 1247 (s), 1001 (m), 922 (m), 764 (m), 700 (s) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 2.00 (dq, $J = 13.4, 6.7$ Hz, 1 H), 2.18 (dddd, $J = 13.4, 7.7, 7.6, 5.4$ Hz, 1 H), 2.64-2.81 (m, 2 H), 2.89-2.94 (m, 1 H), 5.00 (dt, $J = 17.3, 1.2$ Hz, 1 H), 5.07 (dt, $J = 10.5, 1.2$ Hz, 1 H), 5.54 (d, $J = 3.4$ Hz, 1 H), 5.61 (ddd, $J = 17.3, 10.5, 7.5$ Hz, 1 H), 7.27-7.37 (m, 5 H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 23.8, 27.5, 41.9, 82.9, 118.3, 126.0, 127.8, 128.2, 134.0, 137.3, 170.9; High-resolution MS, calcd for C$_{13}$H$_{14}$O$_2$: 202.0994. Found: m/z 203.1026 (M$^+$+H), 202.1000 (M$^+$).

6-(4-Chlorophenyl)-tetrahydro-5-vinylpyran-2-one (5b): IR (neat) 3074 (w), 2909 (w), 1732 (s), 1643 (m), 1599 (m), 1492 (m), 1247 (s) 1053 (m), 1015 (m), 920 (s) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.94-2.04 (m, 1 H), 2.22 (dddd, $J = 13.4, 7.7, 7.6, 5.4$
1-(4-Methoxyphenyl)-6-phenyl-5-vinylpiperidin-2-one (6a): IR (neat) 3271 (br), 3060 (s), 2937 (s), 2835 (w), 1732 (s), 1633 (s), 1603 (m), 1578 (m), 1495 (m), 1380 (m), 1076 (m), 1033 (m), 831 (w), 619 (w) cm⁻¹; ¹H-NMR (400 MHz, CDCl₃, major isomer) δ 1.83 (dq, J = 13.7, 6.8 Hz, 1 H), 2.07 (ddddd, J = 13.7, 7.1, 6.8, 3.9 Hz, 1 H), 2.66-2.78 (m, 3 H), 3.69 (s, 3 H), 4.66 (d, J = 5.6 Hz, 1 H), 5.16 (d, J = 16.8 Hz, 1 H), 5.17 (d, J = 9.5 Hz, 1 H), 5.95 (dd, J = 16.8, 9.5, 6.2 Hz, 1 H), 6.72 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2 H), 7.14-7.31 (m, 5 H); ¹H-NMR (400 MHz, CDCl₃, minor isomer) δ 1.83 (dq, J = 13.7, 6.8 Hz, 1 H), 2.07 (ddddd, J = 13.7, 7.1, 6.8, 3.9 Hz, 1 H), 2.66-2.78 (m, 3 H), 3.70 (s, 3 H), 4.77 (d, J = 4.9 Hz, 1 H), 5.01 (d, J = 10.2 Hz, 1 H), 5.09 (d, J = 17.2 Hz, 1 H), 5.32 (dd, J = 17.2, 10.2, 7.8 Hz, 1 H), 6.72 (d, J = 9.0 Hz, 2H), 6.95 (d, J = 9.0 Hz, 2 H), 7.14-7.31 (m, 5 H); ¹³C-NMR (100 MHz, CDCl₃, major isomer) δ 23.1, 30.3, 45.0, 55.2, 70.1, 114.0, 116.5, 127.2, 127.4, 128.3 (2C), 134.9, 138.0, 140.7, 157.8, 170.4; ¹³C-NMR (100 MHz, CDCl₃, minor isomer) δ 21.8, 31.5, 43.8, 69.4, 114.1, 116.2, 127.3 (2C), 127.8, 128.0, 128.5, 135.4, 137.1, 158.0, 169.9. High-resolution MS, calcd for C₁₃H₁₃ClO₂: 236.0604. Found: m/z 236.0587 (M⁺).

1,6-Diphenyl-5-vinylpiperidin-2-one (6b): IR (neat) 3069 (w), 3032 (w), 2947 (m), 1651 (s), 1595 (m), 1495 (m), 1076 (m), 1030 (m), 747 (s), 696 (s) cm⁻¹; ¹H-NMR (400 MHz, CDCl₃, major isomer) δ 1.84 (dq, J = 13.7, 6.8 Hz, 1 H), 2.07 (ddddd, J = 13.7, 7.3,
6.8, 3.9 Hz, 1 H), 2.67-2.78 (m, 3 H), 4.73 (d, $J = 5.4$ Hz, 1 H), 5.17 (d, $J = 17.8$ Hz, 1 H), 5.18 (d, $J = 10.0$ Hz, 1 H), 5.96 (ddd, $J = 17.8$, 10.0, 6.6 Hz, 1 H), 7.04-7.31 (m, 10 H); $^1$H-NMR (400 MHz, CDCl3, minor isomer) $\delta$1.84 (dq, $J = 13.7$, 6.8 Hz, 1 H), 2.07 (dddd, $J = 13.7$, 7.3, 6.8, 3.9 Hz, 1 H), 2.67-2.78 (m, 3 H), 4.82 (d, $J = 4.9$ Hz, 1 H), 5.02 (d, $J = 10.2$ Hz, 1 H), 5.09 (d, $J = 17.2$ Hz, 1 H), 5.33 (ddd, $J = 17.3$, 10.2, 7.6 Hz, 1 H), 7.04-7.31 (m, 10 H); $^{13}$C-NMR (100 MHz, CDCl3 major isomer) $\delta$23.0, 30.3, 45.0, 69.8, 116.6, 126.6, 127.2 (2C), 127.4, 128.3, 128.6, 138.0, 140.6, 142.1, 170.2; $^{13}$C-NMR (100 MHz, CDCl3 minor isomer) $\delta$ 21.7, 31.5, 43.9, 69.1, 116.3, 126.8, 126.9, 127.7 (2C), 127.8, 128.4, 128.8, 137.0, 142.6, 169.8. High-resolution MS, calcd for C$_{19}$H$_{19}$NO: 277.1467. Found: m/z 277.1458 (M$^+$).

1-(4-Methoxyphenyl)-6-pentyl-5-vinylpiperidin-2-one (6g): IR (neat) 2932 (m), 2858 (m), 1651 (s), 1607 (m), 1587 (m), 1105 (m), 1036 (m), 829 (s), 731 (m) cm$^{-1}$; $^1$H-NMR (400 MHz, CDCl3) $\delta$ 0.78 (t, $J = 7.2$ Hz, 3 H), 0.93-1.01 (m, 3 H), 1.07-1.15 (m, 3 H), 1.23-1.32 (m, 1 H), 1.41 (dddd, $J = 17.8$, 10.7, 5.9, 5.9 Hz, 1 H), 1.47-1.55 (m, 1 H), 1.61-1.68 (m, 1 H), 2.21-2.27 (m, 1 H) 2.32 (ddd, $J = 17.8$, 7.0, 7.0 Hz, 1 H), 2.50 (ddd, $J = 16.7$, 7.0, 6.4 Hz, 1 H), 3.29 (s, 3 H), 3.45 (ddd, $J = 8.6$, 7.5, 5.3 Hz, 1 H), 5.00 (d, $J = 10.4$ Hz, 1 H), 5.03 (d, $J = 17.5$ Hz, 1 H), 5.71 (ddd, $J = 17.5$, 10.4, 7.5 Hz, 1 H), 6.90 (d, $J = 8.8$ Hz, 2 H), 7.08 (d, $J = 8.8$ Hz, 2 H); $^{13}$C-NMR (100 MHz, CDCl3) $\delta$ 13.9, 22.4, 23.6, 24.4, 30.0, 31.6, 31.9, 39.4, 55.4, 64.9, 114.4, 116.2, 128.8, 134.5, 139.4, 158.2, 170.3. High-resolution MS, calcd for C$_{19}$H$_{27}$NO$_2$: 301.2042. Found: m/z 301.2039 (M$^+$).
1.5 References and Notes


2011, 111, 1170.


(7) In the absence of Zn cluster catalyst, no lactonization and lactamization proceeded at all. These cyclizations required Zn cluster catalyst as a promoter to provide lactones and lactams from homoallyl alcohols and homoallylamines, respectively. Simple lactonization or lactamization conditions using acid catalysts and dehydration condensation agents were ineffective.


Chapter 2

Efficient Synthesis of Pyrrolizidine by Pd-Catalyzed Consecutive Double Amphiphilic Allylation of Nitrile

2.1 Abstract

The combination of a Pd catalyst and triethylborane promotes double amphiphilic allylation of nitriles with 2-methylenepropane-1,3-diol to serve as a 1,3-dipolar equivalent, providing pyrrolizidine derivatives. The resulting bicyclic compounds can be used for efficient synthesis of important pyrrolizidine alkaloids.
2.2 Introduction

Since the discovery of the reaction of \( \pi \)-allylpalladium chloride with ethyl malonate and acetoacetate by Tsuji,\(^1\) \( \pi \)-allylpalladium complexes have been one of the most important key intermediates for efficient C–C bond transformation reactions in modern organic chemistry.\(^2\) 1,3-Dipolar cycloaddition reactions provide an efficient and convenient method for construction of five-membered cycloalkanes and heterocycles. Tamaru, Kimura and their co-workers have developed a straightforward and convenient method for \([3+2]\) cycloaddition of aldimine with commercially available 2-methylene-propane-1,3-diol through a formal 1,3-zwitterion species under a Pd catalyst/triethylborane system. One of the allyl alcohol moieties of the symmetrical bisallyl alcohol undergoes nucleophilic allylation with the iminium carbon atom of the aldimine to form 3-hydroxylmethyl-3-butenylamine, while the remaining allyl alcohol moiety selectively reacts intramolecularly as an allyl cation equivalent with the homoallylamine moiety to furnish 3-methylene-pyrrolidines (Scheme 1).\(^3\) The regio- and stereoselectivities of the reaction using substituted 2-methylene-propane-1,3-diols were in contrast with the results of trimethylene-methane (TMM) chemistry reported by B.M. Trost.\(^4\) Thus, amphiphilic allylation was concluded to be among the most efficient and innovative methods for the synthesis of
pyrrolidines in a formal [3+2] cycloaddition manner involving a 1,3-dipolar equivalent with aldimines.

**Scheme 1** Pd-catalyzed amphiphilic allylation of aldimine with 2-methylenepropane-1,3-diol.

Among nitrogen-containing heterocyclic compounds, pyrrolizidine alkaloids are one of the most important natural occurring molecules as necine bases; various species have been shown to exhibit hepatotoxicity, antitumor activity, and carcinogenicity.\(^5\)

Efficient construction of the pyrrolizidine framework represents a significant contribution to the development of total syntheses of natural products such as pyrrolizidine alkaloids.\(^6\) In the course of their studies involving amphiphilic allylation, the author developed amphiphilic allylation reactions of nitriles. The author reveal here that a similar reaction system consisting of a Pd catalyst and triethylborane effectively promotes the consecutive double amphiphilic allylation of nitriles with 2-methylenepropane-1,3-diol to form a pyrrolizidine ring in a single manipulation (Scheme 2).
**Scheme 2** Pd-catalyzed consecutive double amphiphilic allylation of nitrile with 2-methylene propane-1,3-diol.
2.3 Results and Discussion

First, the author investigated Pd-catalyzed amphiphilic allylation of benzonitrile with 2-methylene propane-1,3-diol in the presence of triethylborane. The VPC (vapor phase chromatography) results are summarized in Table 1. 2-Methylene propane-1,3-diol reacted with benzonitrile to form a pyrrolizidine 1a in the presence of triethylborane, 20 mol % Pd(OAc)$_2$ and various phosphine ligands. In some cases, the monocyclized product 2a and the bishomoallylamine 3a were detected as by-products along with the desired product 1a by VPC analysis. The reaction features and the yields were dependent on the type of ligand used. In accord with the previous best result using tri-$n$-butylphosphine for amphiphilic allylation of aldimine with 2-methylene propane-1,3-diol to form a pyrrolidine ring, tri-$n$-butylphosphine turned out to be the most efficient ligand for double amphiphilic allylations of benzonitrile with bis-allylic alcohol, affording 1a in 59% yield in THF (entry 3, Table 1). Triphenylphosphine gave the expected product 1a in modest yield (entry 1, Table 1). Tricyclohexylphosphine was not effective at all (entry 2, Table 1). 2-Dicyclohexylphosphino-2’$'$,4’$'$,6’$'$-triisopropylbiphenyl (XPhos) provided the desired product 1a with the second best yield in THF solvent (entry 4, Table 1). In contrast, Buchwald’s ligands, such as 2-dicyclohexylphosphino-2’$'$,6’$'$-dimethoxybiphenyl
Table 1. Reaction of 2-methylenepropane-1,3-diol with benzonitrile\(^a\)

\[\text{OH} \quad + \quad \text{PhCN} \quad \xrightarrow{\text{Pd cat. Et} \text{_3} \text{B}} \quad \text{solvent} \quad \xrightarrow{50 \, ^\circ \text{C}, 24 \, h} \quad \begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{N} \\
\text{Ph} \\
\text{NH}_2 \\
\text{Ph} \\
\text{N} \\
\text{H}
\end{array} + \begin{array}{c}
\text{1a} \\
\text{2a} \\
\text{3a}
\end{array} \]

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\(^a\)A mixture of 2-methylenepropane-1,3-diol (1.2 mmol), benzonitrile (0.5 mmol), Pd(OAc)\(_2\) (0.1 mmol), ligand (monophosphine 0.4 mmol, bidentatephosphine 0.2 mmol), and triethylborane (5.0 mmol) was stirred at 50 \(^\circ\)C in solvent (1 mL) for 24 h under N\(_2\). \(^b\)Yields are determined by VPC analysis. \(^c\)Isolated yield is shown in parentheses. \(^d\)DCE: 1,2-dichloroethane.
(SPhos) and 2-(di-tert-butylphosphino)biphenyl (JohnPhos), were far less efficient than XPhos (entries 5 and 6, Table 1). The use of diphosphine ligands tended to inhibit the amphiphilic allylation (entries 7–9, Table 1).

Next, author screened the several solvents for the reaction using tri-\(n\)-butylphosphine and XPhos. When tri-\(n\)-butylphosphine was used, the reactions carried out in 1,4-dioxane and 1,2-dichloroethane (DCE) gave the product 1\(a\) in 76% and 63% yields (entries 10 and 11, Table 1), while the use of benzene and hexane gave the lower yields (entries 12 and 13, Table 1). In fact, under the reaction conditions using tri-\(n\)-butylphosphine in 1,4-dioxane, 1\(a\), 2\(a\), and 3\(a\) could be separated by recycling preparative HPLC and were characterized by \(^1\)H and \(^{13}\)C NMR spectroscopy (entry 10, Table 1). \(N,\)\(N\)-Dimethylformamide (DMF) was an ineffective solvent for the reaction owing to the deactivation of triethylborane as a Lewis acid. When XPhos was used as a ligand in 1,4-dioxane, pyrrolizidine 1\(a\) was obtained in lower yield, in contrast with the result using tri-\(n\)-butylphosphine (entry 15, Table 1). The reaction in 1,2-dichloroethane yielded the product 1\(a\) in 72% yield (entry 16, Table 1). The use of benzene and hexane gave 1\(a\) in moderate yields, although DMF was ineffective under the same conditions (entries 17–19, Table 1). Author concluded
that the appropriate conditions for amphiphilic allylation were the use of tri-\textit{n}-butylphosphine in 1,4-dioxane and XPhos in DCE.

In order to shed more light on the reaction mechanism for double amphiphilic allylation of nitrile, the time course of the reaction under the conditions shown in entry 3 of Table 1 was investigated by VPC analysis. The resulting data are shown in Fig. 1. The desired product 1\textit{a} was formed in extremely high ratio among all of products, and both pyrrolidine 2\textit{a} and bis-homoallylamine 3\textit{a} had already been formed even at the initial stage of the reaction. After 24 h, most of bis-allyl alcohol had been consumed quantitatively, converting to almost the total amount of the products 1\textit{a}, 2\textit{a}, and 3\textit{a}. Pyrrolizidine 1\textit{a} did not decompose with extension of the reaction time over 24 h. Furthermore, the independently isolated products 1\textit{a}, 2\textit{a}, and 3\textit{a} were intact and were recovered quantitatively even after being exposed to similar reaction conditions. Although some aspects of the product distribution could not be clarified, these results seem to suggest that the products 2\textit{a} and 3\textit{a} were formed not by decomposition of 1\textit{a} directly, but rather through other amphiphilic allylation processes.

Next, author investigated amphiphilic allylation of various nitriles with 2-methylenepropane-1,3-diol to form pyrrolizidine derivatives (1) under the optimized conditions described above. The isolated yields of the resulting pyrrolizidines 1\textit{b}-1\textit{m}
Fig. 1. Time course of the products 1a, 2a, and 3a under the Pd/Et$_3$B system.

are shown in Table 2. Although the corresponding pyrrolidines 2 and symmetrical homoallylamines 3 tend to be formed as by-products, unfortunately, these could not be completely separated by means of by recycling preparative HPLC. Therefore, isolated yields of 1 are shown in Table 2. The reaction of 4-methylbenzonitrile with 2-methylene-propane-1,3-diol led to formation of the corresponding pyrrolizidine 1b in 72% yield (entry 1, Table 2). 4-Methoxybenzonitrile was converted to 1c in moderate yield (entry 2, Table 2). Halobenzonitriles such as 4-fluorobenzonitrile and 4-chlorobenzonitrile tolerated amphiphilic allylation with 2- methylene-propane-1,3-diol to afford 1d and 1e in 52% and 57% yields (entries 3 and 4, Table 2). When
4-phenylbenzonitrile was employed to react with 2-methylene propane-1,3-diol, pyrrolizidine If was obtained in 41% yield (entry 5, Table 2). The 3-substituted benzonitriles, 3-methylbenzonitrile and 3-chlorobenzonitrile gave the cyclized products

<table>
<thead>
<tr>
<th>entry</th>
<th>nitrile</th>
<th>isolated yield (%) of 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-MeC₆H₄</td>
<td>1b: 72</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC₆H₄</td>
<td>1c: 49</td>
</tr>
<tr>
<td>3</td>
<td>4-FC₆H₄</td>
<td>1d: 52</td>
</tr>
<tr>
<td>4</td>
<td>4-ClC₆H₄</td>
<td>1e: 57</td>
</tr>
<tr>
<td>5</td>
<td>4-PhC₆H₄</td>
<td>1f: 41</td>
</tr>
<tr>
<td>6</td>
<td>3-MeC₆H₄</td>
<td>1g: 31</td>
</tr>
<tr>
<td>7</td>
<td>3-ClC₆H₄</td>
<td>1h: 39</td>
</tr>
<tr>
<td>8ᵇ</td>
<td>cinnamyl</td>
<td>1i: 30</td>
</tr>
<tr>
<td>9</td>
<td>Bn</td>
<td>1j: 72</td>
</tr>
<tr>
<td>10</td>
<td>phenethyl</td>
<td>1k: 36</td>
</tr>
<tr>
<td>11</td>
<td>cyclopropyl</td>
<td>1l: 24</td>
</tr>
<tr>
<td>12</td>
<td>n-Bu</td>
<td>1m: 24</td>
</tr>
</tbody>
</table>

A mixture of 2-methylene propane-1,3-diol (1.2 mmol), nitrile (0.5 mmol), Pd(OAc)₂ (0.1 mmol), P(n-Bu)₃ (0.4 mmol), and triethylborane (5.0 mmol) was stirred at 50 °C in 1,4-dioxane (0.5 mL) for 24 h under N₂.

A mixture of 2-methylene propane-1,3-diol (1.2 mmol), nitrile (0.5 mmol), Pd(OAc)₂ (0.1 mmol), Xphos (0.2 mmol), and triethylborane (5.0 mmol) was stirred at 50 °C in DCE (0.5 mL) for 24 h under N₂.
and \textbf{1h} in lower yields than that of 4-substituted benzonitriles (entries 6 and 7, Table 2). In the case of an $\alpha,\beta$-unsaturated nitrile, the use of XPhos as a ligand gave a better result than the use of tri-$n$-butylphosphine (entry 8, Table 2). Aliphatic nitriles participated in the formation of the desired amphiphilic allylation products. Alkyl nitriles such as $\beta$-phenethyl-, cyclopropyl-, and $n$-butyl-substituted nitriles underwent similar amphiphilic allylation reactions, with isolated yields hovering around 30% (entries 1012, Table 2). Pyrrolizidine \textbf{1j} was obtained as a single product in 72% yield by the use of phenylacetonitrile (entry 9, Table 2).

A plausible reaction pathway for consecutive double amphiphilic allylation is shown in Scheme 3. Intermediates \textbf{I-III} in Scheme 6 were not detected during the reactions. Reduced products \textbf{1a} and \textbf{2a} might be derived from the intermediates \textbf{II} and \textbf{III}, respectively. As the intermediate \textbf{I} is more reactive than nitrile as an electrophile, the intermediate \textbf{I} would readily consume to undergo the nucleophilic allylation. The allyl alcohol moiety reacts with the Pd(0) catalyst to form a p-allylpalladium intermediate via oxidative addition promoted by triethylborane as a Lewis acid. Transmetallation of p-allylpalladium with an ethyl group of triethylborane generates an allyl anion equivalent, which subsequently reacts with nitrile to form aldimine intermediate \textbf{I}. Aldimine \textbf{I} undergoes nucleophilic allylation with a further allyl
anion species to form the symmetrical bis-homoallylamine intermediate II. Eventually, II undergoes intramolecular electrophilic allylation to construct the pyrrolidine ring III in the presence of Pd(0) and triethylborane. The allyl alcohol fragment of intermediate III undergoes further electrophilic allylation intramolecularly to form the final product, pyrrolizidine ring 1. Monocyclized pyrrolidine (2) and symmetrical homoallylamines (3) may be produced via dehydrative reduction as side reactions from intermediate III and intermediate II, respectively, under similar catalytic conditions.

Scheme 3. A plausible reaction mechanism for Pd/Et3B promoted amphiphilic allylation of nitrile.
systems. Thus, it is likely that 2-methylene propane-1,3-diol can serve as a 1,3-zwitterionic species, undergoing the consecutive double amphiphilic allylation with nitrile to form a pyrrolizidine ring as a single manipulation.

In conclusion, the author demonstrated that a combination of Pd(OAc)$_2$ and triethylborane promoted consecutive double amphiphilic allylation of nitriles with 2-methylene propane-1,3-diol and succeeded in producing pyrrolizidine derivatives. The resulting 2,6-bismethylene pyrrolizidines are an important building block for efficient synthesis of pyrrolizidine alkaloids.
2.4 Experimental

General experimental

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 60F254). Flash chromatography columns were packed with silica gel as a slurry in hexane. Gradient flash chromatography was conducted eluting with a continuous gradient from hexane to the indicated solvent. Proton and carbon NMR data were obtained with a JEOL JNM- AL400 with tetramethylsilane as an internal standard. Chemical shift values were given in parts per million (ppm) downfield from the internal standard. Infrared spectra were recorded with a JASCO A-100 FT-IR spectrophotometer. High-resolution mass spectra (HRMS) were measured with a JEOL JMS-700N. Analytical vapor-phase chromatography (VPC) was carried out on a Shimadzu GC-2014 gas chromatograph equipped with a Stabilwax®-DA column (30 m 0.25 mm ID 0.25 mm df) and FID detector (injection: 250 °C, 2.0 ml, 50:1 split, oven: 100 °C (15 min), 10 °C/min to 250 °C, carrier gas: helium 30 cm/s, constant, FID temperature: 280 C).

Solvents and Reagents

1,4-Dioxane was dried and distilled from benzophenone and sodium immediately prior to use under nitrogen atmosphere. Pd(OAc)$_2$, $n$-Bu$_3$P, Et$_3$B (1.0 M hexane solution), 2-methylenepropane-1,3-diol, 4-methylbenzonitrile, 4-methoxybenzonitrile, 4-fluorobenzonitrile, 4-chlorobenzonitrile, and 4-phenylbenzonitrile were purchased and
used without further purification. Benzonitrile, 3-methylbenzonitrile, 3-chlorobenzonitrile, phenylacetonitrile, cinnamonic acid, cyclopropionitrile, and butyronitrile were purchased and distilled prior to use by Kugelrohr apparatus.

**General procedure for synthesis of 5-phenyl-3,7-dimethylene pyrrolizidine (1a)** (entry 10, Table 1)

A flask was charged with Pd(OAc)$_2$ (22.5 mg, 0.1 mmol). The flask was evacuated and filled with nitrogen. To the flask were added 1,4-dioxane (1.0 ml), $n$-Bu$_3$P (50 μl, 0.2 mmol), 2-methylenepropane-1,3-diol (106.2 mg, 1.2 mmol), and benzonitrile (51.5 mg, 0.5 mmol). Et$_3$B (5.0 mmol) was added to the reaction mixture. The mixture was stirred at 50 °C for 24 h. The progress of the reaction was monitored by TLC. After the reaction was complete, saturated aqueous NaHCO$_3$ was added, and the mixture was extracted with AcOEt for 3 times. The combined organic layers were dried with MgSO$_4$, then the solvent was evaporated in vacuo. The residue was subjected to column chromatography over silica gel to give 1a ($n$-hexane/AcOEt = 50/1, 68.5 mg, 0.32 mmol, 67% yield). By-products, 2a and 3a were separated by recycling preparative HPLC instrument (eluent: CHCl$_3$, KC9100, Japan Analytical Industry, CO., Ltd).

**5-Phenyl-3,7-dimethylene pyrrolizidine (1a)**

$^1$H NMR(CDCl$_3$, 400 MHz) δ 2.78-2.80 (m, 4H), 3.33 (d, $J = 15.1$ HZ, 2H), 3.75 (d, $J = 15.1$ HZ, 2H), 4.86-4.88 (m, 2H), 4.90-4.93 (m, 2H), 7.17 (tt, $J = 0.61$, 7.42 HZ, 1H), 7.27-7.31 (m, 2H), 7.43-7.47 (m, 2H); $^{13}$C NMR(CDCl$_3$, 100 MHz) 45.0, 59.2, 76.3,
5-(2-Methyl-2-propene)-5-phenyl-3-methylenepyrrolidine (2a)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.24 (s, 3H), 1.92-2.02 (br, 2H), 2.48 (s, 1H), 2.49 (s, 1H), 2.76 (s, 2H), 3.60 (dm, $J = 1.55$ Hz, 1H), 3.68 (dm, $J = 1.55$ Hz, 1H), 4.54-4.56 (m, 1H), 4.77-4.79 (m, 1H), 4.89 (m, 1H), 4.98 (m, 1H), 7.20 (tt, $J = 1.48$, 7.20 Hz, 1H), 7.28-7.32 (m, 2H), 7.37-7.40 (m, 2H); $^{13}$C NMR(CDCl$_3$, 100 MHz) 24.0, 46.4, 48.6, 49.8, 67.1, 105.3, 114.5, 126.1, 126.4, 128.1, 142.8, 146.3, 149.6; IR(neat) 3333 (br), 3072 (m), 2926 (m), 2855 (w), 1643 (m), 1582 (w), 1447 (s), 1375 (m), 1263 (w), 1030 (w), 893 (s), 700 (s), 635 (w); High-resolution MS(EI) calcd for C$_{15}$H$_{17}$N: 211.1361, Found m/z: 211.1360 (M$^+$).

2,6-Dimethyl-4-phenyl-1,6-heptadiene-4-amine (3a)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.25 (s, 6H), 1.60-1.82 (br, 2H), 2.44 (d, $J = 13.2$ Hz, 2H), 2.69 (d, $J = 13.2$ Hz, 2H), 4.67-4.68 (m, 2H), 4.79-4.80 (m, 2H), 7.20 (tt, $J = 1.24$, 7.32 Hz, 1H), 7.43-7.47 (m, 2H), 7.18-7.33 (m, 2H); $^{13}$C NMR(CDCl$_3$, 100 MHz) 24.4, 52.7, 56.6, 115.3, 126.1, 126.1, 128.0, 142.5, 147.1; IR(neat) 3379 (br), 3072 (m), 2926 (m), 2855 (w), 1643 (m), 1582 (w), 1447 (s), 1375 (m), 1263 (w), 1030 (w), 893 (s), 700 (s), 635 (w); High-resolution MS(EI) calcd for C$_{15}$H$_{21}$N: 215.1674, Found m/z: 215.1677 (M$^+$).

Time Course of the Reaction of Benzonitrile with 2-Methylene propane-1,3-diol
A flask was charged with Pd(OAc)$_2$ (33.8 mg, 0.15 mmol). The flask was evacuated and filled with nitrogen. To the flask were added THF (0.75 ml), $n$-Bu$_3$P (75 μl, 0.3 mmol), 2-methylenepropane-1,3-diol (158.6 mg, 1.8 mmol), and benzonitrile (77.3 mg, 0.75 mmol). Et$_3$B (7.5 mmol) was added to the reaction mixture. The mixture was stirred at 50 °C. The reaction was monitored by VPC using cyclododecane as an internal standard [retention time: 5.11 min (cyclododecane), 10.79 min (3a), 11.96 min (2a), 12.24 min (1a)].

**5-(4-Methylphenyl)-3,7-dimethylenepyrrolizidine (1b)**

$^1$H NMR (CDCl$_3$, 400 MHz) δ 2.32 (s, 3H), 2.78 (s, 4H), 3.32 (d, $J = 15.4$ Hz, 2H), 3.73 (d, $J = 15.4$ Hz, 2H), 4.87-4.87 (m, 2H), 4.92-4.95 (m, 2H), 7.13 (d, $J = 8.32$ Hz, 2H), 7.36 (d, $J = 8.32$ Hz, 2H); $^{13}$C NMR(CDCl$_3$, 100 MHz) 20.9, 44.8, 59.0, 76.1, 105.9, 125.6, 129.0, 135.8, 143.7, 149.1; High-resolution MS(EI) calcd for C$_{16}$H$_{19}$N: 225.1517, Found m/z: 225.1517 (M$^+$).

**5-(4-Methoxyphenyl)-3,7-dimethylenepyrrolizidine (1c)**

$^1$H NMR (CDCl$_3$, 400 MHz) δ 2.73-2.75 (m, 4H), 3.30 (dm, $J = 15.4$ Hz, 2H), 3.71 (dm, $J = 15.4$ Hz, 2H), 3.76 (s, 3H), 4.86 (dquintet, $J = 0.48$, 1.72 Hz, 2H), 4.91 (dquintet, $J = 0.48$, 1.72 Hz, 2H), 6.82 (d, $J = 8.80$ Hz, 2H), 7.36 (d, $J = 8.80$ Hz, 2H); $^{13}$C NMR(CDCl$_3$, 100 MHz) 44.7, 55.1, 58.9, 75.8, 105.9, 113.5, 126.8, 138.7, 149.1, 158.1; High-resolution MS(EI) calcd for C$_{16}$H$_{19}$NO: 241.1467, Found m/z: 241.1464 (M$^+$).
5-(4-Fluorophenyl)-3,7-dimethylenepyrrolizidine (1d)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.70-2.81 (m, 4H), 3.32 (dm, $J = 15.2$ Hz, 2H), 3.72 (dm, $J = 15.2$ Hz, 2H), 4.86-4.89 (m, 2H), 4.91-4.94 (m, 2H), 6.95-6.99 (m, 2H), 7.39-7.44 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz) 44.9, 59.0, 75.8, 106.1, 114.9 (d, $2J_{CF} = 20.6$), 127.4 (d, $3J_{CF} = 7.41$), 142.4 (d, $4J_{CF} = 3.29$), 148.8, 161.6 (d, $1J_{CF} = 242.9$); High-resolution MS (EI) calcd for C$_{15}$H$_{16}$FN: 229.1267, Found m/z: 229.1246 (M$^+$).

5-(4-Chlorophenyl)-3,7-dimethylenepyrrolizidine (1e)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.71 (d, $J = 16.1$ Hz, 2H), 2.79 (d, $J = 16.1$ Hz, 2H), 3.32 (d, $J = 15.1$ Hz, 2H), 3.72 (d, $J = 15.1$ Hz, 2H), 4.87-4.89 (m, 2H), 4.91-4.93 (m, 2H), 7.26 (d, $J = 8.56$ Hz, 2H), 7.40 (d, $J = 8.56$ Hz, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz) 44.8, 59.0, 75.8, 106.2, 127.2, 128.3, 132.0, 145.4, 148.6; High-resolution MS (EI) calcd for C$_{15}$H$_{16}$ClN: 245.0971, Found m/z: 245.0959 (M$^+$).

5-Biphenyl-3,7-dimethylenepyrrolizidine (1f)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.83-2.85 (m, 4H), 3.37 (dm, $J = 15.2$ Hz, 2H), 3.81 (dm, $J = 15.2$ Hz, 2H), 4.91-4.93 (m, 2H), 4.96-4.98 (m, 2H), 7.32 (tt, $J = 1.34, 7.33$ Hz, 1H), 7.40-7.44 (m, 2H), 7.54-7.55 (m, 4H), 7.57-7.60 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz) 44.9, 59.1, 76.3, 106.1, 126.2, 126.9, 127.0, 127.1, 127.2, 127.3, 128.7, 139.2, 140.9; High-resolution MS (EI) calcd for C$_{21}$H$_{21}$N: 287.1674, Found m/z: 287.1658 (M$^+$).

5-(3-Methylphenyl)-3,7-dimethylenepyrrolizidine (1g)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.36 (s, 3H), 2.81 (m, 4H), 3.35 (dm, $J = 15.2$ Hz, 2H), 3.78 (dm, $J = 15.2$ Hz, 2H), 4.89-4.91 (m, 2H), 4.94-4.96 (m, 2H), 7.02-7.04 (m, 1H),
7.20-7.27 (m, 2H), 7.31 (s, 1H); $^{13}$C NMR(CDCl$_3$, 100 MHz) 21.5, 44.8, 59.0, 76.2, 105.9, 122.8, 126.3, 127.1, 128.1, 137.8, 146.6, 149.0; High-resolution MS(EI) calcd for C$_{16}$H$_{19}$N: 225.1517, Found m/z: 225.1513 (M$^+$).

5-(3-Chlorophenyl)-3,7-dimethylenepyrrolizidine (1h)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.73 (d, $J = 16.2$ HZ, 2H), 2.80 (d, $J = 16.2$ HZ, 2H), 3.33 (d, $J = 14.9$ HZ, 2H) 3.74 (d, $J = 14.9$ HZ, 2H), 4.89 (s, 2H), 4.93 (s, 2H), 7.17 (d, $J = 7.82$ HZ, 1H), 7.23 (t, $J = 7.82$ HZ, 1H), 7.32 (d, $J = 7.82$ HZ, 1H), 7.49 (s, 1H); $^{13}$C NMR(CDCl$_3$, 100 MHz) 44.9, 59.1, 76.0, 106.2, 124.0, 126.1, 126.5, 129.6, 134.3, 148.5, 149.3; High-resolution MS(EI) calcd for C$_{15}$H$_{16}$ClN: 245.0971, Found m/z: 245.0930 (M$^+$).

5-(2-Phenylethylene)-3,7-dimethylenepyrrolizidine (1i)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.58 (d, $J = 16.4$ HZ, 2H), 2.69 (d, $J = 16.4$ HZ, 2H), 3.27 (d, $J = 16.4$ HZ, 2H), 3.74 (d, $J = 16.4$ HZ, 2H), 4.93 (s, 2H), 5.00 (s, 2H), 6.23 (d, $J = 16.1$ HZ, 1H), 6.52 (d, $J = 16.1$ HZ, 1H), 7.20 (t, $J = 7.32$ HZ, 1H), 7.29 (t, $J = 7.32$ HZ, 2H), 7.38 (d, $J = 7.32$ HZ, 2H); $^{13}$C NMR(CDCl$_3$, 100 MHz) 41.8, 58.5, 74.1, 106.3, 126.4, 127.4, 128.2, 128.5, 134.7, 137.2, 148.9; High-resolution MS(EI) calcd for C$_{17}$H$_{19}$N: 237.1517, Found m/z: 223.1499 (M$^+$).

5-Benzyl-3,7-dimethylenepyrrolizidine (1j)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 2.26 (d, $J = 15.9$ HZ, 2H), 2.57 (d, $J = 15.9$ HZ, 2H), 2.72 (s, 2H), 3.25 (d, $J = 15.4$ HZ, 2H), 3.79 (d, $J = 15.4$ HZ, 2H), 4.92 (s, 2H), 4.96 (s, 2H), 7.18-7.24 (m, 3H), 7.26-7.30 (m, 2H); $^{13}$C NMR(CDCl$_3$, 100 MHz) 40.5, 44.6,
59.0, 74.3, 106.2, 126.2, 128.1, 130.2, 138.8, 149.1; High-resolution MS(EI) calcd for C_{16}H_{19}N: 225.1517, Found m/z: 225.1495 (M^+).

5-Phenylethyl-3,7-dimethylenepyrrolizidine (1k)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.71-1.77 (m, 2H), 2.50 (d, $J = 16.4$ HZ, 2H), 2.54 (d, $J = 16.4$ HZ, 2H), 2.61-2.64 (m, 2H), 3.24 (d, $J = 15.1$ HZ, 2H), 3.71 (d, $J = 15.1$ HZ, 2H), 4.93 (s, 2H), 4.98 (s, 2H), 7.17-7.19 (m, 3H), 7.25-7.29 (m, 2H); $^{13}$C NMR(CDCl$_3$, 100 MHz) 31.3, 40.6, 40.9, 58.9, 73.5, 106.3, 125.7, 128.3, 128.4, 142.6, 149.1; High-resolution MS(EI) calcd for C$_{17}$H$_{21}$N: 239.1674, Found m/z: 239.1668 (M^+).

5-Cyclopropyl-3,7-dimethylenepyrrolizidine (1l)

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.19-0.23 (m, 2H), 0.35-0.40 (m, 2H), 0.91 (tt, $J = 5.60$, 8.28 HZ, 1H), 2.30 (s, 4H), 3.19 (d, $J = 15.1$ HZ, 2H), 3.74 (d, $J = 15.1$ HZ, 2H), 4.89 (s, 2H), 4.93 (s, 2H); $^{13}$C NMR(CDCl$_3$, 100 MHz) 0.9, 18.7, 40.5, 59.6, 73.5, 105.8, 149.6; High-resolution MS(EI) calcd for C$_{12}$H$_{17}$N: 175.1361, Found m/z: 175.1360 (M^+).

5-Propyl-3,7-dimethylenepyrrolizidine (1m)

$^1$H NMR (CDCl$_3$, 400 MHz) 0.90-0.94 (m, 5H), 1.83 (d, $J = 10.2$ HZ, 2H), 2.36 (d, $J = 15.4$ HZ, 2H), 2.44 (d, $J = 15.4$ HZ, 2H), 3.21 (d, $J = 15.4$ HZ, 2H), 3.69 (d, $J = 15.4$ HZ, 2H), 4.91 (s, 2H), 4.96 (s, 2H); $^{13}$C NMR(CDCl$_3$, 100 MHz) 14.7, 18.4, 40.8, 41.5, 58.8, 73.7, 106.1, 149.4; High-resolution MS(EI) calcd for C$_{12}$H$_{19}$N: 177.1517, Found m/z: 177.1502 (M^+).
2.5 References and Notes


Chapter 3

Palladium-Catalyzed [4 + 2] Cycloaddition of Aldimines and 1,4-Dipolar Equivalents via Amphiphilic Allylation

3.1 Abstract

The combination of Pd catalyst and diethylzinc with triethylborane promotes the amphiphilic allylation of aldimines with 2,3-bismethylenebutane-1,4-diol derivatives to serve as bis-allylic zwitterion species to form 3,4-bismethylenepiperidines via a formal [4 + 2] cycloaddition reaction. 3,4-Bismethylenepiperidine rings are applicable for the synthesis of isoquinoline derivatives via the Diels–Alder reaction followed by an oxidation reaction with DDQ.
3.2 Introduction

Tamaru, Kimura and their co-workers demonstrated a Pd catalyst and triethylborane or diethylzinc promoted via the amphiphilic allylation of aldimines with allyl anion and allyl cation zwitterion species derived from 2-methylene propane-1,3-diol to form 3-methylene pyrrolidines in a single manipulation (Scheme 1).\(^1\) Aldimines were exposed to a mixture of 2-methylene propane-1,3-diols, Scheme 1. Pd-catalyzed amphiphilic allylation of aldimine with 2-methylene propane-1,3-diol.

\[
\text{Pd cat.} + \text{Et}_3\text{BN} \rightarrow \text{N}^+ \text{R}^2 \xrightarrow{\text{Pd cat.}} \text{N}^+ \text{R}^1 \rightarrow \text{N}^+ \text{R}^2 \xrightarrow{\text{Pd cat.}} \text{N}^+ \text{R}^1
\]

Pd catalyst, and triethylborane or diethylzinc and underwent \([3 + 2]\) cycloaddition reactions of 1,3-zwitterion species to form the pyrrolidine rings. Triethylborane promoted the amphiphilic allylation of bis-allyl alcohols with aldimines to construct the pyrrolidine rings at 50 °C, while diethylzinc promoted a similar cycloaddition reaction with bis-allyl alcohol benzyl ethers to form the same cyclized products at room temperature. The regio- and stereoselectivities using substituted 2-methylene propane-1,3-diols are in contrast to the results of TMM (trimethylenemethane) chemistry developed by Trost et al.\(^2\) Thus, the amphiphilic
allylation is among the most efficient and innovative methods for the synthesis of pyrrolidines in a [3 + 2] cycloaddition manner with 1,3-dipolar equivalent and aldimines. Recently, the author have developed the double amphiphilic allylation of nitriles with 2-methylenepropane-1,3-diol promoted by a Pd catalyst and triethylborane system and succeeded in producing pyrrolizidine derivatives via double [3+2] cycloaddition reaction.

Efficient construction of 6-membered nitrogen-containing heterocyclic compounds is an important and crucial method for modern organic synthesis. In particular, piperidine rings are widely distributed in nature and are useful physiologically active molecules as important building blocks. Piperidine alkaloids are a representative class of the potent biological activity and the broad range of the synthetic strategies, such as intramolecular mannich reaction, olefin metathesis, and biosynthesis, which have been reported. Herein, author disclose the novel and efficient synthetic methods for the formation of piperidine ring promoted by π-allylpalladium
**Scheme 2.** Amphiphilic Allylation of Aldimines with 2,3-Dimethylenebutane-1,4-diols

intermediates (Scheme 2). This is the first example of the amphiphilic allylation of aldimes with bis-allylic moieties via [4 + 2] cycloaddition reaction followed by oxidative treatment with DDQ to construct isoquinoline analogues from 2,3-bismethylenebutane-1,4-diol.
3.3 Results and Discussion

The author investigated the amphiphilic allylation of aromatic aldimines, which are prepared from benzaldehyde and \( p \)-anisidine. The results of the amphiphilic allylation with bisallylating agents, such as bis-allyl alcohol, acetate, and benzyl ether, utilizing triethylborane and diethylzinc as promoters are summarized in Table 1. Among these investigations using various kinds of Pd catalysts, promoters, and bis-allylating agents, it turned out that bis-allyl acetate serves as the most reactive 1,4-dipolar precursor in the presence of the \( \text{PdCl}_2(\text{PPh}_3)_2 \) catalyst with diethylzinc, although the amphiphilic allylation with 2-methylenebutane-1,3-diol is smoothly undertaken under the conditions of triethylborane.\(^1\) Based on these results of Table 1, author has examined the reactions of wide variety of aldimines prepared from aromatic and aliphatic amines with benzaldehyde (Table 2). Irrespective of the kinds of substituents of various aromatic amines which possess electron-donating and electron-deficient groups, the desired coupling products 1 were obtained in good to reasonable yields (entries 1–3, Table 2). Aliphatic amines such as benzylamine, \( n \)-hexylamine, and \( c \)-hexylamine also served as effective amines to provide the piperidines 1d-1f in high yields (entries 4–6, Table 2). Increasing the nucleophilicity of the amines produced higher yields of cyclized products 1. These results suggest that
amines with a higher electron density enhance the nucleophilicity of $\pi$-allylpalladium intermediate for the intramolecular electrophilic allylation process.

Table 1. Pd-Catalyzed Cycloaddition of Aldimine and 1,4-Dipole

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>promoter</th>
<th>catalyst</th>
<th>temp (°C) / time (h)</th>
<th>yield of 1a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Et$_3$B</td>
<td>Pd(OAc)$_2$</td>
<td>50/72</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>Et$_2$Zn</td>
<td>Pd(OAc)$_2$</td>
<td>rt/48</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>Ac</td>
<td>Et$_2$Zn</td>
<td>Pd(OAc)$_2$</td>
<td>rt/48</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>Ac</td>
<td>Et$_2$Zn</td>
<td>PdCl$_2$(CH$_3$CN)$_2$</td>
<td>rt/48</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>Ac</td>
<td>Et$_2$Zn</td>
<td>PdCl$_2$(PPh$_3$)$_2$</td>
<td>rt/48</td>
<td>75</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: p-anisidine (1.1 mmol) and PhCHO (1 mmol) in dry THF (1 mL) at reflux for 0.5 h; distillation of THF (azeotropic removal of water) and then Pd (0.1 mmol), n-Bu$_3$P (0.2 mmol), 2,3-bismethylene derivative (1.2 mmol), Et$_3$B or Et$_2$Zn (4.8 mmol) in THF (1 mL) under nitrogen atmosphere.

Next, author have developed the amphiphilic allylation of aldimines prepared from various aldehydes and aliphatic amines (Table 3). Substituted benzaldehydes could participate in the cycloaddition reaction to form piperidine derivatives (entries 1–3, Table 3). $\alpha,\beta$-Unsaturated aldehyde and heteroaromatic aldehyde aldimines
Table 2. Cycloaddition of PhCHO−Aldimine and 1,4-Dipole

<table>
<thead>
<tr>
<th>entry</th>
<th>amine R</th>
<th>yield of 1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(p-MeO)Ph</td>
<td>1a: 75</td>
</tr>
<tr>
<td>2</td>
<td>(p-HO)Ph</td>
<td>1b: 64</td>
</tr>
<tr>
<td>3</td>
<td>(p-Cl)Ph</td>
<td>1c: 50</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$Ph</td>
<td>1d: 85</td>
</tr>
<tr>
<td>5</td>
<td>n-Hex</td>
<td>1e: 73</td>
</tr>
<tr>
<td>6</td>
<td>c-Hex</td>
<td>1f: 68</td>
</tr>
</tbody>
</table>

*Reaction conditions: amine (1.1 mmol) and PhCHO (1 mmol) in dry THF (1 mL) at reflux for 0.5 h; distillation of THF (azeotropic removal of water) and then Pd (0.1 mmol), $n$-Bu$_3$P (0.2 mmol), 2,3- bismethyleneiod derivatives (1.2 mmol), Et$_2$Zn (1.2 mmol) in THF (1 mL) at rt for 48 h under nitrogen atmosphere.

the similar coupling products 1j−l in modest to good yields (entries 4−6, Table 3).

Aliphatic aldehyde aldimines were tolerated to the coupling reactions and constructed the 6-membered nitrogen heterocycles (entries 7−11, Table 3). In the presence of triethylborane, in place of diethylzinc, alkylaldehyde aldimine, prepared from $n$-hexanal with $p$-anisidine did not undergo the amphiphilic allylation at all; instead, an intractable mixture was obtained. On the other hand, diethylzinc promoted the expected reaction
smoothly giving rise to the desired products 1n,o in reasonable yields (entries 8 and 9, Table 3). In general, although the aldimines prepared from aliphatic amines and aliphatic aldehydes are so unreactive toward nucleophiles,7 it is noteworthy that all of the combinations of amines and aldehydes could take part in the coupling reactions (entries 10 and 11, Table 3). Although both the triethylborane and diethylzinc systems were utilized for the formation of pyrrolidines from the aliphatic aldehyde and aliphatic amine imines, in this case, diethylzinc was superior to triethylborane for the

Table 3. Cycloaddition of Various Aldimines and 1,4-Dipole

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde R</th>
<th>amine R’</th>
<th>yield of 1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(p-Cl)Ph</td>
<td>CH₂Ph</td>
<td>1g: 70</td>
</tr>
<tr>
<td>2</td>
<td>(p-MeO)Ph</td>
<td>CH₂Ph</td>
<td>1h: 68</td>
</tr>
<tr>
<td>3</td>
<td>(p-Me)Ph</td>
<td>CH₂Ph</td>
<td>1i: 71</td>
</tr>
<tr>
<td>4</td>
<td>PhCHCH₂</td>
<td>CH₂Ph</td>
<td>1j: 50</td>
</tr>
<tr>
<td>5</td>
<td>3-pyridyl</td>
<td>CH₂Ph</td>
<td>1k: 51</td>
</tr>
<tr>
<td>6</td>
<td>2-furyl</td>
<td>n-Hex</td>
<td>1l: 80</td>
</tr>
<tr>
<td>7</td>
<td>c-Hex</td>
<td>CH₂Ph</td>
<td>1m: 77</td>
</tr>
<tr>
<td>8</td>
<td>n-Pent</td>
<td>n-Hex</td>
<td>1n: 53</td>
</tr>
<tr>
<td>9</td>
<td>n-Pent</td>
<td>c-Hex</td>
<td>1o: 51</td>
</tr>
<tr>
<td>10</td>
<td>c-Hex</td>
<td>n-Hex</td>
<td>1p: 60</td>
</tr>
<tr>
<td>11</td>
<td>c-Hex</td>
<td>c-Hex</td>
<td>1q: 65</td>
</tr>
</tbody>
</table>
"Reaction conditions: amine (1.1 mmol), aldehyde (1 mmol) in dry THF (1 mL) at reflux for 0.5 h; distillation of THF (azeotropic removal of water) and then Pd (0.1 mmol), n-Bu₃P (0.2 mmol), 2,3-bismethylene diols derivatives (1.2 mmol), Et₂Zn (1.2 mmol) in THF (1 mL) at rt under nitrogen atmosphere.

formation of piperidine rings.¹

A plausible reaction mechanism is shown in Scheme 4. Oxidative addition of 2,3-bismethylenebutane-1,4-diacetate occurred using the Pd(0) catalyst to form the π-allylpalladium intermediate followed by transmetalation with diethylzinc to form the allylic anion species possessing the allylic acetate. This allyl anion species reacted with aldimine and then would construct the homoallylamine skeletons with the allyl acetate group. Furthermore, this intermediate underwent oxidative addition toward Pd catalyst, and the subsequent intramolecular electrophilic allylation formed piperidine rings with the liberation of Pd(0) catalyst. It might be possible that the steric repulsion of β-substituents on π-allylpalladium and the effect of entropy on 6-membered ring formations make the amphiphilic allylation more difficult than that of 5-membered ring formation so that a more reactive leaving group, such as acetate, would be required for the present amphiphilic allylation. In contrast to the results of 5-membered ring formation using triethylborane, the system using diethylzinc might be more expedient for an intramolecular electrophilic allylation process owing to the higher nucleophilicity
of zinc amide intermediate. Thus, it can be considered that 2,3-bismethylenebutane-1,4-diacetate serves as a 1,4-ziwitterion equivalent for the formal [4 + 2] cycloaddition reaction with aldimes.

**Scheme 4.** Plausible Reaction Mechanism for Pd/Et$_2$Zn-Promoted Amphiphilic Allylation of Aldimine

This transformation is applicable to the selective formation of the substituted 3,4-dimethylenepiperidines. α-Phenyl-substituted 2,3-bismethylenebutane-1,4-diacetate in the presence of a Pd catalyst and diethylzinc provided the benzylidene pyrrolidine 1r as a sole product (eq 1). In this case, the second step of the
electrophilic allylation was particularly suffered from the steric repulsion between Ph group and the vinylic proton, and the less-substituted allylic carbon tends to react with amines to give the Ph-substituted diene moiety with Z-stereoselectivity (Scheme 5). This selectivity may originate from the equilibrium among these $\pi$-allylpalladium complexes, and thermodynamically stable three substituted alkenes would be formed predominantly through the anti-$\pi$-allylpalladium intermediate.

\[ \text{PhCHO (1 mmol)} \xrightarrow{\text{BnNH}_2 (1.1 \text{ mmol})} \xrightarrow{\text{PdCl}_2(\text{PPh}_3)_2 (0.1 \text{ mmol}) \atop \text{Et}_2\text{Zn (4.8 mmol), rt, 48 h}} \xrightarrow{\text{n-Bu}_3\text{P (0.2 mmol)}} \text{1r 65\%} \]

\[ [\text{E:Z} = 20:1] \]
Thus, the formed 3,4-bismethylenepiperidines were used for the synthesis of nitrogen-containing heterocyclic compounds. For example, electron-deficient acetylenes, such as acetylenedicarboxylates, underwent the Diels–Alder reaction to produce bicyclic compounds, i.e., hexahydroisoquinolines in high yields (Scheme 6).
**Scheme 6.** Synthesis of Isoquinoline via Diels–Alder reaction with 3,4-Bismethylenepiperidine and Alkyne

\[
\text{R} \quad \text{Ph} \quad \text{Bn} \quad + \quad \text{E} \quad \text{CH}_2\text{Cl}_2 \quad \text{reflux, 24 h} \quad \rightarrow \quad \text{E} \quad \text{Ph} \quad \text{Ph} \\
1d: R = H \quad 1r: R = \text{Ph} \quad E = \text{CO}_2\text{Me} \quad 2d 94\% \quad 2r 83\% [1.5:1] \\
\text{DDQ} \quad \text{xylene} \quad \text{reflux, 48 h} \quad \rightarrow \quad \text{Ph} \\
3d 80\% \quad 3r 47\%
\]

**Figure 1.** ORTEP drawing of 3d. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.
These heterocyclic compounds were converted into the isoquinoline compounds by treatment with DDQ under oxidized conditions via oxidative debenzylation. Structures of isoquinoline 3d and 3r were determined by X-ray analysis (Figure 1 and 2). Although some examples of the oxidative debenzylation by DDQ have been reported so far, these application processes are utilized for the efficient synthesis of isoquinoline alkaloid from aldmines and 1,4-bisallyl acetate.

In summary, author have developed the Pd-catalyzed amphiphilic allylation of aldmines with 2,3-bismethylenebutane-1,4-diacetates to form piperidines via formal [4 + 2] cycloaddition. These heterocyclic compounds were converted into isoquinoline derivatives via a Diels–Alder reaction followed by an oxidative reaction with DDQ via
the debenzylation process. These procedures could be used for the efficient synthesis of alkaloids and physiologically active molecules.
3.4 Experimental

General experimental

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 60F254). Flash chromatography columns were packed with silica gel as a slurry in hexane. Gradient flash chromatography was conducted eluting with a continuous gradient from hexane to the indicated solvent. Proton and carbon NMR data were obtained with a JEOL JNM-AL400 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 spectrophotometer. High resolution mass spectra (HRMS) were measured with a JEOL JMS-700N.

Solvents and Reagents

Tetrahydrofuran was dried and distilled from benzophenone and sodium immediately prior to use under nitrogen atmosphere. p-Xylene was dried and distilled from sodium under nitrogen atmosphere. PdCl$_2$(PPh$_3$)$_2$, Pd(OAc)$_2$, n-Bu$_3$P, Et$_2$Zn (1.0 M hexane solution), p-anisidine, benzylamine, n-hexylamine, cyclohexylamine, p-chlorobenzaldehyde, and p-hydroxybenzaldehyde were purchased and used without further purification. Benzaldehyde, p-methoxybenzaldehyde, p-tolualdehyde, trans-cinnamaldehyde, 3-pyrindicarboxaldehyde, furfural, c-hexanecarbaldehyde, and n-hexanal were purchased and distilled prior to use. 2,3-Dichloro-5,6-dicyano-p-benzoquinone (DDQ) was purchased and used without further purification.
Preparation of 2,3-dimethylene-1,4-butanediyl diacetate

A flask was charged with DMAP (2.4 g, 20 mmol). A flask was evacuated and filled with nitrogen. 2-Butyne-1,4-diol (8.6 g, 0.1 mol) and pyridine (40 ml) were added to the flask. To the reaction mixture was added acetic anhydride (47 ml, 0.5 mol) dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 24 h. The progress of reaction was monitored by TLC. After the reaction was complete, the solvent was evaporated under vacuum. The residue was diluted with EtOAc and washed with saturated aqueous NaHCO$_3$ and brine, and then the organic phase was dried with MgSO$_4$ and concentrated in vacuo to give colorless oil, which was purified by column chromatography over silica gel (eluent; EtOAc/hexane = 1/4) to give 2-butyne-1,4-diyl diacetate (16.1 g, 95%, $R_f$ = 0.5, EtOAc/hexane = 1/4). As a next step, a flask was charged with Grubbs 2$^{nd}$ Catalyst (168.9 mg, 0.05 mmol). A flask was evacuated and filled with ethylene gas. To a flask was added toluene (30 ml). A solution of 2-butyne-1,4-diyl diacetate (3.4 g, 20 mmol) in toluene (20 ml) was added and the mixture was stirred at 80 °C for 24 h. After being cooled to room temperature, the reaction was quenched with ethyl vinyl ether (10 ml). The mixture was filtrated through a plug of silica gel and evaporated in vacuo. The residue was purified by column chromatography over silica gel (eluent; EtOAc/hexane = 1/2) to give 2,3-dimethylene-1,4-butanediyl diacetate (3.5 g, 89%, $R_f$ = 0.60, EtOAc/hexane = 1/4). $^1$H NMR (CDCl$_3$, 400 MHz): δ 2.10 (s, 6H), 4.78 (s, 4H), 5.32 (s, 2H), 5.34 (s, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 20.8, 64.8, 115.7, 139.2, 170.5; High-resolution MS (EI), calcd for C$_{10}$H$_{14}$O$_4$ ([M]$^+$): 198.0892 Found: m/z 198.0890.

Preparation of 1-phenyl-2,3-dimethylene-1,4-butanediyl diacetate

82
4-[(Tetrahydro-2H-pyran-2-yl)oxy]-1-phenyl-2-butyn-1-ol was prepared as described in the literature. The THP protecting material was deprotected as described in the literature. 1-Phenyl-2,3-dimethylene-1,4-butanediyl diacetate was prepared as above. 

\[ ^1H \text{NMR (CDCl}_3, 400 MHz): \delta 2.05 (s, 3H), 2.11 (s, 3H), 4.69 (s, 2H), 5.24 (s, 2H), 5.39 (s, 2H), 6.57 (s, 1H), 7.26-7.35 (m, 5H); ^{13}C \text{NMR (CDCl}_3, 100 MHz): \delta 20.9, 21.2, 65.3, 75.0, 114.8, 116.9, 127.6, 128.1, 128.3, 138.0, 139.5, 143.5, 169.7, 170.3; \text{High-resolution MS (EI), calcd for C}_{16}H_{18}O_4 ([M]+): 274.1205 \text{ Found: m/z 274.1209.} \]

**Representative procedure for amphiphilic allylation of aldimine with 2,3-dimethylene-1,4-butanediyl diacetate** (entry 5, Table 1): A solution of benzaldehyde (106 mg, 1.0 mmol) and \( p \)-anisidine (129 mg, 1.1 mmol) in dry THF (1 ml) was refluxed for 30 min under nitrogen, and then THF (1 ml) was added and distilled off to remove water under atmospheric pressure of nitrogen. Over the aldimine residue were successively added PdCl\(_2\)(PPh\(_3\))\(_2\) (70.2 mg, 0.1 mmol), \( n \)-Bu\(_3\)P (50 μl, 0.2 mmol), 2,3-dimethylene-1,4-butanediyl diacetate (237.9 mg, 1.2 mmol), THF (1ml), and Et\(_2\)Zn (4.8 mmol, 1 M in hexane). The homogeneous mixture was stirred and heated for 48 hours at ambient temperature under nitrogen. The mixture was diluted with EtOAc and washed with saturated aqueous NaHCO\(_3\) and brine, and then the organic phase was dried with MgSO\(_4\) and concentrated in vacuo to give brown oil, which was purified by column chromatography over silica gel (eluent; EtOAc/hexane = 1/4) to give \( 1a \) (219.4 mg, 75%, \( Rf = 0.60, \) EtOAc/hexane = 1/4)

\( 1-(4\text{-methoxyphenyl})-4,5\text{-dimethylene-2-phenylpiperidine} \ (1a) \)
IR (neat): 2905 (w), 2831 (w), 1736 (w), 1510 (s), 1450 (m), 1244 (s), 1180 (m), 1040 (m), 897 (m), 816 (m), 764 (w), 700 (m) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.66 (dd, \(J = 6.0, 14.3\) Hz, 1H), 2.90 (dd, \(J = 6.0, 14.3\) Hz, 1H), 3.70 (s, 3H), 3.94 (d, \(J = 13.9\) Hz, 1H), 4.02 (d, \(J = 13.9\) Hz, 1H), 4.54 (t, \(J = 6.0\) Hz, 1H), 4.78 (s, 1H), 4.94 (s, 1H), 5.28 (s, 1H), 5.33 (s, 1H), 6.73 (m, 4H), 7.17-7.32 (m, 5H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 40.4, 53.2, 55.6, 62.9, 108.3, 109.5, 114.3, 117.6, 126.6, 126.7, 128.2, 141.8, 143.0, 143.6, 144.6, 152.8; High-resolution MS (EI), calcd for C\(_{20}\)H\(_{21}\)NO: 291.1623, Found \(m/z\) (relation intensity): 291.1613 ([M\(^+\)], 4), 278.1523 (100).

1-(4-hydroxyphenyl)-4,5-dimethylene-2-phenylpiperidine (1b)

IR (neat): 700 (m), 739 (m), 819 (m), 899 (m), 1246 (m), 1373 (m), 1450 (m), 1512 (s), 1599 (w), 1707 (w), 2797 (m), 2959 (m), 3028 (m), 3329 (b) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.64 (dd, \(J = 6.1, 8.2\) Hz, 1H), 2.89 (dd, \(J = 6.1, 8.2\) Hz, 1H), 3.91 (d, \(J = 14.1\) Hz, 1H), 4.00 (d, \(J = 14.1\) Hz, 1H), 4.51 (t, \(J = 6.1\) Hz, 1H), 4.78 (s, 1H), 4.93 (s, 1H), 5.01 (br, 1H), 5.28 (s, 1H), 5.33 (s, 1H), 6.63 (d, \(J = 9.0\) Hz, 2H), 6.68 (d, \(J = 9.0\) Hz, 2H), 7.14-7.19 (m, 5H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 40.3, 53.6, 63.1, 108.5, 109.6, 115.8, 118.3, 126.6, 126.8, 128.1, 141.9, 143.0, 143.3, 144.4, 148.9; High-resolution MS (EI), calcd for C\(_{19}\)H\(_{19}\)NO:277.1467, Found \(m/z\) (relation intensity):277.1467 ([M\(^+\)], 100).

1-(4-chlorophenyl)-4,5-dimethylene-2-phenylpiperidine (1c)

IR (neat): 606 (w), 698 (s), 743 (m), 808 (s), 899 (s), 982 (w), 1028 (w), 1097 (w), 1190 (m), 1240 (m), 1335 (m), 1373 (s), 1435 (m), 1450 (s), 1495 (s), 1597 (s), 1736 (w), 2361 (w), 2804 (w), 3026 (w) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.68 (dd, \(J = 5.9,
14.5 Hz, 1H), 2.99 (dd, J = 5.9, 14.5 Hz, 1H), 4.12 (s, 2H), 4.69 (t, J = 5.9 Hz, 1H), 4.78 (s, 1H), 4.98 (s, 1H), 5.33 (s, 1H), 5.39 (s, 1H), 6.60 (dd, J = 2.2, 6.9 Hz, 2H), 7.07 (dd, J = 2.2, 6.9 Hz, 2H), 7.19-7.32 (m, 5H); 13C NMR (CDCl3, 100 MHz): δ 39.8, 50.2, 61.5, 108.6, 109.9, 114.9, 122.2, 126.1, 126.8, 128.4, 128.7, 140.1, 141.6, 142.9, 148.2; High-resolution MS (EI), calcd for C19H18ClN:295.1128, Found m/z (relation intensity): 295.1108 ([M]⁺, 100).

1-benzyl-4,5-dimethylene-2-phenylpiperidine (1d)
IR (neat): 700 (m), 899 (m), 1117 (m), 1454 (m), 1492 (m), 1641 (w), 2789 (w), 2953 (w), 3028 (w) cm⁻¹; ¹H NMR (CDCl3, 400 MHz): δ 2.52 (dd, J = 3.9, 14.0 Hz, 1H), 2.59 (tdd, J = 2.1, 10.2, 14.0 Hz, 1H), 2.79 (td, J = 1.7, 12.7 Hz, 1H), 2.94 (d, J = 13.6 Hz, 1H), 3.41 (dd, J = 3.9, 10.2 Hz, 1H), 3.44 (d, J = 12.7 Hz, 1H), 3.78 (d, J = 13.6 Hz, 1H), 4.67 (dd, J = 1.7, 1.8 Hz, 1H), 4.73 (dd, J = 1.8, 2.1 Hz, 1H), 5.06 (dd, J = 1.8, 2.1 Hz, 1H), 5.08 (dd, J = 1.7, 1.8 Hz, 1H), 7.18-7.47 (m, 10H); 13C NMR (CDCl3, 100 MHz): δ 42.9, 58.0, 58.6, 67.8, 108.6, 108.8, 126.7, 127.2, 127.5, 128.1, 128.61, 128.63 139.0, 143.6, 144.5, 145.5; High-resolution MS (EI), calcd for C20H21N:275.1667, Found m/z (relation intensity): 275.1667 ([M]⁺, 100).

1-hexyl-4,5-dimethylene-2-phenylpiperidine (1e)
IR (neat): 613 (m), 700 (s), 752 (m), 877 (m), 897 (s), 966 (m), 984 (m), 1074 (m), 1242 (m), 1261 (m), 1312 (m), 1362 (m), 1429 (m), 1454 (s), 1493 (m), 1643 (m), 2692 (m), 2750 (m), 2858 (s), 2928 (s), 2928 (s), 3028 (m), 3062 (m), 3082 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.82 (t, J = 7.0 Hz, 3H), 1.06-1.26 (m, 6H), 1.39 (quin, J = 6.8 Hz, 2H), 1.96 (ddt, J = 1.7, 4.9, 12.8 Hz, 1H), 2.42-2.53 (m, 3H), 2.86 (dt, J = 1.72, 12.7 Hz, 2H), 7.18-7.47 (m, 5H); 13C NMR (CDCl₃, 100 MHz): δ 139.0, 143.6, 144.5, 145.5; High-resolution MS (EI), calcd for C20H21N:275.1667, Found m/z (relation intensity): 275.1667 ([M]⁺, 100).
1H), 3.30 (dd, \( J = 4.9, 10.3 \text{ Hz}, 1\text{H} \)), 3.63 (d, \( J = 12.7 \text{ Hz}, 1\text{H} \)), 4.70 (t, \( J = 1.7 \text{ Hz} 1\text{H} \)), 4.84 (t, \( J = 1.7 \text{ Hz} 1\text{H} \)), 5.07 (t, \( J = 1.7 \text{ Hz}, 1\text{H} \)), 5.13 (t, \( J = 1.7 \text{ Hz} 1\text{H} \)), 7.28-7.35 (m, 5H); \(^{13}\text{C} \text{NMR} (\text{CDCl}_3, 100 \text{ MHz}): \delta 14.0, 22.5, 26.3, 27.0, 31.7, 43.1, 54.4, 58.2, 67.9, 108.3, 108.6, 126.9, 127.5 (2 \text{ C}), 128.2 (2 \text{ C}), 143.5; \text{High-resolution MS (EI)}, \text{calcd for } \text{C}_{19}\text{H}_{27}\text{N}:269.2143, \text{Found } m/z (\text{relation intensity}):269.2158 ([M]^{+}, 37), 198.1225 (100).

1-cyclohexyl-4,5-dimethylene-2-phenylpiperidine (1f)

IR (neat): 700 (s), 893 (s), 1099 (m), 1450 (m), 1491 (m), 1641 (w), 2791 (m), 2853 (s), 2930 (s), 3026 (w) cm\(^{-1}\); \(^1\text{H} \text{NMR} (\text{CDCl}_3, 400 \text{ MHz}): \delta 0.81-1.16 (m, 4\text{H}), 1.39-1.51 (m, 2\text{H}), 1.63-1.73 (m, 4\text{H}), 2.37 (tt, \( J = 3.2, 8.3 \text{ Hz}, 1\text{H} \)), 2.47 (d, \( J = 7.3 \text{ Hz}, 2\text{H} \)), 3.13 (d, \( J = 12.7 \text{ Hz}, 1\text{H} \)), 3.51 (d, \( J = 12.7 \text{ Hz}, 1\text{H} \)), 3.68 (t, \( J = 7.3 \text{ Hz}, 1\text{H} \)), 4.67 (d, \( J = 1.7 \text{ Hz}, 1\text{H} \)), 4.81 (s, 1 \text{H}), 5.07 (s, 1\text{H}), 5.13 (d, \( J = 1.7 \text{ Hz}, 1\text{H} \)), 7.30-7.35 (m, 5H); \(^{13}\text{C} \text{NMR} (\text{CDCl}_3, 100 \text{ MHz}): \delta 24.2, 25.6, 26.31, 26.36, 31.5, 43.5, 51.6, 58.6, 64.4, 107.9, 108.2, 126.9, 127.4, 128.3, 143.8, 145.4, 145.5; \text{High-resolution MS (EI)}, \text{calcd for } \text{C}_{19}\text{H}_{25}\text{N}:267.1987, \text{Found } m/z (\text{relation intensity}):267.1980 ([M]^{+}, 100).

1-benzyl-4,5-dimethylene-2-(4-chlorophenyl)piperidine (1g)

IR (KBr): 696 (s), 719 (s), 746 (s), 814 (s), 907 (s), 1013 (s), 1092 (s), 1261 (s), 1483 (s), 1597 (m), 1639 (m), 2887 (m), 2943 (m) cm\(^{-1}\); \(^1\text{H} \text{NMR} (\text{CDCl}_3, 400 \text{ MHz}): \delta 2.51 (d, \( J = 6.5 \text{ Hz}, 2\text{H} \)), 2.79 (d, \( J = 13.0 \text{ Hz}, 1\text{H} \)), 2.95 (d, \( J = 13.7 \text{ Hz}, 1\text{H} \)), 3.41 (t, \( J = 6.5 \text{ Hz}, 1\text{H} \)), 3.43 (d, \( J = 13.0 \text{ Hz}, 1\text{H} \)), 3.74 (d, \( J = 13.7 \text{ Hz}, 1\text{H} \)), 4.68 (s, 1\text{H}), 4.74 (s, 1\text{H}), 5.08 (s, 1\text{H}), 5.09 (s, 1\text{H}), 7.20-7.32 (m, 5H), 7.31 (d, \( J = 8.4 \text{ Hz}, 2\text{H} \)), 7.41 (d, \( J = 8.4 \text{ Hz}, 2\text{H} \)); \(^{13}\text{C} \text{NMR} (\text{CDCl}_3, 100 \text{ MHz}): \delta 42.6, 57.8, 58.5, 66.9, 108.9, 109.0, 126.8,
128.2, 128.5, 128.7, 128.8, 132.8, 138.7, 142.2, 144.2, 145.1; High-resolution MS (FAB), calcd for C₂₀H₂₁ClN: 310.1366, Found m/z (relation intensity): 310.1363 ([M+H]⁺, 100).

1-benzyl-4,5-dimethylene-2-(4-methoxyphenyl)piperidine (1h)
IR (neat): 698 (s), 737 (s), 814 (s), 837 (s), 905 (s), 1031 (s), 1173 (s), 1238 (s), 1261 (s), 1301 (s), 1508 (s), 1612 (m), 2899 (m), 2939 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 2.50 (dd, J = 3.9, 14.2 Hz, 1H), 2.57 (tdd, J = 2.0, 10.3, 14.2 Hz, 1H), 2.78 (td, J = 1.7, 12.7 Hz, 1H), 2.92 (d, J = 13.7 Hz, 1H), 3.37 (dd, J = 3.9, 10.3 Hz, 1H), 3.42 (d, J = 12.7 Hz, 1H), 3.77 (d, J = 13.7 Hz, 1H), 3.79 (s, 3H), 4.66 (t, J = 1.7 Hz, 1H), 4.72 (t, J = 2.0 Hz, 1H), 5.05 (t, J = 2.0 Hz, 1H), 5.07 (t, J = 1.7 Hz, 1H), 6.87 (d, J = 8.8 Hz, 2H), 7.19-7.29 (m, 5H), 7.37 (d, J = 8.8 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 42.9, 55.2, 58.1, 58.4, 67.1, 108.5, 108.7, 113.9, 126.6, 128.0, 128.52, 128.57, 135.6, 139.1, 144.6, 145.6, 158.7; High-resolution MS (FAB), calcd for C₂₁H₂₂NO: 304.1701, Found m/z (relation intensity): 304.1690 ([M-H]⁻, 75), 305.1760 ([M]⁺, 100)

1-benzyl-4,5-dimethylene-2-p-tolylpiperidine (1i)
IR (KBr): 696 (s), 745 (s), 812 (s), 908 (s), 1011 (s), 1111 (s), 1236 (s), 1261 (s), 1495 (s), 1514 (s), 1641 (m), 2739 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 2.31 (s, 3H), 2.50 (dd, J = 3.8, 14.0 Hz, 1H), 2.58 (dd, J = 10.4, 14.0 Hz, 1H), 2.77 (d, J = 12.7 Hz, 1H), 2.92 (d, J = 13.4 Hz, 1H), 3.37 (dd, J = 3.8, 10.4 Hz, 1H), 3.43 (d, J = 12.9 Hz, 1H), 3.79 (d, J = 13.4 Hz, 1H), 4.67 (s, 1H), 4.72 (s, 1H), 5.06 (s, 1H), 5.07 (s, 1H), 7.15-7.37 (m, 9H); ¹³C NMR (CDCl₃, 100 MHz): δ 21.0, 43.0, 58.1, 58.5, 67.5, 108.5, 108.8, 126.7, 127.4, 128.1, 128.5, 129.2, 136.7, 139.1, 140.6, 144.5, 145.6;
High-resolution MS (FAB), calcd for C_{21}H_{23}N: 289.1830, Found m/z (relation intensity): 289.1831 ([M]^+, 100).

1-benzyl-4,5-dimethylene-2-styrylpiperidine (1j)
IR (KBr): 692 (s), 741 (s), 897 (s), 912 (s), 1107 (s), 1194 (s), 1450 (s), 1495 (s), 1599 (m), 2885 (s), 2930 (s) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.45 (dd, \(J = 8.6, 13.9\) Hz, 1H), 2.54 (dd, \(J = 3.9, 13.9\) Hz, 1H), 2.88 (d, \(J = 13.3\) Hz, 1H), 3.24 (ddd, \(J = 3.9, 8.2, 8.6\) Hz, 1H), 3.34 (d, \(J = 10.1\) Hz, 1H), 3.37 (d, \(J = 10.1\) Hz, 1H), 3.96 (d, \(J = 13.3\) Hz, 1H), 4.68 (s, 1H), 4.76 (s, 1H), 5.086 (s, 1H), 5.087 (s, 1H) 6.29 (dd, \(J = 8.2, 16.0\) Hz, 1H), 6.56 (d, \(J = 16.0\) Hz, 1H), 7.20-7.38 (m, 10H); \(^1^3\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 39.9, 56.6, 58.5, 63.9, 108.9, 109.2, 126.2, 126.7, 127.4, 128.1, 128.4, 128.8, 131.0, 131.8, 136.9, 138.9, 144.4, 144.6; High-resolution MS (FAB), calcd for C_{22}H_{22}N: 300.1752, Found m/z (relation intensity): 300.1747 ([M-H]^+, 100).

1-benzyl-4,5-dimethylene-2-(3-pyridyl)piperidine (1k)
IR (KBr) 3028 (w), 2943 (w), 2799 (w), 1639 (m), 1578 (s), 1477 (m), 1427 (s), 1371 (s), 1354 (m), 1180 (s), 1103 (s), 903 (s), 880 (m), 808 (m), 748 (m), 698 (s) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.57 (d, \(J = 8.0\) Hz, 2H), 2.85 (dt, \(J = 1.5, 13.0\) Hz, 1H ), 3.03 (d, \(J = 13.7\) Hz, 1H), 3.45 (d, \(J = 13.0\) Hz, 1H), 3.52 (t, \(J = 7.1\) Hz, 1H), 3.73 (d, \(J = 13.7\) Hz, 1H), 4.70(s, 1H), 4.77 (d, \(J = 1.5\) Hz, 1H), 5.113 (s, 1H), 5.117 (s, 1H), 7.21-7.32 (m, 6H), 7.84 (dt, \(J = 8.0, 1.6\) Hz, 1H), 8.52(dd, \(J = 4.8, 1.6\) Hz, 1H), 8.68 (s, 1H); \(^1^3\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 42.2, 57.6, 58.5, 64.8, 109.29, 109.32, 123.7, 127.0, 128.3, 128.5, 135.0, 138.5, 139.0, 144.0, 144.6, 148.9, 149.5; High-resolution MS (EI), calcd for C_{19}H_{20}N_{2}: 276.1626, Found m/z: 287.1626 ([M]^+, 100).
1-benzyl-4,5-dimethylene-2-(2-furyl)piperidine (1I)

IR (KBr) 3063(w), 3028(w), 2954(w), 2790(w), 1639(w), 1454(m), 1434(m), 1010(m), 900(s), 739(s), 698(s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 2.71 (dd, J = 14, 21 Hz, 2H), 3.03 (d, J = 13.2 Hz, 1H), 3.29 (d, J = 13.2 Hz, 1H), 3.41 (d, J = 13.2 Hz, 1H), 3.61 (d, J = 13.2 Hz, 1H), 3.92 (t, J = 5.5 Hz, 1H), 4.70(s, 1H), 4.79 (s, 1H), 5.13 (s, 1H), 5.16 (s, 1H), 6.30 (d, J = 3.0 Hz, 1H), 6.34 (dd, J = 1.7, 3.0 Hz, 1H) 7.21-7.55 (m, 5H), 7.67 (dd, J = 1.2, 7.2 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 37.0, 55.4, 57.1, 58.1, 107.9, 109.7, 110.0, 127.0, 128.2, 128.4, 128.5, 129.0, 131.8, 131.9, 132.0, 132.1, 141.6; High-resolution MS (FAB), calcd for C₁₈H₁₉NO: 265.1467, Found m/z: 265.1467 ([M]+, 92), 266.1547 (100).

1-benzyl-4,5-dimethylene-2-cyclohexylpiperidine (1m)

IR (KBr): 696 (s), 734 (s), 891 (s), 1448 (s), 1495 (m), 1634 (w), 2851 (s), 2922 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.86-1.29 (m, 5H), 1.43-1.83 (m, 5H), 2.17-2.52 (m, 4H), 2.99 (d, J = 14.7 Hz, 1H), 3.34 (d, J = 14.7 Hz, 1H), 3.63 (d, J = 13.4 Hz, 1H), 3.68 (d, J = 13.4 Hz, 1H), 4.60 (s, 1H), 4.71 (s, 1H), 5.05 (s, 1H), 5.16 (s, 1H), 7.21-7.35 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz): δ 26.4, 26.7, 30.0, 30.2, 31.8, 39.0, 53.7, 54.5, 65.0, 108.3, 109.2, 126.7, 128.2, 128.8, 140.1, 144.2, 145.8; High-resolution MS (FAB), calcd for C₂₀H₂₇N: 282.2222, Found m/z (relation intensity):282.2209 ([M+H]⁺, 100).

1-hexyl-4,5-dimethylene-2-pentylpiperidine (1n)
IR (neat): 735 (s), 908 (s), 1113 (m), 1352 (w), 1447 (w), 2860 (m), 2932 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.88 (t, J = 6.3 Hz, 3H), 0.89 (t, J = 6.3 Hz, 3H), 1.25-1.53 (m, 16H), 2.15 (dd, J = 7.3, 14.0 Hz, 1H), 2.39 (dd, J = 4.6, 14.0 Hz, 1H) 2.44 (ddd, J = 6.0, 6.5, 7.0 Hz, 1H), 2.48 (dddd, J = 6.0, 6.5, 7.0 Hz, 1H), 2.68 (dddd, J = 4.4, 4.6, 4.9, 7.3 Hz, 1H), 3.11 (d, J = 13.8 Hz, 1H), 3.40 (d, J = 13.8 Hz, 1H), 4.67 (d, J = 1.0 Hz, 1H), 4.71 (d, J = 1.0 Hz, 1H), 5.02 (d, J = 1.0 Hz, 1H), 5.10 (d, J = 1.0 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 14.03, 14.04, 22.62, 22.63, 26.1, 27.2, 27.5, 30.9, 31.8, 32.1, 35.9, 50.6, 55.3, 59.4, 108.6, 108.9, 144.6, 145.5; High-resolution MS (EI), calcd for C₁₉H₃₃N:263.2613, Found m/z (relation intensity): 263.2595 ([M]+, 100).

1-hexyl-4,5-dimethylene-2-cyclohexylpiperidine (1o)

IR (neat): 735 (s), 889 (s), 986 (m), 1022 (m), 1090 (m), 1103 (m), 1261 (m), 1447 (s), 1634 (m), 2853 (s), 2928 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 0.88 (t, J = 6.8 Hz, 3H), 0.83-0.97 (m, 2H), 1.08-1.50 (m, 12H), 1.64-1.96 (m, 4H), 1.93-1.96 (m, 1H), 2.18 (dd, J = 7.4, 13.3 Hz, 1H), 2.32-2.46 (m, 2H), 2.39 (dd, J = 4.3, 13.3 Hz, 1H), 2.44 (ddd, J = 4.3, 7.4, 13.3 Hz, 1H), 2.39 (dd, J = 4.3, 13.3 Hz, 1H), 3.08 (d, J = 14.4 Hz, 1H), 3.47 (d, J = 14.4, 1H), 4.67 (d, J = 1.5 Hz, 1H), 4.68 (d, J = 1.5 Hz, 1H), 5.03 (d, J = 1.5 Hz, 1H), 5.13 (d, J = 1.5 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 14.1, 22.7, 26.4, 26.5, 26.7, 27.1, 27.7, 30.0, 30.4, 31.8, 32.0, 39.1, 50.4, 54.9, 64.9, 108.0, 108.5, 144.6, 145.9; High-resolution MS (EI), calcd for C₁₉H₃₃N:275.2613, Found m/z (relation intensity): 275.2589 ([M]+, 100).

1-cyclohexyl-4,5-dimethylene-2-pentylpiperidine (1p)

IR (neat): 696 (m), 743 (m), 889 (s), 1096 (m), 1259 (m), 1377 (m), 1450 (s), 1636 (m), 1786 (w), 2791 (m), 2855 (s), 2928 (s), 3078 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ
0.89 (t, J = 6.8 Hz, 3H), 1.09-1.49 (m, 13H), 1.58-1.63 (m, 1H), 1.76-1.86 (m, 4H), 2.15 (dd, J = 13.8, 5.5 Hz, 1H), 2.46 (dd, J = 13.8, 5.5 Hz, 1H), 2.55 (tt, J = 3.5, 10.5 Hz, 1H), 2.84 (tdd, J = 5.5, 5.5, 7.9 Hz, 1H), 3.22 (d, J = 13.7 Hz, 1H), 3.34 (d, J = 13.7 Hz, 1H), 4.64 (d, J = 1.5 Hz, 1H), 4.70 (d, J = 1.5 Hz, 1H), 5.098 (s, 1H), 5.099 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 14.0, 22.7, 25.9 (2 C), 26.1, 26.3, 28.6, 31.6, 31.9, 32.1, 37.0, 50.2, 55.7, 58.6, 107.4, 108.5, 144.9, 145.4; High-resolution MS (EI), calcd for C\(_{18}\)H\(_{31}\)N: 261.2457, Found m/z (relation intensity): 261.2446 ([M]^+\(^{13}\), 88), 218.1940 (100).

**1,2-dicyclohexyl-4,5-dimethylene piperidine (1q)**

IR (neat) 3290 (w), 3074 (s), 2852 (s), 2852 (s), 1633 (m), 1448 (s), 1099 (w), 983 (w), 887 (s), 742 (w), 696 (w) cm\(^{-1}\); \(^{1}\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 0.84-0.95 (m, 2H), 1.06-1.31 (m, 8H), 1.46 (dquin, J = 3.2, 7.8 Hz, 1H), 1.56-1.87 (m, 10H), 2.22 (dd, J = 6.6, 13.9 Hz, 1H), 2.38 (dd, J = 5.1, 13.9 Hz, 1H), 2.49(ddd, J = 5.1, 6.6, 7.8 Hz, 1H), 2.51 (quin, J = 6.4 Hz, 1H), 3.25 (d, J = 8.0 Hz, 1H), 3.39 (d, J = 8.0 Hz, 1H), 4.67 (d, J = 1.2 Hz, 1H), 4.68(d, J = 1.2 Hz, 1H), 5.09(d, J = 1.2 Hz, 1H), 5.09 (d, J = 1.2 Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 25.8, 25.9, 26.3, 26.6, 26.7, 26.8, 29.0, 29.3, 30.4, 32.2, 32.9, 39.9, 49.6, 59.4, 60.9, 106.6, 107.9, 145.4, 146.2; High-resolution MS (FAB), calcd for C\(_{19}\)H\(_{31}\)N: 273.2457, Found m/z (relative intensity): 273.2444 ([M]^+\(^{13}\), 35), 272.2388 (100).

**(Z)-1-benzyl-5-benzylidene-4-methylene-2-phenyl piperidine (1r)**

IR (neat): 698 (s), 745 (s), 760 (s), 883 (s), 1452 (m), 1493 (m), 1632 (w), 2787 (m), 2936 (m), 3028 (s) cm\(^{-1}\); \(^{1}\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.74 (dd, J = 4.2, 14.0 Hz, 1H),
2.68 (tdd, $J = 1.7, 10.0, 14.0$ Hz, 1H), 2.88 (dd, $J = 1.7, 13.2$ Hz, 1H), 3.03 (d, $J = 13.2$ Hz, 1H), 3.60 (dd, $J = 4.2, 10.0$ Hz, 1H), 3.79 (d, $J = 13.2$ Hz, 1H), 4.07 (d, $J = 13.2$ Hz, 1H), 4.84 (d, $J = 1.7$ Hz, 1H), 5.19 (d, $J = 1.7$ Hz, 1H), 6.72 (d, $J = 1.7$ Hz, 1H), 7.08-7.57 (m, 15H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 42.6, 52.3, 58.2, 67.4, 108.7, 123.9, 126.5, 126.7, 127.2, 127.6, 127.91, 127.95, 128.6, 128.92, 128.96, 136.8, 138.0, 138.8, 143.6, 147.2; High-resolution MS (FAB), calcd for C$_{26}$H$_{25}$N: 351.1987 Found $m/z$ (relation intensity): 351.2003 ([M]$^+$, 100).

**General procedure for Diels- Alder reaction of 1d with dimethyl acetylenedicarboxylate** To a schlenk flask under a nitrogen atmosphere were added 1d (137.7 mg, 0.5 mmol), dimethyl acetylenedicarboxylate (71.0 mg, 0.5 mmol), and 2 ml of a CH$_2$Cl$_2$. The reaction mixture was stirred at reflux for 24 h and then the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (eluent; EtOAc/hexane = 1/1) to give 2d (196.3 mg, 94%, $R_f$ = 0.27, EtOAc/hexane = 1/4).

**dimethyl 2-benzyl-1,2,3,4,5,8-hexahydro-3-phenylisoquinoline-6,7-dicarboxylate (2d)**

IR (neat): 702 (s), 737 (s), 1069 (s), 1177 (m), 1198 (m), 1267 (s), 1435 (m), 1724 (s), 2800 (w), 2867 (w), 2953 (w), 3030 (w) cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): δ 2.21 (dd, $J = 1.7, 16.6$ Hz, 1H), 2.38 (dd, $J = 8.8, 16.6$ Hz, 1H), 2.72 (d, $J = 16.4$ Hz, 1H), 2.78-2.99 (m, 3H), 2.83 (d, $J = 6.0$ Hz, 1H), 2.89 (d, $J = 6.0$ Hz, 1H), 2.96 (d, $J = 13.2$ Hz, 1H), 3.03 (d, $J = 16.4$ Hz, 1H), 3.62 (dd, $J = 4.5, 8.7$ Hz, 1H), 3.74 (s, 3H), 3.77 (s, 3H), 7.19-7.44 (m, 10H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 30.2, 32.0, 38.3, 52.2, 52.2,
54.5, 59.2, 64.2, 122.5, 122.6, 126.9, 127.4, 127.8, 128.2, 128.7, 128.8, 131.9, 132.9, 138.9, 142.9, 168.1, 168.4; High-resolution MS (EI), calcd for C_{26}H_{27}NO_{4}: 417.1940, Found \textit{m/z} (relative intensity): 417.1952 ([M]^+, 100)

dimethyl 2-benzyl-1,2,3,4,5,8-hexahydro-3,8-diphenylisoquinoline-6,7-dicarboxylate (2r)

IR (KBr): 702 (s), 745 (s), 1028 (s), 1067 (s), 1155 (s), 1261 (s), 1435 (s), 1452 (s), 1493 (s), 1601 (m), 1655 (s), 1726 (s), 2800 (m), 2893 (m), 2949 (m), 3028 (m), 3059 (m), 3084 (m) cm^{-1}; ^1H NMR (CDCl$_3$, 400 MHz): δ 2.32-2.50 (m, 2H), 2.70-2.82 (m, 1.4H), 2.89-3.06 (m, 1.6H), 3.16-3.43 (m, 2H), 3.51 (s, 1.8H), 3.54 (s, 1.2H), 3.67-3.73 (m, 1.6H), 3.75 (s, 1.8H), 3.78 (s, 1.2H), 3.86 (t, J = 6.1 Hz, 0.4H), 4.08 (t, J = 6.1 Hz, 0.6H), 4.10-4.12 (m, 0.4H), 7.01-7.47 (m, 15H); ^13C NMR (CDCl$_3$, 100 MHz, one isomer): δ 31.7, 38.1, 47.5, 51.8, 52.2, 53.7, 58.5, 63.9, 123.2, 126.7, 126.9, 127.2, 127.4, 127.7, 128.1, 128.3, 128.4, 128.5, 128.7, 130.8, 137.0, 139.1, 140.6, 143.1, 167.7, 167.9; ^13C NMR (CDCl$_3$, 100 MHz, the other isomer): δ32.3, 35.2, 46.9, 50.8, 51.9, 52.2, 57.0 61.4, 122.7, 126.5, 126.8, 127.1, 127.2, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 131.5, 136.6, 138.9, 140.4, 141.5, 167.7, 168.1; High-resolution MS (FAB), calcd for C_{32}H_{31}NO_{4}: 493.2253, Found \textit{m/z} (relative intensity): 493.2250 ([M]^+, 65), 494.2326 (100).

General procedure for oxidation of 2d To a schlenk flask under a nitrogen atmosphere were added 2d (208.7 mg, 0.5 mmol), DDQ (340.5 mg, 1.5 mmol) and 15 ml of a $p$-xylene. The reaction mixture was stirred at reflux for 48 h and then the solvent was removed under vacuum. The residue was purified by column chromatography over
silica gel (eluent; EtOAc/hexane = 1/2) to give 3d (218.7 mg, 80%, $R_f = 0.40$, EtOAc/hexane = 1/2).

**dimethyl 3-phenylisoquinoline-6,7-dicarboxylate (3d)**

IR (KBr) 3026(w), 2960(w), 1711(s), 1629(s), 1439(s), 1211(s), 1169(s), 1049(s), 914(s), 702(s) cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.98 (s, 3H), 3.99 (s, 3H), 4.46 (tt, $J = 2.44$, 7.32 Hz, 1H), 7.53 (dt, $J = 1.72$, 7.32 Hz, 2H), 8.12 (dt, $J = 2.44$, 7.32 Hz, 2H), 8.12 (s, 1H) 8.17 (s, 1H) 8.47 (s, 1H) 9.42 (s, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 52.8, 53.0, 116.3, 127.0, 127.1, 128.3, 128.92, 128.93, 129.3, 130.2, 133.7, 137.1, 138.5, 153.0, 154.0, 166.8, 167.9; High-resolution MS (FAB), calcd for C$_{19}$H$_{15}$NO$_4$: 322.1079, Found m/z (relative intensity): 322.1074 ([M+H]$^+$, 100).

**dimethyl 3,8-diphenylisoquinoline-6,7-dicarboxylate (3r)**

IR (KBr) 3066(w), 2947(m), 2843(w), 1718(s), 1616(s), 1564(s), 1437(s), 1184(s), 1136(s), 1041(s), 1028(s), 970(s) cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 3.62 (s, 3H), 3.99 (s, 3H), 7.39-7.47 (m, 3H), 7.48-7.54 (m, 5H) 8.11-8.14 (m, 2H), 8.18 (d, $J = 0.48$ Hz, 1H) 8.59 (d, $J = 0.48$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 52.3, 52.9, 116.5, 127.0, 127.3, 128.2, 128.6, 128.9, 129.0, 129.1, 130.0, 130.1, 132.0, 134.7, 136.0, 138.5, 139.6, 151.9, 152.7, 165.7, 168.4; High-resolution MS (FAB), calcd for C$_{25}$H$_{19}$NO$_4$: 398.1392, Found m/z (relative intensity): 398.1401 ([M+H]$^+$, 100).

**X-ray Crystallographic Studies of 3d and 3r**

Colorless crystals of 3d and 3r suitable for X-ray analysis were obtained by recrystallization from CH$_2$Cl$_2$/n-hexane. A single crystal was mounted using
Perfluoropolyether RS 3000 (Riedel-de Haën) on a MicroMount (MiTeGen) and used for data collection. All measurements were made on a Rigaku MicroMax-007HF diffractometer equipped with a Rigaku Saturn 724+ CCD area detector using graphite monochromated Mo-Kα radiation. The structure was solved by direct methods with SHELXS-97 and refined by full-matrix least-squares against F² using SHELXL-97 software. An ORTEP drawing is shown in Figure S1 and S2. The details of the crystal and data collection parameters are summarized in Table S1 and S2. The analysis was carried out using Yadokari-XG. The program ORTEP3 was used to generate X-ray structural diagrams. CCDC 914512 and 914512 contains the supplementary crystallographic data for this thesis. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
**Figure S1.** ORTEP drawing of 3d. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

**Table S2.** Crystal data and data refinement for 3d

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\[ R_1 = \frac{\sum |F_o| - |F_c|}{\sum |F_o|} \]

\[ wR_2 = \left( \frac{\sum w(|F_o| - |F_c|)^2}{\sum wF_o^2} \right)^{1/2} \]
**Figure S2.** ORTEP drawing of 3r. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are drawn at 50% probability.

**Table S2.** Crystal data and data refinement for 3r

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<td>$\beta$ (°)</td>
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<td>$\bar{d}_{calc}$ (mm$^{-1}$)</td>
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<td>No. of unique data</td>
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$^a R_1 = \sum||F_o||-|F_c||/\sum|F_o|.$

$^b wR_2 = \sqrt{\sum w(|F_o|-|F_c|)^2}/\sum wF_o^2}^{1/2}.$
3.5 References and Notes


(7) CCDC-914512 contains the supplementary crystallographic data for 3r. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


Chapter 4

Direct Allylic Amination of Allyl Alcohol Catalyzed by Palladium Complex with Phosphine-Borane Ligand

4.1 Abstract

The Author described that phosphine-borane compound can be used as an efficient ligand for the palladium catalyzed direct allylic amination. The palladium catalyst with phosphine-borane ligand promotes direct amination of allylic alcohols with amines to provide allylamines. The linkage between phosphine and borane moieties and the structure of the linker in phosphine-borane ligand is considered to be important for high catalytic activity.
4.2 Introduction

Catalytic allylic substitution with Tsuji-Trost reaction\(^1\) is one of the most useful processes for the organic synthesis. In original Tsuji-Trost reaction, various allylic electrophiles such as allylic chloride, acetates, carbonates, and other type of allylic esters could be used to give the allylated products. These allylic electrophiles could be derived from allyl alcohols via halogenation and esterification accompanying with a stoichiometric amount of byproduct. From the viewpoint of the step economy synthesis and reducing the waste, the development of highly efficient direct allylic substitution of allyl alcohol has been demanded in the field of organic synthesis.\(^2\)\(^,\)\(^3\) The direct allylic substitution gives the corresponding allylic compound in one step along with only one equivalent of water as a byproduct. In the case of a transition-metal-catalyzed direct allylic substitution, the oxidative addition of an allyl alcohol proceeds to form an electrophilic \(\pi\)-allylmetal species and hydroxide anion. This hydroxide anion deprotonates the pronucleophile, so this reaction is performed under base-free condition. In our laboratory, we have studied the direct allylic substitution by use of palladium catalyst and organometallic reagent such as organoborane and organozinc. In the course of this study, we developed not only the direct electrophilic allylation,\(^4\) but also the direct nucleophilic\(^5\) and amphiphilic\(^6\)
allylation using allyl alcohol. The electrophilic direct allylic substitution catalyzed by palladium and BEt$_3$ is shown in Scheme 1 (a). In this reaction, allyl alcohol was activated by Lewis acidic BEt$_3$ to give π-allylpalladium species via an oxidative addition. This π-allylpalladium was electrophilic and attacked by a nucleophile to give the product and water. The rate-determining step of this reaction seems to be an oxidative addition of allyl alcohol cleaving the C–O bond. The author assumed that the modification of this intermolecular oxidative addition to intramolecular process was effective for the acceleration of the direct allylic substitution. To execute the intramolecular oxidative addition, the author noticed the phosphine-borane compound as a phosphine ligand bearing a boryl group. Our working hypothesis is shown in Scheme 1 (b). Boryl group of Pd/phosphine-borane catalyst acts as Lewis acid moiety to activate the allyl alcohol. Successive oxidative addition proceeds intramolecularly to give the π-allylpalladium intermediate attacked by a nucleophile.
Various monophosphine-borane compounds have been synthesized and used as ligands for the transition-metal complexes. Bourissou and his co-workers reported some catalytic reactions using phosphine-borane ligand. In their initiative works, the \( o -(d i a r y l b o r y l) p h e n y l p h o s p h i n e \) ligand behaves like a biaryl phosphine ligand. On the other hand, the author tried to use the Lewis acidity of borane moiety of the phosphine-borane ligand to catalyze the direct allylic substitution. Herein the author would like to report the palladium-catalyzed direct allylic amination of allyl alcohol by use of phosphine-borane ligand.

**Scheme 1** Reaction pathway and working hypothesis for the direct allylic substitution.
4.3 Results and Discussion

Palladium-catalyzed allylic amination of cinnamyl alcohol (1a) with $N$-methylaniline (2a) using phosphine-borane ligand was investigated (Table 1). The complete regioselectivities were observed in all cases to give linear allylamine product 3aa. $B$-(2-Diphenylphosphinoethyl)-9-borabicyclononane (L1) was effective for this reaction (entry 2). The yield was the same level with the reaction using Pd/BEt$_3$ catalyst system (entry 1). The ligands bearing dicyclohexylboryl group and dicyclohexylphosphino group did not show the catalytic activity (entries 3 and 4). The linking moiety between phosphino and boryl group was important in this reaction. Propylene- and $o$-phenylene-linked phosphine-borane ligands (L4 and L5) were less effective than L1 (entries 5 and 6). The flexibility and the length of ethylene linker in L1 were well matched to this reaction. Almost no reaction was observed by use of phosphine-boronate ligand L6 bearing a pinacol unit (entry 7). Bidentate diphosphines might be the useful ligands for transition-metal-catalysis, then the author newly prepared the diphosphine-borane L7 and used this ligand for the direct allylic amination, but unfortunately the reaction did not proceed (entry 8). PdCl$_2$ and Pd$_2$(dba)$_3$ could not be used as a catalyst precursor in this reaction (entries 9 and 10). By use of Et$_2$O and toluene as a solvent instead of THF, the reactions catalyzed by
Pd/L1 were completed for 3 h to give allylated product in quantitative yields, respectively (entries 11 and 12). Catalyst loading could be reduced in the concentrated reaction condition (entry 13). Next, the ratio of L1 to Pd was optimized. Three equivalent of L1 to Pd was enough (entry 14). Although the yield was slightly decreased in the case of 2 equivalent of L1, the use of an equimolar amount of L1 was not effective for this reaction (entries 15 and 16). These results suggest that one equivalent of L1 is used as a reductant for Pd(OAc)₂ to form Pd(0) species.

Table 1: Reaction of cinnamyl alcohol (1a) with N-methylaniline (2a).[a]

| Entry | Pd catalyst | Ligand | Solvent | Time [h] | Yield [%] 
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<th></th>
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</thead>
<tbody>
<tr>
<td>1[c]</td>
<td>Pd(OAc)₂ (5)</td>
<td>PPh₃ (20)</td>
<td>THF (5)</td>
<td>24</td>
<td>99</td>
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<tr>
<td>2</td>
<td>Pd(OAc)₂ (5)</td>
<td>L1 (20)</td>
<td>THF (5)</td>
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<td>91</td>
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<td>THF (5)</td>
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<td>2</td>
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<td>THF (5)</td>
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<td>Pd(OAc)₂ (5)</td>
<td>L4 (20)</td>
<td>THF (5)</td>
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<td>THF (5)</td>
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Reactions of cinnamyl alcohol (1a) with various secondary amines 2b-g under the optimized reaction conditions (Table 1, entry 14) were summarized in Table 2. The regioselectivities of the reactions of 1a with 2b-g were perfect to give the corresponding cinnamyl amines 3ab-3ag as single products, respectively. N-Ethylaniline (2b) and dibenzylamine (2c) gave the products 3ab and 3ac in quantitative yields (entries 1 and
Sterically more hindered amines 2d-f needed higher reaction temperature or longer reaction time. Diphenylamine (2d), N-benzylaniline (2e) and dicyclohexylamine (2h) could be used in this reaction under heated toluene to give the products 3ad and 3ah in high yields (entries 3, 4 and 7). When dibenzoazepine was used in this reaction, the excellent yield of the mixture of allylamines 3af and 3’af were obtained in the ratio of 85/15 (entry 5). Indoline gave the corresponding allyl amine 3ag in quantitative yield (entry 6). The reactions of 1a with diisopropylamine (2i), piperidine (2j) and pyrrolidine (2k) needed a longer reaction time and gave the product 3ai, 3aj and 3ak in high yields (entries 8-10). Morpholine and N-phenylpiperazine gave 3ag and 3am in high yield (entries 11-12).

**Table 2: Reactions of cinnamyl alcohol (1a) with various secondary amines 2.**[^a]

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Temperature</th>
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<td>3ab</td>
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<td>HN(Bn)₂</td>
<td>2c</td>
<td>rt</td>
<td>1.5</td>
<td>3ac</td>
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<td>1.5</td>
<td>3ad</td>
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<tr>
<td>4</td>
<td>HNPhBn</td>
<td>2e</td>
<td>rt</td>
<td>1</td>
<td>3ae</td>
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The reaction of cinnamyl alcohol (1a) with aniline (2n) as a primary amine was investigated (Scheme 2). The reaction proceeded at room temperature to give \( N \)-cinnamylaniline (3an) in high yield along with a small amount of \( N,N \)-dicinnamylaniline (4an) even if the 2 equivalent of 2n was used.

**Scheme 2.** Reaction of cinnamyl alcohol (1a) with aniline (2n).
Various allyl alcohols could be used in this allylic amination. The results of the reactions with dibenzylamine (2c) are summarized in Table 3. Allyl alcohol (1b) gave the corresponding allylamine 3bc in quantitative yield (entry 1). The reactions of cinnamyl alcohol derivatives (1c-1i) proceeded to give the corresponding allylamines (3cc-3ic) in high yields with complete regio- and stereoselectivities (entries 2-8). Furthermore, highly unstable furan- and thiophene-substituted allylic alcohols 1j and 1k, respectively (entries 9 and 10), were also successfully converted into the corresponding allylamines without decomposition. When crotyl alcohol (1l) was used in this reaction, the excellent yield of the mixture of allylamines 3lc and 3'lc were obtained in the ratio of 78/22 (entry 11). The E-selectivity of 3lc was 92% (entry 11). Cinnamylamine 3ac was also produced by the reaction of 1-phenyl-2-propen-1-ol (1m) with 2c in quantitative yield as a single product (entry 12). 4-Buten-2-ol (1n) gave the products 3lc and 3'lc in 97% yield with good regio- and stereoselectivities (entry 13). The yields and the ratios of product from α-substituted allyl alcohols 1m and 1n were nearly the same in the cases of cinnamyl alcohol (1a) and crotyl alcohol (1l), so these allylation reactions were considered to proceed via π-allylpalladium intermediates. β-Substituted allyl alcohols 1o and 1p could be used in this reaction to give the corresponding allylamines in high yields, respectively (entries 14 and 15). The
reaction of (E)-3-phenyl-2-methyl-2-propen-1-ol (1q) resulted in the high conversion into the allylamine 3qc with the ratio of 88/12.
Table 3 Reactions of various allyl alcohols 1 with dibenzylamine (2c).\textsuperscript{[a]}

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<th>Products</th>
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<td>H</td>
<td>H</td>
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\textsuperscript{[a]} A mixture of 1 (1.2 mmol), 2c (1.0 mmol), Pd(OAc)\textsubscript{2}, L1, and toluene was stirred at
rt under N₂.  [b] Isolated yield.  [c] Determined by $^1$H NMR.  [d] Determined by $^1$H NMR.

The remarkable effect of linking the phosphine and borane moiety was observed in the amination reaction of prenyl alcohol (1r) and 2-methyl-3-buten-2-ol (1s). It is hard to generate the π-allylpalladium intermediate from 1r and 1s because of their steric hindrance. By use of Pd(OAc)$_2$/L1 catalyst system, prenylamine 3rc was obtained in high yields from 1r and 1s (Scheme 3). On the other hand, when EtPPh$_2$ and B-$n$-hexyl-9-BBN was used instead of L1, the yields of desired product 3rc and 3'sc were extremely low and the complex mixture was formed in the reaction mixture. These results show that the linkage between phosphine and borane moieties is important for the high catalytic activity.

**Scheme 3.** Reaction of prenyl alcohol (1r) and 2-methyl-3-buten-2-ol (1s) with dibenzyllamine (2c).
Next, the author investigated the application of this amination to the reaction of vinylepoxide (5) with N-methylaniline (2a) (Scheme 4). Vinylepoxide have been used as electrophiles for the palladium-catalyzed allylic substitution. In this reaction, the $\pi$-allylpalladium species was attacked by N-methylaniline (2a) to give the allyl alcohol having amino group. This allyl alcohol could be activated by Pd(OAc)$_2$/L1 catalyst to form $\pi$-allylpalladium species reacting with another molecule of N-methylaniline (2a) to give 1,4-diamino-2-butene 6 in high yield.

**Scheme 4.** Reaction of vinylcyclopropane (5) with N-methylaniline (2a).

In summary, the author has found that phosphine-borane compound can be used as an effective ligand in a palladium-catalyzed direct allylic substitution of allyl alcohol with amine. The linkage between phosphine and borane moieties and the structure of the linker in phosphine-borane ligand is considered to be important for high catalytic activity. Further studies on expanding the scope of nucleophiles and the mechanistic studies are currently in progress.
4.4 Experimental

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 60F245). Flash chromatography columns were packed with silica gel as a slurry in hexane. Gradient flash chromatography was conducted eluting with a continuous gradient from hexane to the indicated solvent. Proton and carbon NMR data were obtained with a JEOL JNM-AL400 and Varian NMR System 500PS with tetramethylsilane as an internal standard. Chemical shift values were given in ppm downfield from the internal standard. $^{11}$B and $^{31}$P NMR data were recorded on a JEOL JNM-AL400 with B(OMe)$_3$ and P(OMe)$_3$ as external standard, respectively. High resolution mass spectra (HRMS) were measured with a JEOL JMS-700N. Elemental analyses were conducted on a Perkin Elmer 2400II.

Solvents and Reagents

Tetrahydrofuran were dried and distilled from benzophenone and sodium immediately prior to use under nitrogen atmosphere. Pd(OAc)$_2$, Et$_3$B (1.0 M hexane solution), N-methylaniline (2a), N-ethylaniline (2b), dibenzylamine (2c), diphenylamine (2d) phenylbenzylamine (2e), dibenzoazepine (2f), indole (2g), dicyclohexylamine (2h), diisopropylamine (2i), piperidine (2j), pyrrolidine (2k), morpholine (2l), N-phenylpiperazine (2m), allyl alcohol (1b), croctyl alcohol (1l), 1-phenyl-2-propene-1-ol (1m), 3-buten-2-ol (1n), 2-methyl-2-propen-1-ol (1p), and 2-methyl-3-phenyl-2-propen-1-ol (1q) were purchased and used without further purification. 2-ethenyloxirane (5) was purchased and used without further
purification. Allyl alcohols \textit{1c, 1d, 1e, 1f, 1g, 1h, 1i, 1j}, and \textit{1k}, were prepared from corresponding aldehydes according to the literature.\textsuperscript{9} Phosphine-Borane ligand \textit{L2}\textsuperscript{10}, \textit{L4}\textsuperscript{11}, and \textit{L6}\textsuperscript{12} were prepared according to the literature.

\textbf{Preparation of B-(2-diphenylphosphinoethyl)-9-borabicyclononane (L1)}

\[
\begin{align*}
\text{Ph}_2\text{PCl} & \xrightarrow{\text{MgBr, THF, -78 °C, overnight}} \text{Ph}_2\text{P} \\
& \xrightarrow{9\text{-BBN, toluene, 80 °C, overnight}} \text{Ph}_2\text{P} \end{align*}
\]

The title compound was synthesized by a similar method as described in the literature.\textsuperscript{10} To a THF (40 ml) solution of chlorodiphenylphosphine (3.8 ml, 20 mmol) was added 1M vinylmagnesium bromide in THF solution (25 ml, 25 mmol) at -78 °C. The reaction mixture was allowed to stir at -78 °C for a further 0.5 h before being allowed to warm to room temperature and stirred for overnight. The reaction was quenched with 2N aqueous HCl and extracted with Et\textsubscript{2}O. The extract was washed with brine and then dried over MgSO\textsubscript{4}. The solvent was removed under vacuum followed by purification by a column chromatography on silica gel (hexane/AcOEt = 80/20) afforded vinylidiphenylphosphine as colorless oil (3.4 g, 75%). As a next step, to a toluene (50 ml) solution of vinylidiphenylphosphine (1.7 g, 8 mmol) was added 9-borabicyclononane (16 ml, 8 mmol) at room temperature and stirred at 80 °C for overnight. The solvent was removed under vacuum, affording a white solid. The solid was washed with methanol and dried under vacuum, affording \textit{B-(2-diphenylphosphinoethyl)-9-borabicyclononane (L1)} as a white solid in 58% yield.

\textbf{B-(2-Diphenylphosphinoethyl)-9-borabicyclononane (L1)}

\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \textsuperscript{\delta} 1.1-1.3 (m, 2H), 1.4-1.5 (m, 2H), 1.6-1.7 (m, 6H), 1.7-1.9 (m, 6H), 2.22 (t, \textit{J} = 8.0 Hz, 2H) 7.3-7.4 (m, 6H), 7.4-7.5 (m, 4H); \textsuperscript{13}C-NMR
(100 MHz, CDCl$_3$) $\delta$ 22.2 (d, $J$ = 53.5 Hz), 23.0 (br), 23.1, 31.0 (br), 33.2, 128.4 (d, $J$ = 32.0 Hz), 128.5, 132.8 (d, $J$ = 90.5 Hz), 139.1 (d, $J$ = 63.0 Hz); $^{31}$P-NMR (161 MHz, CDCl$_3$) $\delta$ -150.8; $^{11}$B-NMR (128 MHz, CDCl$_3$) $\delta$ 79.3; High-resolution MS (EI$^+$), calcd for C$_{22}$H$_{28}$PB: 334.2022, Found: m/z 334.2022 (M$^+$).

**Preparation of B-(2-dicyclohexylphosphinoethyl)-9-borabicyclononane (L3)**

![Chemical Reaction Diagram]

The title compound was synthesized by a similar method as described in the literature.$^{13}$ To a THF (40 ml) solution of chlorodicyclohexylphosphine (4.6 g, 20 mmol) was added 1M vinylmagnesium bromide in THF solution (25 ml, 25 mmol) at -78 °C. The reaction mixture was allowed to stir at -78 °C for a further 0.5 h before being allowed to warm to room temperature and stirred for overnight. The reaction mixture was concentrated under vacuum and the residue dissolved in hexane (10 ml). The solution was then filtered off via cannula and the magnesium salts were washed twice with hexane (10 ml x 2). After removal of the volatiles, the vinylidicyclohexylphosphine was used next step without further purification. As a next step, to a toluene (50 ml) solution of vinylidicyclohexylphosphine (1.9 g, 8 mmol) was added 9-borabicyclononane (16 ml, 8 mmol) at room temperature and stirred at 80 °C for overnight. The solvent was removed under vacuum, affording a white solid. The solid was washed with methanol and dried under vacuum, affording B-(2-dicyclohexylphosphinoethyl)-9-borabicyclononane (L3) as a white solid in 43% yield.
Preparation of $B$-(2-dicyclohexylphosphinophenyl)-9-borabicyclononane (L5)

A 100 ml round bottom flask equipped with a stir bar, reflux condenser, a rubber septum was added magnesium metal turnings (144 mg, 6 mmol) and small crystal of iodine and purged with nitrogen. 10 ml of THF were added to the flask, solving the iodine crystal forming a brown solution. To the round-bottomed flask was added 2-bromophenylidiphenylphosphine (1.7 g, 5 mmol) in THF solution. The reaction was then initiated by warming with a heat gun. The Grignard solution was warmed to reflux under nitrogen for 2 hour. After the reaction, 1M $B$-methoxy-9-BBN (5 ml, 5 mmol) in hexane solution was added to the Grignard solution. The reaction mixture was stirred at 60 °C overnight. The reaction mixture was filtered from the precipitated magnesium salts and concentrated under vacuum. The residue was then washed with hexane and dried under vacuum, affording $B$-(2-diphenylphosphinophenyl)-9-borabicyclononane (L5) as a white solid in 53% yield.

$B$-(2-diphenylphosphinophenyl)-9-borabicyclononane (L5)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.5-1.6 (m, 2H), 1.65 (br, 2H), 1.9-2.1 (m, 10H), 7.23 (d, $J = 7.0$ Hz, 1H) 7.3-7.4 (m, 12H), 7.50 (d, $J = 7.4$ Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 23.7, 31.0 (br), 33.6, 127.8 (d, $J = 4.0$ Hz), 128.4, 128.6 (d, $J = 7.4$ Hz), 129.0 (d, $J = 11.3$ Hz), 129.1 (d, $J = 17.4$ Hz), 129.5, 131.4, 133.2 (d, $J = 15.7$ Hz), 135.4, 135.9 (d, $J = 13.2$ Hz); $^{31}$P-NMR (161 MHz, CDCl$_3$) $\delta$ –5.4; $^{11}$B-NMR (128 MHz,
CDCl₃) δ 46.9 High-resolution MS (EI⁺), calcd for C₂₆H₂₈PB: 382.2022, Found: m/z 382.2022 (M⁺).

**Preparation of [2-(diphenylphosphino)phenyl]vinylphenylphosphine**

To a solution of (2-Bromophenyl)diphenylphosphine (3.4 g, 10 mmol) in dry Et₂O (40 ml) was added dropwise 2.5 M n-BuLi (4 ml, 10 mmol) in hexane solution under nitrogen at -78 °C. The resulting solution was allowed to stir at room temperature during 0.5 hour and dichlorophenylphosphine (1.5 ml, 11 mmol) was then added at once at -40 °C. After stirring for 2 hour at room temperature, the reaction mixture was cooled to -40 °C and added 1.0 M vinylmagnesium bromide (25 ml, 25 mmol) in THF solution. The resulting solution was stirred at room temperature for 12 hour. The reaction was quenched with 2N aqueous HCl and extracted with Et₂O. The extract was washed with brine and then dried over MgSO₄. The solvent was removed under vacuum followed by purification by a column chromatography on silica gel (hexane/AcOEt = 95/5) afforded vinylidiphenylphosphine as colorless oil (1.86 g, 47%).

¹H-NMR (500 MHz, CDCl₃) δ 5.34 (ddd, J = 1.0, 18.5 and JₜH₂C⁻P = 12.8 Hz, 1H), 5.78 (ddd, J = 1.0, 12.0 and JₜH₂C⁻P = 28.8 Hz, 1H), 6.53 (ddd, J = 12.0, 18.5 and JₜH₂C⁻P = 16.5 Hz, 1H), 6.97-7.01 (m, 1H), 7.14-7.30 (m, 16H) 7.39-7.42 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃) δ 128.06, 128.07, 128.14 (d, J = 6.25 Hz), 128.24 (d, J = 6.25 Hz), 128.31, 128.6 (d, J = 20.0 Hz), 129.09 (d, J = 20.0 Hz), 133.0 (d, J = 18.8 Hz), 133.5 (d, J = 7.5 Hz), 133.7 (d, J = 7.5 Hz), 133.8 (d, J = 12.5 Hz), 133.9 (d, J = 13.8 Hz), 136.3 (dd, J = 7.5, 15.6 Hz), 136.8 (dd, J = 6.25, 11.25 Hz), 137.2 (dd, J = 6.25, 11.25 Hz), 137.4 (dd, J = 6.25, 12.5 Hz), 143.0 (d, J = 10.0 Hz), 143.2 (d, J = 10.0 Hz), 143.7 (d, J = 11.25 Hz), 144.0 (d, J = 11.25 Hz).
Preparation of

**B**-[2-(diphenylphosphinophenyl)phenylphosphino-2-ethyl]-9-borabicyclononane (L5)

![Chemical diagram]

To a THF (10 ml) solution of [2-(diphenylphosphino)phenyl]vinylphenylphosphine (1.3 g, 3.4 mmol) was added 9-borabicyclononane (7 ml, 3.4 mmol) at room temperature and stirred at 60 °C for overnight. The solvent was removed under vacuum, affording a white solid. The solid was washed with hexane and dried under vacuum, affording **B**-[2-(diphenylphosphinophenyl)phenylphosphino-2-ethyl]-9-borabicyclononane (L7) as a white solid in 65% yield.

**B**-[2-(diphenylphosphinophenyl)phenylphosphino-2-ethyl]-9-borabicyclononane (L7)

\[\text{H-NMR (400 MHz, CDCl}_3\text{) } \delta 1.1-1.2 \text{ (m, 2H), 1.37-1.44 (m, 2H), 1.6 (br, 6H), 1.7-1.9 (br, 6H), 2.08 (quin, } J = 7.2 \text{ Hz, 2H), 2.16 (quin, } J = 7.2 \text{ Hz, 2H), 6.9-7.0 \text{ (m, 1H), 7.1-7.3 (m, 17H), 7.3-7.4 (m, 1H); }^{13}\text{C-NMR (100 MHz, CDCl}_3\text{) } \delta 22.17 \text{ (d, } J = 13 \text{ Hz), 22.23 (d, } J = 13 \text{ Hz), 23.1, 31.8 (br), 33.1, 127.9, 128.5 (d, } J = 9.0 \text{ Hz), 128.3 (d, } J = 7.0 \text{ Hz), 128.5, 128.9 (d, } J = 12.2 \text{ Hz), 132.2 (d, } J = 7.0 \text{ Hz), 132.6 (d, } J = 17.3 \text{Hz), 133.7 (d, } J = 7.3 \text{Hz), 134.0 (d, } J = 23.9\text{Hz), 134.2 (d, } J = 4.0 \text{ Hz), 137.2 (dd, } J = 5.2, 11.6 \text{ Hz), 137.7 (dd, } J = 6.9, 12.7 \text{ Hz), 144.2 (dd, } J = 8.8, 32.1 \text{ Hz), 144.8 (dd, } J = 12.7 \text{, 30.8 Hz); }^{31}\text{P-NMR (161 MHz, CDCl}_3\text{) } \delta -159.9 \text{ (d, } J = 149.7 \text{ Hz), -161.9 (d, } J = 149.7 \text{ Hz); }^{11}\text{B-NMR (128 MHz, CDCl}_3\text{) } \delta 73.4; \text{ High-resolution MS (EI)}^+\text{, calcd for C}_{34}\text{H}_{37}\text{P}_2\text{B: } 518.2464, \text{ Found: } m/zb 518.2444 (M)^+.\]
General procedure for electrophilic allylation of amine with allylalcohol (Table 1, entry 14)

Phosphine-borane ligand L1 (25.1 mg, 0.075 mmol) and Pd(OAc)$_2$ (5.6 mg, 0.025 mmol) were dissolved in toluene (1.0 mL) under nitrogen. The mixture was stirred at room temperature for 1 hour and changed to a dark red solution. To the solution was added cinnamyl alcohol (1a, 161.0 mg, 1.2 mmol) and $N$-methylaniline (2a, 107.1 mg, 1.0 mmol). After stirring at room temperature for 1 hour, the resulting solution was concentrated and purified via column chromatography over silica gel (hexane/AcOEt = 80/20 v/v) to give 3aa (220.3 mg, 99%, Rf = 0.7; hexane/ AcOEt = 80/20 v/v).

$N$-Methyl-$N$-[(E)-3-phenyl-2-propenyl]aniline (3aa)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 2.97 (s, 3H), 4.07 (d, 5.6 Hz, 2H), 6.24 (dt, $J = 15.9$, 5.6 Hz, 1H), 6.51 (d, $J = 15.9$ Hz, 1H), 6.72 (t, $J = 7.3$ Hz, 1H) 6.78 (d, $J = 7.6$ Hz, 2H), 7.19-7.35 (m, 7H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 40.0, 54.9, 112.6, 116.6, 125.7, 126.3, 127.4, 128.5, 129.2, 131.2, 136.9, 149.5; High-resolution MS, calcd for C$_{16}$H$_{17}$N: 223.1361, Found: m/z 223.1360 (M$^+$).

$N$-Ethyl-$N$-[(E)-3-phenyl-2-propenyl]aniline (3ab)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.22 (t, $J = 8.9$ Hz, 3H), 3.46 (q, $J = 8.9$ Hz, 2H), 4.09 (d, $J = 6.1$ Hz, 2H), 6.28 (dt, $J = 19.8$, 6.1 Hz, 1H), 6.55 (d, $J = 19.8$ Hz, 1H), 6.71 (t, $J = 8.7$ Hz, 1H), 6.78 (d, $J = 11.0$ Hz, 2H), 7.23-7.39 (m, 7H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 12.2, 44.6, 52.1, 112.2, 116.0, 126.3, 126.5, 127.4, 128.6, 129.3, 130.8, 137.0, 148.3; High-resolution MS, calcd for C$_{17}$H$_{19}$N: 237.1517, Found: m/z 237.1517 (M$^+$).
\textit{N-[(E)-3-phenyl-2-propenyl]-N,N-dibenzylamine (3ac)}

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.22 (d, \(J = 8.0\) Hz, 2H), 3.63 (s, 4H), 6.30 (dt, \(J = 20.0, 8.0\) Hz, 1H), 6.53 (d, \(J = 20\) Hz, 1H), 7.19-7.41 (m, 15H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 55.7, 57.9, 55.7, 57.9, 126.3, 127.8, 128.3, 128.6, 128.8, 132.5, 137.3, 139.7; High-resolution MS, calcd for C\(_{23}\)H\(_{23}\)N: 313.1830, Found: m/z 313.1837 (M\(^+\)).

\textit{N-[(E)-3-phenyl-2-propenyl] -N,N-diphenylamine (3ad)}

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.50 (d, \(J = 5.2\) Hz, 2H), 6.31 (dt, \(J = 15.9, 5.2\) Hz, 1H), 6.56 (d, \(J = 15.9\) Hz, 1H), 6.93 (t, \(J = 7.4\) Hz, 2H), 7.05 (d, \(J = 8.6\) Hz, 4H), 7.18 (t, \(J = 7.2\) Hz, 1H), 7.22-7.32 (m, 8H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 54.3, 120.8, 121.4, 126.2, 126.4, 127.4, 128.5, 129.3, 131.4, 147.9; High-resolution MS, calcd for C\(_{21}\)H\(_{19}\)N: 285.1517, Found: m/z 285.1522 (M\(^+\)).

\textit{N-Benzyl-N-[(E)-3-phenyl-2-propenyl]aniline (3ae)}

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) for (E)-3ae \(\delta\) 4.18 (d, \(J = 5.4\) Hz, 2H), 4.60 (s, 2H), 6.27 (dt, \(J = 15.9, 5.4\) Hz, 1H), 6.51 (d, \(J = 15.9\) Hz, 1H), 6.71 (t, \(J = 7.2\) Hz, 1H), 6.78 (d, \(J = 8.1\) Hz, 2H), 7.18-7.35 (m, 12H); \(^1\)H-NMR (400 MHz, CDCl\(_3\)) for (Z)-3'ae \(\delta\) 4.21 (d, \(J = 4.7\) Hz, 2H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) for (E)-3ae \(\delta\) 52.5, 53.8, 112.5, 116.7, 125.6, 126.4, 126.7, 126.9, 127.5, 128.6, 128.7, 129.3, 131.4, 136.9, 138.9, 149.1; High-resolution MS, calcd for C\(_{22}\)H\(_{21}\)N: 299.1674, Found: m/z 299.1677 (M\(^+\)).

\textit{N-[(E)-3-phenyl-2-propenyl]dibenzazepine (3af)}

\(^1\)H-NMR (400 MHz, CDCl\(_3\)) for (E)-3af \(\delta\) 4.54 (d, \(J = 4.4\) Hz, 2H), 6.13 (dt, \(J = 15.9, 4.4\) Hz, 1H), 6.62 (d, \(J = 15.9\) Hz, 1H), 6.76, (s, 2H), 6.96 (t, \(J = 7.5\) Hz, 2H), 7.01 (d, \(J
= 7.3 Hz, 2H), 7.05 (d, J = 6.1 Hz, 2H), 7.20-7.26 (m, 7H); $^1$H-NMR (400 MHz, CDCl$_3$) for (Z)-3’af $\delta$ 4.20 (d, J = 4.7 Hz, 2H), 6.32 (dt, J = 16.1, 4.7 Hz, 1H), 6.63 (d, J = 16.1 Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$) for (E)-3af $\delta$ 53.1, 120.5, 123.4, 126.3, 127.0, 127.3, 128.4, 128.7, 129.1, 132.2, 132.4, 133.7, 137.1, 150.68; $^{13}$C-NMR (100 MHz, CDCl$_3$) for (Z)-3’af $\delta$ 70.7, 125.3, 126.0, 126.5, 127.7, 128.2, 128.5, 129.0, 132.6; High-resolution MS, calcd for C$_{23}$H$_{19}$N: 309.1517, Found: m/z 309.1517 (M$^+$).

(E)-1-(3-phenyl-2-propenyl)-2,3-dihydroindole (3ag)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 2.97 (t, J = 8.3 Hz, 2H), 3.34 (t, J = 8.3 Hz, 2H), 3.87 (d, J = 6.1 Hz, 2H), 6.31 (dt, J = 15.6, 6.1 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H) 6.63 (d, J = 15.6 Hz, 1H), 6.67 (t, J = 7.3 Hz, 1H), 7.06-7.10 (m, 2H), 7.21-7.24 (m, 1H), 7.31 (t, J = 7.6 Hz, 2H), 7.38 (d, J = 7.4 Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 28.5, 51.6, 53.3, 107.4, 117.8, 124.5, 125.9, 126.3, 127.3, 127.5, 128.5, 130.3, 132.3, 136.8, 152.1; High-resolution MS, calcd for C$_{17}$H$_{17}$N: 235.1361, Found: m/z 235.1357 (M$^+$).

N-[(E)-3-phenyl-2-propenyl] -N,N-dicyclohexylamine (3ah)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.00-1.08 (m, 2H), 1.16-1.30 (m, 8H), 1.55-1.58 (m-2H), 1.72-1.74 (m, 8H), 2.58 (br, 2H), 3.36 (d, J = 5.4 Hz, 2H), 6.20 (dt, J = 15.9, 5.4 Hz, 1H), 6.46 (d, J = 15.9 Hz, 1H), 7.17 (t, J = 7.3 Hz, 1H), 7.28 (t, J = 7.3 Hz, 2H), 7.35 (d, J = 7.3 Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 26.3, 26.4, 48.7, 58.0, 126.1, 126.8, 128.4, 129.5, 132.5, 137.8; High-resolution MS, calcd for C$_{21}$H$_{31}$N: 297.2457, Found: m/z 297.2452 (M$^+$).

N-[(E)-3-phenyl-2-propenyl] -N,N-diisopropylamine (3ai)

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$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.05 (d, $J = 8.2$ Hz, 12H), 3.11 (sept, $J = 8.2$ Hz, 2H), 3.29 (d, $J = 7.6$ Hz, 2H), 6.25 (dt, $J = 19.5$, 7.6 Hz, 1H), 6.51 (d, $J = 19.5$ Hz, 1H), 7.19-7.39 (m, 5H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 20.7, 47.6, 48.2, 126.2, 127.0, 128.5, 123.0, 132.0, 137.7, High-resolution MS, calcd for C$_{15}$H$_{23}$N: 217.1830, Found: m/z 217.1835 (M$^+$).

(E)-1-(3-phenyl-2-propenyl)piperidine (3aj)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.42 (br, 2H), 1.58 (quin, $J = 5.8$ Hz, 4H), 2.41 (br, 4H), 3.09 (d, $J = 6.6$ Hz, 2H), 6.26 (dt, $J = 15.9$, 6.6 Hz, 1H), 6.47 (d, $J = 15.9$ Hz, 1H), 7.19 (t, $J = 7.3$ Hz, 1H), 7.27 (t, $J = 7.3$ Hz, 2H), 7.35 (d, $J = 7.3$ Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 24.3, 26.0, 54.6, 61.9, 126.2, 127.3, 127.3, 128.5, 132.6, 137.1; High-resolution MS, calcd for C$_{14}$H$_{19}$N: 201.1517, Found: m/z 201.1519 (M$^+$).

(E)-1-(3-phenyl-2-propenyl)pyrrolidine (3ak)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.78 (quin, $J = 3.7$ Hz, 4H), 2.53 (m, 4H), 3.24 (d, $J = 6.0$ Hz, 2H), 6.31 (dt, $J = 15.9$, 6.0 Hz, 1H), 6.51 (d, $J = 15.9$ Hz, 1H), 7.19 (t, $J = 7.3$ Hz, 1H), 7.28 (t, $J = 7.3$ Hz, 2H), 7.35 (d, $J = 7.3$ Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 23.5, 54.1, 58.4, 126.3, 127.3, 127.9, 128.5, 131.7, 137.2; High-resolution MS, calcd for C$_{13}$H$_{17}$N: 187.1361, Found: m/z 187.1358 (M$^+$).

(E)-4-(3-phenyl-2-propenyl)morpholine (3al)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 2.51 (br, 4H), 3.16 (d, $J = 8.2$ Hz, 2H), 3.74 (t, $J = 5.7$ Hz, 4H), 6.26 (dt, $J = 19.8$, 8.2 Hz, 1H), 6.54 (d, $J = 19.8$ Hz, 1H), 7.21-7.26 (m, 1H), 7.31 (t, $J = 9.2$ Hz, 2H), 7.38 (d, $J = 9.2$ Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 53.6,
1-Phenyl-4-[(E)-3-phenyl-2-propenyl]piperazine (3am)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 2.65 (t, $J = 5.0$ Hz, 4H), 3.20-3.22 (m, 6H), 6.26 (dt, $J = 15.9$, 6.1 Hz, 1H), 6.54 (d, $J = 15.9$ Hz, 1H), 6.83 (t, $J = 7.4$ Hz, 1H), 6.92 (d, $J = 7.9$ Hz, 2H), 7.20-7.31 (m, 3H), 7.30 (t, $J = 7.6$ Hz, 2H), 7.37 (d, $J = 7.1$ Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 49.2, 53.2, 61.1, 116.1, 119.7, 126.3, 126.4, 127.6, 128.6, 129.1, 133.3, 136.9, 151.3; High-resolution MS, calcd for C$_{19}$H$_{22}$N$_2$: 278.1783, Found: m/z 278.1779 (M$^+$).

Mixture of N-[(E)-3-phenyl-2-propenyl]aniline (3an) and N,N-Bis[(E)-3-phenyl-2-propenyl]aniline (4an)

$^1$H-NMR (400 MHz, CDCl$_3$) for 3an $\delta$ 3.83 (br, 1H), 3.93 (d, $J = 5.6$ Hz, 2H), 6.32 (dt, $J = 15.9$, 5.6 Hz, 1H), 6.62 (d, $J = 15.9$ Hz, 1H), 6.66 (d, $J = 7.8$ Hz, 2H), 6.72 (t, $J = 7.3$ Hz, 1H), 7.17-7.23 (m, 3H), 7.30 (t, $J = 6.85$ Hz, 2H), 7.36 (d, $J = 8.1$ Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) for 3an $\delta$ 46.2, 113.0, 117.7, 126.3, 127.0, 127.5, 128.6, 129.3, 131.5, 136.8, 148.0; High-resolution MS, calcd for C$_{15}$H$_{15}$N: 209.1204, Found: m/z 209.1206 (M$^+$). $^1$H-NMR (400 MHz, CDCl$_3$) for 4an $\delta$ 4.13 (d, $J = 5.2$ Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) for 4an $\delta$ 52.2, 112.6, 125.9, 128.5, 129.0; High-resolution MS, calcd for C$_{24}$H$_{23}$N: 325.1830, Found: m/z 325.1832 (M$^+$).

N- Allyl-N,N-dibenzylamine (3bc)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 3.21 (d, $J = 8.0$ Hz, 2 H), 3.57 (s, 4H), 5.21 (ddt, $J =$
10.1, 3.2, 1.6 Hz, 1 H), 5.21 (ddt, J = 17.3, 3.2, 1.6 Hz, 1 H), 5.91 (ddt, J = 17.3, 10.1, 6.4 Hz, 1 H), 7.20-7.38 (m, 10H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 56.3, 57.7, 117.4, 126.8, 128.2, 128.8, 136.1, 139.7; High-resolution MS, calcd for C$_{17}$H$_{19}$N: 237.1517, Found: m/z 237.1517 (M$^+$).

$N$-[(E)-3-(4-Chlorophenyl)-2-propenyl]-$N,N$-dibenzylamine (3cc)

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 3.21 (d, $J = 8.0$ Hz, 2 H), 3.62 (s, 4H), 6.26 (dt, $J = 16.0$, 6.4, 6.2 Hz, 1 H), 6.48 (dt, $J = 16.0$, 6.5, 1.6 Hz, 1H), 7.2-7.4 (m, 14H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 55.7, 58.0, 126.9, 127.5, 128.3, 128.7, 128.8, 131.1, 132.9, 135.8, 139.6; High-resolution MS, calcd for C$_{23}$H$_{22}$ClN: 347.1441, Found: m/z 347.1442 (M$^+$).

$N$-[(E)-3-(2-Methylphenyl)-2-propenyl]-$N,N$-dibenzylamine (3dc)

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 2.33 (s, 3H), 3.25 (dd, $J = 6.5$, 1.5 Hz, 2H), 3.65 (s, 4H), 6.48 (dt, $J = 16.0$, 6.5 Hz, 1H), 6.74 (dt, $J = 16.0$, 1.5 Hz, 1H), 7.1-7.4 (m, 14H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 19.9, 55.9, 57.9, 125.7, 126.0, 126.8, 127.2, 128.2, 128.8, 129.0, 130.2, 130.4, 135.1, 136.4, 139.6; High-resolution MS, calcd for C$_{24}$H$_{25}$N: 327.1987, Found: m/z 327.1985 (M$^+$).

$N$-[(E)-3-(3-Methylphenyl)-2-propenyl]-$N,N$-dibenzylamine (3ec)

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 2.34 (s, 3H), 3.21 (d, $J = 6.5$ Hz, 2H), 3.63 (s, 4H), 6.29 (dt, $J = 16.0$, 6.5 Hz, 1H), 6.50 (d, $J = 16.0$ Hz, 1H), 7.03 (d, $J = 7$ Hz, 1H), 7.1-7.4 (m, 13H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 21.4, 55.8, 57.9, 123.4, 126.8, 126.9, 127.5, 128.1, 128.2, 128.4, 128.8, 132.5, 137.1, 138.0, 139.7; High-resolution MS, calcd for C$_{24}$H$_{25}$N: 327.1987, Found: m/z 327.1985 (M$^+$).
**N-[(E)-3-(4-Methylphenyl)-2-propenyl]-N,N-dibenzylamine (3fc)**

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 2.32 (s, 3H), 3.21 (dd, $J = 6.5, 1.5$ Hz, 2H), 3.62 (s, 4H), 6.24 (dt, $J = 16.0, 6.5$ Hz, 1H), 6.49 (d, $J = 16.0$ Hz, 1H), 7.11 (d, $J = 8.5$ Hz, 1H), 7.2-7.4 (m, 13H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 21.2, 55.8, 57.9, 126.1, 126.6, 126.8, 128.2, 128.8, 129.2, 132.4, 134.4, 137.1, 139.7; High-resolution MS, calcd for C$_{24}$H$_{25}$N: 327.1987, Found : m/z 327.1988 (M$^+$).

**N-[(E)-3-(4-Methoxyphenyl)-2-propenyl]-N,N-dibenzylamine (3gc)**

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 3.19 (d, $J = 8.0$ Hz, 2H), 3.62 (s, 4H), 3.79 (s, 3H), 6.15 (dt, $J = 19.5, 6.5$ Hz, 1H), 6.46 (d, $J = 19.5$ Hz, 1H), 6.84 (d, $J = 11.0$ Hz, 1H), 7.2-7.4 (m, 13H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 55.2, 55.8, 57.9, 114.0, 125.5, 126.8, 127.4, 128.3, 128.8, 130.1, 132.0, 139.8, 159.1; High-resolution MS, calcd for C$_{24}$H$_{25}$NO: 343.1936, Found : m/z 343.1920 (M$^+$).

**N-[(E)-3-(1-Naphthyl)-2-propenyl]-N,N-dibenzylamine (3hc)**

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 3.35 (dd, $J = 6.5, 1.5$ Hz, 2H), 3.70 (s, 4H), 6.33 (dt, $J = 15.5, 6.5$ Hz, 1H), 7.2-7.5 (m, 16H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.86 (d, $J = 7.0$ Hz, 1H), 8.10 (d, $J = 5.8$ Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 56.0, 58.1, 123.8, 125.6, 125.7, 125.9, 126.9, 127.6, 128.2, 128.5, 128.8, 129.7, 131.0, 131.1, 133.6, 135.0, 139.6; High-resolution MS, calcd for C$_{27}$H$_{25}$N: 363.1987, Found : m/z 363.1985 (M$^+$).

**N-[(E)-3-(2-Naphthyl)-2-propenyl]-N,N-dibenzylamine (3ic)**

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 3.28 (dd, $J = 6.8, 1.5$ Hz, 2H), 3.66 (s, 4H), 6.42 (dt, $J =$
16.0, 6.5 Hz, 1H), 6.69 (d, J = 16.0 Hz, 1H), 7.2-7.3 (m, 2H), 7.33 (dd, J = 8.0, 8.0 Hz, 1H), 7.34-7.46 (m, 5H), 7.58 (dd, J = 8.0, 8.0 Hz, 1H), 7.68 (s, 1H), 7.77 (dd, J = 8.0, 8.0 Hz, 3H); \(\text{\(^{13}\)}C\text{-NMR (100 MHz, CDCl}_3\) \delta 55.9, 58.0, 123.6, 125.7, 125.9, 126.2, 126.8, 127.6, 127.9, 128.1, 128.2, 128.3, 128.8, 132.5, 132.8, 133.6, 134.7, 139.6; High-resolution MS, calcd for C\(_{27}\)H\(_{25}\)N: 363.1987, Found : m/z 363.1987 (M\(^+\)).

\(N\)-[(\(E\))-3-(2-Furyl)-2-propenyl]-\(N,\)\(N\)-dibenzylamine (3jc)

\(^1\)H-NMR (500 MHz, CDCl\(_3\) \delta 3.22 (dd, J = 6.5, 1.5 Hz, 2H), 3.65 (s, 4H), 6.21 (d, J = 3.0 Hz, 1H), 6.27 (dt, J = 16.0, 6.5 Hz, 1H), 6.38 (dd, J = 3.0, 1.5 Hz, 1H), 6.40 (d, J = 16.0 Hz, 1H), 7.26 (t, J = 7.5 Hz, 2H), 7.3-7.4 (m, 9H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\) \delta 55.2, 57.8, 107.0, 111.2, 120.8, 126.5, 126.8, 128.2, 128.7, 139.6, 141.6, 152.8; High-resolution MS, calcd for C\(_{21}\)H\(_{21}\)NO: 303.1623, Found : m/z 303.1621 (M\(^+\)).

\(N\)-[(\(E\))-3-(2-Thienyl)-2-propenyl]-\(N,\)\(N\)-dibenzylamine (3kc)

\(^1\)H-NMR (500 MHz, CDCl\(_3\) \delta 3.18 (dd, J = 6.7, 1.5 Hz, 2H), 3.62 (s, 4H), 6.13 (dt, J = 16.0, 6.7 Hz, 1H), 6.66 (d, J = 16.0 Hz, 1H), 6.90 (d, J = 3.0 Hz, 1H), 6.94 (dd, J = 5.0, 3.0 Hz, 1H), 7.12 (d, J = 5.0 Hz, 1H), 7.23 (t, J = 7.5 Hz, 2H), 7.3-7.4 (m, 10H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\) \delta 55.5, 57.9, 123.8, 125.0, 125.6, 126.8, 127.2, 127.5, 128.2, 128.7, 139.5, 142.4; High-resolution MS, calcd for C\(_{21}\)H\(_{22}\)NS: 319.1395, Found : m/z 319.1394 (M\(^+\)).

Mixture of \(N\)-(but-2-enyl)-\(N,\)\(N\)-dibenzylamine (3lc) and \(N\)-(but-3-en-2-yl)-\(N,\)\(N\)-dibenzylamine (3’lc) (3lc:3’lc = 8:2)

\(^1\)H-NMR (500 MHz, CDCl\(_3\) for (\(E\))-3lc \delta 1.68 (dd, J = 6.0, 1.0 Hz, 3H), 2.98 (d, J = 6.5 Hz, 2H),
Hz, 2H), 3.55 (s, 4H), 5.5-5.6 (m, 2H), 7.1-7.4 (m, 10H); $^1$H-NMR (500 MHz, CDCl$_3$) for (Z)-3lc δ 1.68 (d, $J = 6.0$ Hz, 3H), 3.07 (d, $J = 6.5$ Hz, 2H), 3.55 (s, 4H), 5.5-5.6 (m, 2H), 7.1-7.4 (m, 10H); $^1$H-NMR (500 MHz, CDCl$_3$) for 3'$^1$lc δ 1.17 (d, $J = 6.5$ Hz, 3H), 3.30 (dq, $J = 6.5$, 6.5 Hz, 1H), 3.54 (d, $J = 18.0$ Hz, 2H), 3.62 (d, $J = 18.0$ Hz, 2H), 5.08 (ddd, $J = 18.0$, 1.5, 1.5 Hz, 1H), 5.16 (ddd, $J = 10.5$, 1.5, 1.5 Hz, 1H), 5.93 (ddd, $J = 18.0$, 10.5, 6.5 Hz, 1H), 7.1-7.4 (m, 10H); $^{13}$C-NMR (100 MHz, CDCl$_3$) for (E)-3lc δ 17.9, 55.5, 57.6, 126.7, 128.1, 128.4, 128.5, 128.7, 139.9; $^{13}$C-NMR (100 MHz, CDCl$_3$) for (Z)-3lc δ 13.2, 49.7, 57.9, 126.7, 126.9, 127.8, 128.1, 128.8, 139.8; $^{13}$C-NMR (100 MHz, CDCl$_3$) for 3'$^1$lc δ 14.7, 53.5, 55.0, 115.6, 126.6, 128.1, 128.4, 128.8, 140.6; High-resolution MS, calcd for C$_{18}$H$_{21}$N: 251.1674, Found: m/z 251.1671 (M$^+$).

**N-(2-Phenyl-2-propenyl)-N,N-dibenzylamine (3oc)**

$^1$H-NMR (400 MHz, CDCl$_3$) δ 3.41 (s, 2H), 3.52 (s, 4H), 5.36 (d, $J = 2.0$ Hz, 1H), 5.42 (d, $J = 2.0$ Hz, 1H), 7.1-7.3 (m, 15H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 57.9, 58.3, 115.1, 126.8, 126.8, 127.3, 127.8, 128.0, 129.0, 139.5, 140.2, 146.3; High-resolution MS, calcd for C$_{23}$H$_{23}$N: 313.1830, Found: m/z 313.1831 (M$^+$).

**N-(2-Methyl-2-propenyl)-N,N-dibenzylamine (3pc)**

$^1$H-NMR (400 MHz, CDCl$_3$) δ 1.77 (s, 3H), 2.92 (s, 2H), 3.50 (s, 4H), 4.86 (s, 1H), 4.97 (s, 1H), 7.22 (t, $J = 8.5$ Hz, 2H), 7.30 (dd, $J = 8.5$, 8.5 Hz, 4H), 7.38 (d, $J = 8.5$ Hz, 4H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 20.7, 57.9, 60.7, 112.8, 126.8, 128.2, 128.7, 139.9, 144.0; High-resolution MS, calcd for C$_{18}$H$_{21}$N: 251.1674, Found: m/z 251.1676 (M$^+$).
**N-[(E)-(3-Phenyl-2-methyl-2-propenyl)]-N,N-dibenzylamine (3qc)**

$^1$H-NMR (500 MHz, CDCl$_3$) for (E)-3lc $\delta$ 1.92 (s, 3H), 3.07 (s, 2H), 3.56 (s, 4H), 6.51 (s, 1H), 7.1-7.4 (m, 15H); $^1$H-NMR (500 MHz, CDCl$_3$) for (Z)-3lc $\delta$ 2.01 (s, 3H), 3.16 (s, 2H), 3.42 (s, 4H), 6.49 (s, 1H), 7.1-7.4 (m, 15H); $^{13}$C-NMR (100 MHz, CDCl$_3$) for (E)-3lc $\delta$ 16.6, 58.0, 63.3, 126.1, 126.8, 127.5, 128.0, 128.2, 128.7, 128.8, 137.1, 138.0, 139.8; $^{13}$C-NMR (100 MHz, CDCl$_3$) for (Z)-3lc $\delta$22.8, 33.6, 54.2, 126.1, 126.7, 127.9, 128.1, 128.4, 128.7, 129.0, 137.6, 137.9, 139.8; High-resolution MS, calcd for C$_{24}$H$_{25}$N: 327.1987, Found : m/z 327.1978 (M$^+$).

**N-(3-Methylbut-2-enyl)-N,N-dibenzylamine (3rc)**

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.56 (s, 3H), 1.71 (s, 3H), 3.00 (d, $J = 9.0$ Hz, 2H), 3.55 (s, 4H), 5.32 (t, $J = 6.5$ Hz, 1H), 7.19-7.22 (m, 2H), 7.27-7.33 (m, 4H), 7.35-7.38 (m, 4H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 17.9, 25.8, 51.0, 57.9, 121.9, 126.7, 128.1, 128.8, 134.9, 140.0; High-resolution MS, calcd for C$_{19}$H$_{23}$N: 265.1830, Found : m/z 265.1833 (M$^+$).

**1,4-bis(N-methyl-N-phenylamino)-2-butene (6)**

$^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ 2.88 (s, 3H), 3.88 (d, $J = 3.5z$ Hz, 2H), 5.63 (dt, $J = 1.5$, 3.5z Hz, 1H), 6.69-6.72 (m, 3H), 7.20-7.23 (m, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 37.9, 54.3, 112.7, 116.5, 127.8, 129.1, 149.4; High-resolution MS, calcd for C$_{18}$H$_{22}$N$_2$: 266.1783, Found : m/z 266.1783 (M$^+$).
4.5 References and Notes


Summary and Outlook

Environmental pollution is a raising problem on a global scale that will have serious consequences for the next generation, unless we act today to prevent this problem. Burning of fossil fuels to supply the energy that all humankind require to sustain all human activities. However, it is the main causes for the environmental pollution, climate change and generally expending the natural reserves. As such, the excessive use of fossil-based carbon feedstocks should be reduced. Additionally, the diminishing petroleum reserves will be a major problem in the future anyways and therefore humankind needs to find alternatives to sustain our demand for energy, and economic growth. As a scientist, it is our responsibility to facilitate the transition to a perfect sustainable society that is in the environmental harmony. To arrive at such ideal society, organic chemists need to develop new catalytic tools that enable sustainable, green and clean synthetic methods with high efficiency, thus leading to less wastes. The work described in this thesis has been carried out in the context of these views, as new catalytic methodology has been developed clean, synthetically useful and novel amphiphilic allylation via umpolung of \( \pi \)-allylpalladium intermediates.
Chapter 1 described palladium catalyst and diethylzinc system promoted nucleophilic allylation of aldehydes and aldimes with vinylcyclopropane. A palladium-catalyzed nucleophilic allylation of aldehydes with vinylcyclopropane in the presence of diethylzinc proceeded to provide homoallyl alcohols with *anti* stereoselectivity (Scheme 1). Aldimines prepared from aldehyde and primary amines in situ underwent a similar nucleophilic allylation to give homoallylamines with *syn* stereoselectivity. The resulting homoallyl alcohols and homoallylamines could be converted by treatment with a tetraneuclear zinc cluster into γ-vinyl-δ-valerolactones and γ-vinyl-δ-valerolactams, respectively.

**Scheme 1** Pd-catalyzed nucleophilic allylation of aldehydes or aldimes with allyl alcohols
In chapter 2, consecutive double amphiphilic allylation of nitriles with 2-methylenepropane-1,3-diol catalyzed by palladium/triethylborane system was described. The combination of a Pd catalyst and triethylborane promotes the double amphiphilic allylation of nitriles with 2-methylenepropane-1,3-diol to serve as a 1,3-dipolar equivalent, providing pyrrolizidine derivatives. This double amphiphilic allylation can be expected as a highly efficient synthetic method of important pyrrolizidine alkaloids.

In chapter 3, the amphiphilic allylation of aldimines with 2,3-bismethylenebutane-1,4-diol derivatives to serve as a 1,4-dipolar equivalent proceeded by combination of palladium catalyst and diethylzinc preparing 3,4-bismethyleneepiperidines was described. The combination of Pd catalyst and diethylzinc promotes the amphiphilic allylation of aldimines with 2,3-bismethylenebutane-1,4-diol derivatives to serve as a 1,4-dipolar equivalent to form 3,4-bismethyleneepiperidines via a formal [4 + 2] cycloaddition reaction (Scheme 2). 3,4-Bismethyleneepiperidine rings are applicable for the synthesis of isoquinoline derivatives via the Diels–Alder reaction followed by an oxidation reaction with DDQ.
Chapter 4 described palladium having phosphine-borane ligand system promoted high efficient direct electrophilic allylation of amines with allyl alcohols. \( B\)-(2-Diphenylphosphinoethyl)-9-borabicyclononane (L1) was effective for this reaction (scheme 3). The linkage between phosphine and borane moieties and the structure of the linker in phosphine-borane ligand is considered to be important for high catalytic activity.

**Scheme 2** Amphiphilic Allylation of Aldimines with 2,3-Dimethylenebutane-1,4-diols

![Scheme 2](image)

**Scheme 3** Reaction of cinnamyl alcohol with \( N\)-methylaniline.

![Scheme 3](image)
This thesis contributes to the development of clean, synthetically useful and novel amphiphilic allylation via allyl cation equivalents and allyl anion equivalents by use of a palladium catalyst and Lewis acid and without stoichiometric pre-activation of allyl alcohol. Future studies in this area will involve investigation on the scope of various substrates using palladium/Lewis acids system. The author hopes that this thesis will contribute to further development of clean, synthetically useful and novel reaction via palladium/Lewis acids system.
List of Publications

Chapter 1

“Synthesis of Lactones and Lactams from Vinylcyclopropane by Palladium-Catalyzed Nucleophilic Allylation”

Chapter 2

“Efficient synthesis of pyrrolizidine by Pd-catalyzed consecutive double amphiphilic allylation of nitrile”

Chapter 3

“Palladium-Catalyzed [4 + 2] Cycloaddition of Aldimines and 1,4-Dipolar Equivalents via Amphiphilic Allylation”
17, 600-603.

Chapter 4

“Direct Allylic Amination of Allyl Alcohol Catalyzed by Palladium Complex with Phosphine-Borane Ligand”

G. Hirata, H. Satomura, H. Kumagae, G. Onodera, M. Kimura,

Submitted for Publication

Other Publications

“Synthesis and X-ray crystal structure of novel cobalt(II) complexes having oligopyridine ligands”

Gen Onodera, Goki Hirata, Takanao Seike, Ryo Takeuchi, Masanari Kimura,

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