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Development of New Synthetic Reactions
Using
Rhodium Catalysts and Organoboronic Acid Derivatives

Hiroshi Shimizu
2012
Preface

The studies described in this thesis have been carried out under the direction of Professor Masahiro Murakami during 2006-2011. These studies concern with novel carbon-carbon bond forming reactions using rhodium catalysts and organoboronic acid derivatives.

This thesis had been completed with the aid of so many people of Kyoto University such as a supervisor, collaborators and colleagues. The author would like to show his gratitude them.

First of all, the author would like to express his sincerest appreciation to Supervisor Professor Masahiro Murakami for providing an opportunity to study state of the art organic chemistry. All the works in this thesis could be achieved with his constant supervisions.

The author is deeply grateful to Lecture Tomoya Miura whose comments and support made enormous contribution to my work.

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The author special thanks Ms. Yuki Hasegawa and Ms. Chiyo Nagae for general support in his laboratory life.

The author thanks Mr. Haruo Fujita and Ms. Keiko Kuwata for the measurement of NMR spectra and Mass spectra.

Furthermore, this study had been accomplished by the aid of Otsuka Pharmaceutical Co., Ltd. The author received especially generous support from the following people.
The author is deeply grateful to Dr. Fujio Tabusa for giving the author the opportunity to study in academic laboratory.

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Finally, the author would also like to express my gratitude to my wife, Noriko, and two sons, Atsuki and Ryohei, for their moral support and warm encouragement.

Hiroshi Shimizu

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January, 2012
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General Introduction

Organic syntheses have significantly contributed to modern civilization. For example, various chemically synthesized pharmaceuticals and agrochemicals have improved our health and eating habits, and many organic electronic materials have promoted our comfortable lives. Therefore, further development of organic syntheses would provide more advanced civilization in the future.

Significant progress in organic syntheses has relied on the advances in organometallic chemistry since the second half of the last century. In particular, transition-metal catalysts have greatly contributed to innovation for organic synthesis. The unique reactivities of them have enabled many difficult transformations which had not been achieved by classical organic synthesis. On that account, it will lead to a further progress of organic synthesis to find new reactivities of transition-metal catalysts, and to utilize them to synthetic reactions.

The discovery and development of new catalytic methods for efficient carbon-carbon bond formations is one of the most important subjects in organic synthesis. For this subject, transition metal-catalyzed reactions have great potential. Thus, the author focused on rhodium as a transition metal, and tried to develop new rhodium-catalyzed reactions based on the following themes.

I. Reactions utilizing the unique reactivity of the organorhodium species
II. Reactions utilizing the capability of the rhodium complexes to isomerize alkenes

In this thesis, the author described the result of his investigation on development of new rhodium-catalyzed reactions using organoboronic acid derivatives as substrate, which have advantages in terms of (i) the low toxicity, (ii) the stability to air and moisture and (iii) the easy accessibility.

I. Reaction utilizing the unique reactivity of the organorhodium species

Recently, the rhodium-catalyzed reactions of organoboronic acid derivatives with unsaturated organic compounds have emerged as a powerful method for carbon-carbon bond formation, and many useful reactions have been found. For example, addition reactions to non-polar functional groups such as simple alkynes and alkenes have been reported. Such reactions do not occur in the cases of main group organometallics such as organomagnesium and organolithium compounds. For rhodium-catalyzed addition
reactions to polar functional groups like aldehydes and imines, asymmetric reactions using appropriate chiral ligands have also been developed.

Mechanistically, it is supposed that the formal oxidation state of rhodium remains $1^+$ throughout the catalytic cycle unlike most palladium-catalyzed reactions of organoboron compounds which involve a redox cycle. More specifically, those reactions are explained as follows. An organorhodium(I) species generated by transmetalation between a Rh(I)-OR species ($\text{OR} = \text{hydroxy or alkoxy}$) and an organoboron compound undergoes intermolecular 1,2-addition to an unsaturated moiety. There are two types of termination steps available in order to regenerate the Rh(I)–OR species for the next catalytic cycle. One is protodemetalation with $\text{H}_2\text{O}$ or ROH, and the other is $\beta$-oxygen elimination from $\beta$-oxy-substituted organorhodium(I) intermediate. The termination step using the oxygen affinity of rhodium is one of the characteristic features of the rhodium-catalyzed reaction.

![Diagram](image)

**Figure 1.** General reaction pathway of Rh(I)-catalyzed addition reaction of organoboronic acids

![Diagram](image)

**Figure 2.** Two types of termination step for Rh(I)-catalyzed addition reaction
The author examined the rhodium-catalyzed addition reaction of organoboronic acid derivatives using two kinds of substrates in order to find reactivities of organorhodium species which were different from those of main group organometallics or other organotransition metal species.

(1) Addition reactions to cyanoformate
(2) Addition reactions to allenic alcohols

(1) Addition reactions to cyanoformate
Main group organometallics such as organolithium and organomagnesium compounds readily undergoes nucleophilic addition to an ester group and a cyano group to provide carbon-carbon bond-forming products. Ester groups generally show a higher reactivity than cyano groups. On the other hand, Murakami et al reported that an organorhodium intermediate generated by an appropriate method is reactive enough to add to a cyano group in an intramolecular fashion. In some cases, the organorhodium species exhibits a higher reactivity to a cyano group than to an ester group. However, organorhodium species are less polar, and hence less nucleophilic than main group organometallics. Therefore, only limited examples are known for intermolecular addition reactions of organorhodium species to cyano groups and ester groups.

Cyanoformate is an interesting electrophilic substrate in order to compare the reactivities of the cyano group and the ester group toward nucleophiles. Since the two functionalities are both electron-withdrawing, their electrophilic reactivities are enhanced relative to isolated ester or nitrile groups. Generally, hard nucleophiles such as organomagnesium and organolithium compounds, alcohols, and amines selectively add to the ester’s carbonyl group of cyanoformate with elimination of the cyano group to afford the corresponding alkoxy carbonylated products. In particular, the reaction with the lithium enolates is widely used as synthetic method for β-ketoesters. On the other hand, nucleophilic addition to the cyano group preferentially occurs by soft nucleophiles such as electron-rich aromatic compounds and active methylene compounds under acidic reaction conditions.
The previously described reactivity of organorodium species in the intramolecular reactions led the author to expect that organorhodium species can add intermolecularly to the cyano group of cyanoformate showing an interesting chemo-selectivity which was opposite to main group organometallics. Thus, the author examined the rhodium(I)-catalyzed reaction of cyanoformate with organoboronic acid derivatives.

In chapter 1, a rhodium-catalyzed reaction of cyanoformate with arylboronic acids was described. Ethyl cyanoformate reacted with arylboronic acids in the presence of \([\text{Rh(OH)(cod)}]_2\) and boric acid to give \(\alpha\)-ketoesters in good yields. The reaction proceeds through selective 1,2-addition of an arylrhodium(I) species to the cyano group of cyanoformate. This result stands in sharp contrast to those obtained with arylmagnesium bromide and aryllithium, which selectively attack the ester group.

In chapter 2, an application of the reaction described in chapter 1 was shown. The author succeeded in incorporating a nitrogen atom of cyanoformate into the resulting isoindole skeleton. The reaction proceeded through chemo-selective addition of organorhodium intermediate generated from \(\text{ortho}-\text{borylbenzalacetone}\) derivatives onto the cyano group of cyanoformate, and the following intramolecular cyclization of an
imine intermediate. Isoindoles\textsuperscript{20} have attracted much attention in materials science due to their interesting photophysical properties in fluorescence and electroluminescence.\textsuperscript{21} The isoindoles obtained by this reaction possess an ester group at the 2-position and the carbonyl group on the side chain; these functional groups are able to act as the reactive site for further synthetic reactions.

In chapter 3, a reaction of 2-alkynylbenzoyl cyanides with carboxylic acids was explained. It was found during the study on the reaction using 2-alkynylbenzoyl cyanides in place of cyanoformate that a 2-alkynylbenzoyl cyanide cyclized on heating together with a carboxylic acid to produce a 2-acylamino-3-acylindenone. The reaction proceeded via a cyclic allenyl intermediate which was generated by assistance of the enhanced electrophilic nature of the cyano group. The reaction occurred in the absence of organoboronic acids and rhodium catalysts to form a carbon-carbon bond intramolecularly between the cyano group and the alkynyl group. The produced 2-acylamino-3-acylindenones could be utilized for the synthesis of fused heterocycles with an indenone skeleton.
(2) Addition reaction to allenic alcohols

The oxygen affinity of rhodium can be efficiently utilized in the regeneration step of the active catalyst of a rhodium(I)-catalyzed addition reaction of organoboron compounds to unsaturated functional groups. When an oxygen functionality (OR) is located at the β-position of an organorhodium(I) intermediate, β-oxygen elimination occurs in preference to β-hydrogen elimination or protodemetalation.22, 23

Allenic alcohols possess a hydroxy group and two highly reactive olefin units connected by an sp-carbon atom. Both of those two olefin units can be attacked by organotransition metals from two directions respectively, as shown in Figure 4. Ihara et al. reported a palladium(0)-catalyzed reaction of allenic alcohols with arylboronic acids.24 In this case, the reaction proceeds through an oxidative SN2’ reaction of palladium(0) species, which occurs from the less hindered side (d-side) as shown in Figure 5 to produce an E-product.

![Figure 4. attack to allenic alcohol](image)

![Figure 5. Pd(0)-catalyzed reaction](image)

The author was interested in whether the affinity of rhodium to the oxygen atom could affect the reaction of the same substrate as in the case of palladium(0).

In chapter 4, a rhodium-catalyzed addition reaction of arylboronic acids to allenic alcohols was described. The arylboronic acids readily reacted with the allenic alcohols in the presence of [Rh(OH)(cod)]2 to afford 3-arylated 1,3-dienes. When the terminal substituent of the allenyl group was an aryl group, a (Z)-form of 1,3-diarylated 1,3-diene was obtained stereoselectively. It was interesting that the stereochemical outcome is opposite to that of the palladium-catalyzed reaction of the same substrates.24 The author ascribed the (Z)-selectivity in this rhodium-catalyzed reaction to δ-elimination of Rh(I)-OH through a six-membered cyclic transition state. This δ-elimination of Rh(I)-OH presents a new termination step of rhodium-catalyzed reactions.
II. Reaction utilizing the capability of the rhodium complexes which induce alkene isomerization

Cationic rhodium complexes are possible to induce isomerization of alkenes\textsuperscript{25} by the following mechanism; (i) allylic C-H activation, (ii) $\pi$-allyl complex generation and (iii) reductive elimination (Figure 6). This isomerization of alkenes is often used for isomerization of allyl ethers, allyl alcohols and allyl amines to enol ethers, carbonyl compounds and enamines, and these asymmetric reactions have been studied extensively\textsuperscript{26}. For example, an asymmetric isomerization of geranylamine by the [Rh]$^+$/BINAP has been applied as one step in industrial process for the production of (-)-menthol.

Thus, if the equilibrium of the isomerization is directed toward the desired isomer, like the cases of the allyl ether/enol ether isomerization and the allyl amine/enamine isomerization, the reaction would become synthetically useful. On the contrary, the reaction would lack in usefulness if the equilibrium of the isomerization cannot be controlled.
The author envisaged that it would become a useful reaction if only one isomer among various isomers generated was reactive for the next transformation which subsequently occurred in situ. In the next chapter, an isomerization reaction to generate an active intermediate for carbon-carbon bond formation was investigated.

2-Alkenylboronic acid (allylboration) derivatives react with aldehydes at the $\gamma$-position to boron selectively to give the homoallylic alcohols without any catalysts. This allylation reaction proceeds via a six-membered transition state based on coordination of the boron atom to the carbonyl oxygen. It results in diastereoselective production of homoallylic alcohols where the stereochemistry was defined by the geometry of used allylborationcompounds. However, stereoselective preparation of geometrically-defined allylborationcompounds suffers from several problems such as functional group tolerance and difficulty of chromatographic purification due to their hydrolysis. Therefore, it is desired to develop a new preparative method addressing these issues.

In chapter 5, a rhodium catalyzed allylation reaction of aldehydes with 1-alkenylboronates as the surrogate for (E)-allylboration reagents was described. 1-Alkenylboronic pinacolates reacted with aldehydes in the presence of $[\text{Rh}]^+/\text{dppm}$ complex to give anti-configured homoallylic alcohols with high diastereoselectivity. This reaction proceeds through the generation of kinetically preferred (E)-allylborationates from 1-alkenylboronates by the catalysis of a cationic rhodium complex. 1-Alkenylboronates are readily prepared in one step by hydroboration of terminal alkynes. Hence, this allylation reaction provides a convenient and straightforward synthetic method of stereo-defined homoallyl alcohols from terminal alkynes and aldehydes.

\[
\begin{align*}
\text{R}^2\text{=C}^\text{\=C}^\text{-Bpin} & \quad \text{cat.} \quad [\text{Rh(nbd)}(\text{CH}_3\text{CN})_3] \text{SbF}_6 \\
\text{ClCH}_2\text{CH}_2\text{Cl} & \quad \text{90 °C} \\
\text{transient intermediate} & \quad \text{R}^1\text{CHO} \quad \text{OH} \\
& \quad \text{R}^2
\end{align*}
\]
General Introduction

References


General Introduction
Abstract: An arylrhodium(I) species selectively reacts with the cyano group of ethyl cyanoformate to afford the corresponding $\alpha$-keto ester in good yield. This result stands in sharp contrast to the reactivity of arylmagnesium bromide and aryllithium that attack to the ester group.
Introduction

The rhodium-catalysed reaction of organoboron species with unsaturated organic compounds has emerged as a powerful method for carbon–carbon bond formation. The reaction generally proceeds by transmetallation to generate an intermediate organorhodium species, which then undergoes 1,2-addition to alkynes, alkenes, aldehydes, imines, esters, acid anhydrides, 1,2-dicarbonyl compounds and nitriles in an intermolecular fashion. Murakami et al have developed cascade reactions in which an organorhodium intermediate adds intramolecularly to a cyano group, and found that in some cases the organorhodium species exhibited a higher propensity to react with a cyano group than with an ester group. Ethyl cyanoformate is an interesting electrophilic substrate to compare the reactivities of the cyano group and the ester group toward nucleophiles (Figure 1). Since the two functionalities are both electron-withdrawing, their electrophilic reactivities are enhanced relative to isolated ester or nitrile groups. Nucleophiles such as organomagnesium and –lithium compounds, lithium enolates, lithiated amides, alcohols, and amines selectively attack the ester carbonyl group of ethyl cyanoformate with the cyano group acting as a leaving group to afford the corresponding ethoxycarbonylated products. On the other hand, selective addition to the cyano group proceeds when ethyl cyanoformate is reacted under acidic conditions with softer nucleophilic species, like active methylene compounds, electron-rich benzenes, and organocadmium compounds. The previous studies in Murakami laboratory on rhodium-catalysed cascade reactions led me to examine the reaction of ethyl cyanoformate with phenylboronic acid in the presence of a rhodium catalyst in order to determine which functionality is more vulnerable to intermolecular attack by a phenylrhodium species.

![Ambident electrophilicity of cyanoformate](image-url)
Results and discussions

A mixture of ethyl cyanoformate (1), phenylboronic acid (2a, 1.5 equiv), and [Rh(OH)(cod)]₂ (2.5 mol %, 5% of Rh) in dioxane was heated at 80 °C for 3 h. Aqueous work-up followed by chromatographic isolation afforded ethyl benzoylformate (3a) in 40% yield (Table 1, entry 1). No ethyl benzoate was detected in the ¹H NMR spectrum of the crude reaction mixture. The selective formation of 3a suggests that the phenylrhodium intermediate generated by transmetalation undergoes 1,2-addition to the cyano group in preference to the ester group. Addition of boric acid (B(OH)₃, 1.0 equiv) improved the yield to 62% yield (Table 1, entry 2). The other additives as proton source, such as H₂O, PhOH, NH₄Cl and AcOH, showed no effect. It was tried further optimization using boronic acid as an additive (Table 2). The best yield of 83% was obtained in the reaction at 60 °C using 1.2 equiv of phenylboronic acid (2a) and 2.0 equiv of boric acid (Table 2, entry 4).

The results obtained with other arylboronic acids are summarized in Table 3. The corresponding α-keto esters are produced in yields ranging from 46% to 87%. Good yields were obtained with arylboronic acids having a methoxy substituent at either the o-, m- or p-position of the phenyl ring (entries 2–4). Although o-tolylboronic acid was a suitable substrate (entry 9), o- biphenylboronic acid gave only a moderate yield (entry 10). Electron-withdrawing groups at o- and p-positions decreased the yield (entries 8, 11). Of note was that a formyl group remained intact under the reaction conditions (entry 12).

Table 1. The effect of additives

<table>
<thead>
<tr>
<th>entry</th>
<th>additive (1.0eq)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>B(OH)₃</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>H₂O</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>PhOH</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>NH₄Cl</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>AcOH</td>
<td>trace</td>
</tr>
</tbody>
</table>

Table 2. The effect of B(OH)₃ as an additive

<table>
<thead>
<tr>
<th>entry</th>
<th>B(OH)₃</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>80</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>1.0eq</td>
<td>80</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>2.0eq</td>
<td>80</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>2.0eq</td>
<td>60</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>2.0eq</td>
<td>40</td>
<td>53</td>
</tr>
</tbody>
</table>

a) 1.5 eq of PhB(OH)₂ was used. b) the reaction was performed at 80°C.
Formation of considerable amounts of arenes by protonolysis of arylboronic acids was observed in cases when the desired products 3 were obtained in moderate yield (entries 10–12).

Table 3. Reaction of ethylcyanoformate (1) with arylboronic acids 2

<table>
<thead>
<tr>
<th>entry</th>
<th>2</th>
<th>Ar</th>
<th>3 product</th>
<th>yield (%)a</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>Ph</td>
<td>3a</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>4-MeO-C₆H₄</td>
<td>3b</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>3-MeO-C₆H₄</td>
<td>3c</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>2-MeO-C₆H₄</td>
<td>3d</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>4-Br-C₆H₄</td>
<td>3e</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>4-F-C₆H₄</td>
<td>3f</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>3-Cl-C₆H₄</td>
<td>3g</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>2h</td>
<td>2-Cl-C₆H₄</td>
<td>3h</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>2i</td>
<td>2-Me-C₆H₄</td>
<td>3i</td>
<td>83</td>
</tr>
<tr>
<td>10</td>
<td>2j</td>
<td>2-Ph-C₆H₄</td>
<td>3j</td>
<td>50</td>
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<tr>
<td>11</td>
<td>2k</td>
<td>4-MeO₂C-C₆H₄</td>
<td>3k</td>
<td>58</td>
</tr>
<tr>
<td>12</td>
<td>2l</td>
<td>3-CHO-C₆H₄</td>
<td>3l</td>
<td>50</td>
</tr>
</tbody>
</table>

a Isolated yields

The mechanism depicted in Scheme 1 is assumed for the formation of 3. Arylrhodium(I) 4 is generated by transmetallation, and then undergoes selective 1,2-addition to the cyano group. The resultant iminorhodium(I) species 5 is protonated with boric acid (or with 2) to afford imine 6 and rhodium(I) boronate (7), which is then transmetalated with arylboronic acid 2 to regenerate arylrhodium(I) 4. α-Keto ester 3 is then formed by hydrolysis of 6. Boric acid is presumed to facilitate the release of rhodium from the iminorhodium(I).
intermediate 5 by protonolysis. The effect of the acidic proton of boric acid is apparent from the contrasting results of the reaction of 1 with phenylboroxine (9) with and without boric acid (eqn 1).

![Chemical reaction equation]

(1)

The selective reaction of the cyano group of 1 with organometallic reagents is rare. The reaction of 1 with phenylcadmium bromide in the presence of zinc dichloride has been reported to give 3 in 31% yield. For comparison, we carried out reactions of 1 with phenylmagnesium bromide and phenyllithium. When 1 was reacted with phenylmagnesium bromide (1.05 equiv) in THF with the reaction temperature being raised from –20 °C to room temperature, ethyl benzoate was obtained in 89% yield and none of 3a was observed. The reaction of 1 with phenyllithium in ether afforded ethyl benzoate in 36% yield together with various other compounds including triphenylmethanol and benzophenone (eqn 2). The selective formation of α-keto esters in the present reaction is in sharp contrast to the results obtained with phenylmagnesium bromide and phenyllithium.

![Chemical reaction equation]

(2)

**Conclusion**

In conclusion, the rhodium-catalysed reaction of ethyl cyanoformate with arylboronic acids provides a convenient method for the synthesis of arylated α-keto esters. It was demonstrated that arylrhodium(I) species preferentially add to the cyano group of 1 rather than to the ester carbonyl group.
Experimental section

General. $^1$H- and $^{13}$C-NMR spectra were recorded on a Varian Gemini 2000 ($^1$H at 300 MHz and $^{13}$C at 75 MHz) spectrometer using CHCl$_3$ ($^1$H, $\delta = 7.26$) and CDCl$_3$ ($^{13}$C, $\delta = 77.16$) as an internal standard. High-resolution mass spectra were recorded on a JEOL JMS-SX102A spectrometer. Preparative thin-layer chromatography was performed with silica gel 60 PF$_{254}$ (Merck).

Materials. 1,4-Dioxane was freshly distilled from sodium benzophenone ketyl. [Rh(OH)(cod)$_2$]$_2$ was prepared according to the reported procedure. Boric acid and all arylboronic acids were purchased from commercial sources and used without further purification. Ethyl cyanoformate was purchased from TCI and used after distillation. Phenylboroxine were prepared from the commercially available phenylboronic acids by azeotropic removal of water from its toluene solution and purified by washing the crude boroxines repeatedly with hexane.

General procedure for rhodium-catalysed reaction of cyanoformate with arylboronic acids A mixture of arylboronic acid 2 (0.6 mmol, 1.2 equiv), H$_3$BO$_3$ (1.0 mmol, 2.0 equiv), [Rh(OH)(cod)$_2$] (0.0125 mmol, 2.5 mol%) and ethyl cyanoformate (1, 0.5 mmol, 1.0 equiv) in 1,4-dioxane (1 ml) was stirred for 30 min at room temperature and then at 60 °C for 3 h under an Ar atmosphere. Then the reaction mixture was cooled and diluted with AcOEt (10 ml) and citric acid (10% aq. 5 ml). The organic layer was separated and the aqueous layer was extracted with AcOEt (5 ml x 3). The combined extracts were washed with water and brine, and dried over Na$_2$SO$_4$. The solvent was removed under reduced pressure and the residue was purified by preparative thin-layer chromatography (hexane:AcOEt) to give the product 3, which were characterized by $^1$H and $^{13}$C NMR spectra.

Ethyl benzoylformate (3a)$^{22}$

![CO$_2$Et](image)

According to general procedure, 3a (73.7 mg, 83%) was prepared from 1 (49.5 mg, 0.5 mmol) and 2a (73.2 mg, 0.6 mmol).: $^1$H NMR: $\delta = 1.43$ (t, $J = 7.2$ Hz, 3H), 4.46 (q, $J = 7.2$ Hz, 2H), 7.49-7.55 (m, 2H), 7.63-7.69 (m, 1H), 8.00-8.03 (m, 2H); $^{13}$C NMR: $\delta = 14.2$, 62.4, 128.9, 130.0, 132.4, 135.0, 163.8, 186.4
Chapter 1

Ethyl 4-methoxybenzoylformate (3b)

![Chemical Structure of Ethyl 4-methoxybenzoylformate](image1)

According to general procedure, 3b (83.6 mg, 80%) was prepared from 1 (49.5 mg, 0.5 mmol) and 2b (91.2 mg, 0.6 mmol). $^1$H NMR: $\delta$ = 1.42 (t, $J$ = 7.2 Hz, 3H), 3.90 (s, 3H), 4.43 (q, $J$ = 7.2 Hz, 2H), 6.96-6.99 (m, 2H), 7.99-8.02 (m, 2H); $^{13}$C NMR: $\delta$ = 14.2, 55.7, 62.3, 114.3, 125.5, 132.6, 164.2, 165.0, 184.9

Ethyl 3-methoxybenzoylformate (3c)

![Chemical Structure of Ethyl 3-methoxybenzoylformate](image2)

According to general procedure, 3c (77.5 mg, 74%) was prepared from 1 (49.5 mg, 0.5 mmol) and 2c (91.2 mg, 0.6 mmol). $^1$H NMR: $\delta$ = 1.43 (t, $J$ = 7.2 Hz, 3H), 3.87 (s, 3H), 4.45 (q, $J$ = 7.2 Hz, 2H), 7.20 (ddd, $J$ = 0.9Hz, 2.7Hz, 8.1Hz, 1H), 7.42 (t, $J$ = 8.1Hz, 1H), 7.51-7.59 (m, 2H); $^{13}$C NMR: $\delta$ = 14.2, 55.6, 62.5, 113.3, 121.9, 123.2, 130.0, 133.7, 160.0, 163.9, 186.4

Ethyl 2-methoxybenzoylformate (3d)

![Chemical Structure of Ethyl 2-methoxybenzoylformate](image3)

According to general procedure, 3d (90.1 mg, 87%) was prepared from 1 (49.5 mg, 0.5 mmol) and 2d (91.2 mg, 0.6 mmol). $^1$H NMR: $\delta$ = 1.40 (t, $J$ = 7.2 Hz, 3H), 3.87 (s, 3H), 4.49 (q, $J$ = 7.2 Hz, 2H), 6.99 (d, $J$ = 6.6Hz, 1H), 7.04-7.11 (m, 1H), 7.55-7.63 (m, 1H), 7.88 (dd, $J$ = 1.8Hz, 7.8Hz, 1H); $^{13}$C NMR: $\delta$ = 14.2, 56.1, 61.9, 112.1, 121.3, 122.7, 130.7, 136.4, 160.3, 165.3, 186.6

Ethyl 4-bromobenzoylformate (3e)

![Chemical Structure of Ethyl 4-bromobenzoylformate](image4)

According to general procedure, 3e (105.2 mg, 82%) was prepared from 1 (49.5 mg, 0.5 mmol) and 2e (120.5 mg, 0.6 mmol). $^1$H NMR: $\delta$ = 1.43 (t, $J$ = 6.9 Hz, 3H), 4.45 (q, $J$ = 6.9 Hz, 2H), 7.64-7.68 (m, 2H), 7.88-7.92 (m, 2H); $^{13}$C NMR: $\delta$ = 14.2, 62.7, 130.6,
Chapter 1

131.3, 131.5, 132.3, 163.2, 185.1

**Ethyl 4-fluorobenzoylformate (3f)**\(^{23}\)

![Ethyl 4-fluorobenzoylformate (3f)](image1)

According to general procedure, 3f (71.3 mg, 73%) was prepared from 1 (49.5 mg, 0.5 mmol) and 2f (84.0 mg, 0.6 mmol). \(^1\)H NMR: \(\delta = 1.43\) (t, \(J = 7.2\) Hz, 3H), 4.45 (q, \(J = 7.2\) Hz, 2H), 7.15-7.23 (m, 2H), 8.05-8.15 (m, 2H); \(^13\)C NMR: \(\delta = 14.2, 62.6, 116.3\) (d, \(J_{C-F} = 22.1\)Hz), 129.0 (d, \(J_{C-F} = 3.5\)Hz), 133.0 (d, \(J_{C-F} = 9.3\)Hz), 163.4, 166.8 (d, \(J_{C-F} = 257.5\)Hz), 184.6

**Ethyl 3-chlorobenzoylformate (3g)**\(^{26}\)

![Ethyl 3-chlorobenzoylformate (3g)](image2)

According to general procedure, 3g (85.8 mg, 81%) was prepared from 1 (49.5 mg, 0.5 mmol) and 2g (93.8 mg, 0.6 mmol). \(^1\)H NMR: \(\delta = 1.43\) (t, \(J = 7.2\) Hz, 3H), 4.46 (q, \(J = 7.2\) Hz, 2H), 7.47 (t, \(J = 7.8\) Hz, 1H), 7.60-7.65 (m, 1H), 7.89-7.94 (m, 1H), 8.00-8.03 (m, 1H); \(^13\)C NMR: \(\delta = 14.2, 62.8, 128.3, 129.9, 130.3, 134.1, 134.9, 135.3, 163.0, 184.9\)

**Ethyl 2-chlorobenzoylformate (3h)**\(^{27}\)

![Ethyl 2-chlorobenzoylformate (3h)](image3)

According to general procedure, 3h (48.6 mg, 46%) was prepared from 1 (49.5 mg, 0.5 mmol) and 2h (93.8 mg, 0.6 mmol). \(^1\)H NMR: \(\delta = 1.41\) (t, \(J = 6.9\) Hz, 3H), 4.43 (q, \(J = 6.9\) Hz, 2H), 7.37-7.45 (m, 2H), 7.50-7.57 (m, 1H), 7.77 (dd, \(J = 1.8\)Hz, 7.8Hz, 1H); \(^13\)C NMR: \(\delta = 14.0, 63.0, 127.4, 130.6, 131.7, 133.4, 133.9, 134.4, 163.2, 186.7\)

**Ethyl 2-methylbenzoylformate (3i)**\(^{28}\)

![Ethyl 2-methylbenzoylformate (3i)](image4)

According to general procedure, 3i (79.7 mg, 83%) was prepared from 1 (49.5 mg, 0.5
mmol) and 2i (81.2 mg, 0.6 mmol). : $^1$H NMR: $\delta = 1.42$ (t, $J = 7.2$ Hz, 3H), 2.61 (s, 3H), 4.43 (q, $J = 7.2$ Hz, 2H), 7.32 (t, $J = 7.5$ Hz, 2H), 7.45-7.53 (m, 1H), 7.69 (d, $J = 7.5$ Hz, 1H), $^{13}$C NMR: $\delta = 14.2, 21.6, 62.3, 126.0, 131.2, 132.3, 132.4, 133.7, 141.3, 164.7, 188.8$

**Ethyl 2-phenylbenzoylformate (3j)**

![Ethyl 2-phenylbenzoylformate](image)

According to general procedure, 3j (63.5 mg, 50%) was prepared from 1 (49.5 mg, 0.5 mmol) and 2j (118.8 mg, 0.6 mmol). : $^1$H NMR: $\delta = 1.04$ (t, $J = 6.9$ Hz, 3H), 3.72 (q, $J = 6.9$ Hz, 2H), 7.29-7.38 (m, 2H), 7.38-7.54 (m, 5H), 7.65 (dt, $J = 1.5$ Hz, 7.5 Hz, 1H), 7.82 (dd, $J = 1.2$ Hz, 7.8 Hz, 1H); $^{13}$C NMR: $\delta = 13.7, 62.2, 127.7, 128.3, 128.8, 129.6, 130.2, 130.4, 132.9, 134.5, 139.4, 143.1, 162.6, 189.7$; HRMS (FAB+): Calcd for C$_{16}$H$_{14}$O$_3$, (M+H)$^+$ 254.0943. Found m/z 254.0945.

**Ethyl 4-methoxycarbonylbenzoylformate (3k)**

![Ethyl 4-methoxycarbonylbenzoylformate](image)

According to general procedure, 3k (68.6 mg, 58%) was prepared from 1 (49.5 mg, 0.5 mmol) and 2k (108.0 mg, 0.6 mmol). : $^1$H NMR: $\delta = 1.44$ (t, $J = 7.2$ Hz, 3H), 3.97 (s, 3H), 4.47 (q, $J = 7.2$ Hz, 2H), 8.06-8.12 (m, 2H), 8.14-8.20 (m, 2H); $^{13}$C NMR: $\delta = 14.3, 52.8, 62.8, 130.05, 130.10, 135.4, 135.7, 163.2, 166.0, 185.7$; HRMS (FAB+): Calcd for C$_{12}$H$_{13}$O$_5$, (M+H)$^+$ 237.0763. Found m/z 237.0770.

**Ethyl 3-formylbenzoylformate (3l)**

![Ethyl 3-formylbenzoylformate](image)

According to general procedure, 3l (51.7 mg, 50%) was prepared from 1 (49.5 mg, 0.5 mmol) and 2l (90.0 mg, 0.6 mmol). : $^1$H NMR: $\delta = 1.45$ (t, $J = 6.9$ Hz, 3H), 4.49 (q, $J = 6.9$ Hz, 2H), 7.72 (t, $J = 7.8$ Hz, 1H), 8.19 (dt, $J = 1.5$ Hz, 7.8 Hz, 1H), 8.32 (dt, $J =
1.5Hz, 7.8Hz, 1H), 8.53 (t, J = 1.5Hz, 1H), 10.10 (s, 1H); $^1$H NMR: δ = 14.2, 62.9, 129.9, 131.7, 133.5, 134.8, 135.4, 136.8, 162.9, 185.0, 191.0; HRMS (FAB+): Calcd for C$_{11}$H$_{11}$O$_4$, (M+H)$^+$ 207.0657. Found m/z 207.0668.
References


Chapter 2

Synthesis of Functionalized Isoindoles
by the Rhodium-Catalyzed Reaction of Cyanoformates
with ortho-Borylbenzalacetone Derivatives

Abstract: Isoindole skeleton is constructed by the reaction of cyanoformate with ortho-borylbenzalacetone derivatives in the presence of a rhodium (I) catalyst. The reaction proceeds through selective 1, 2-addition of an arylrhodium(I) species to the cyano group of cyanoformate and subsequent intramolecular cyclization.
Introduction

In the past decade, rhodium-catalyzed addition reactions of organoboron compounds to unsaturated organic functionalities have been intensively investigated. Organorhodium species generated by transmetallation between boron and rhodium exhibit unique reactivities which are unavailable with other main group organometallics and organotransition metal complexes. In chapter 1, the author mentioned that the synthesis of α-keto esters by the rhodium-catalyzed reaction of cyanoformates with arylboronic acids. An intermediary organorhodium species undergoes 1,2-addition regioselectively onto the cyano group of cyanoformate and a resultant iminorhodium species is hydrolyzed to a carbonyl group with loss of the nitrogen atom. This unique reactivity of organorhodium species towards the activated cyano group stands in contrast to the reactivities of arylmagnesium and aryllithium species that attack to the ester group of cyanoformates in preference to the cyano group. The author next envisaged that it would increase the synthetic utility of the unique reactivity of organorhodium species toward cyano groups if the nitrogen atom of the cyano group could be retained in a reaction product. Thus, the application to the synthesis of aza heterocyclic compounds was next attempted. In this chapter, it is described the synthesis of isoindoles by the rhodium-catalyzed reaction of cyanoformate with ortho-borylbenzalacetone derivatives. The nitrogen atom of the cyano group is incorporated in the produced isoindole skeleton.

Results and discussions

Initially, ethyl cyanoformate (2a) was reacted with benzalacetone having a boronic ester group at the ortho-position 1a under the reaction conditions which were used for the reaction of 2a with phenylboronic acid in chapter 1 (Equation 1). Thus, a mixture of 1a and ethyl cyanoformate (2a, 1.5 equiv.) in dioxane was heated in the presence of B(OH)3 (1.0 equiv.) and [Rh(OH)(cod)]2 (2.5 mol %, 5 % of Rh) at 80 °C for 15 h. After aqueous workup, the reaction mixture was analyzed by 1H NMR, which disclosed that the mixture consisted of isoindole 3a, benzalacetone (4) and 1a (1a : 3a : 4 = 13 : 33 : 54).
A plausible mechanism for the formation of isoindole 3a is shown in Figure 1. An arylrhodium species is initially generated from 1a by transmetallation between boron and rhodium. It undergoes intermolecular 1,2-addition chemoselectively onto the cyano group of 2a. A resultant iminorhodium species undergoes intramolecular conjugate addition onto the electron-deficient alkene at the ortho position in a 5-exo mode to construct a five-membered ring heterocycle, which then undergoes a prototropic shift to establish a pyrrole system with extended conjugation. Finally, a rhodium enolate is protonated to give 3a and the rhodium(I) catalyst. Benzalacetone was formed by direct hydrolysis of the C-B bond of 1a.

Table 1. Optimization for the formation of 3a from 1a and 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>2a (equiv.)</th>
<th>B(OH)₃ (equiv.)</th>
<th>Time (h)</th>
<th>1a : 3a : 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dioxane</td>
<td>1.5</td>
<td>1.0</td>
<td>15</td>
<td>13 : 33 : 54</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>1.5</td>
<td>1.0</td>
<td>15</td>
<td>0 : 0 : 100</td>
</tr>
<tr>
<td>3</td>
<td>NMP</td>
<td>1.5</td>
<td>1.0</td>
<td>15</td>
<td>56 : 27 : 17</td>
</tr>
<tr>
<td>4</td>
<td>NMP</td>
<td>1.5</td>
<td>3.0</td>
<td>3</td>
<td>0 : 71 : 29</td>
</tr>
<tr>
<td>5</td>
<td>NMP</td>
<td>3.0</td>
<td>3.0</td>
<td>3</td>
<td>0 : 87 : 13</td>
</tr>
</tbody>
</table>

a Determined by 1H NMR integral value of crude reaction mixture.

b Isolated yield of 3a.
Chapter 2

The results of the optimization of the reaction conditions are shown in Table 1. Only hydrolysis of 1a occurred when toluene was used as the solvent (entry 2). On the other hand, the use of N-methylpyrrolidone (NMP) decreased the production of benzalacetone although a considerable amount of the unreacted 1a remained (entry 3). Increasing the amounts of cyanoformate and B(OH)$_3$ to 3.0 equivalents significantly improved the yield of the isoindole 3a (75% isolated yield, entry 5).

The reaction conditions used in entry 5 could be regarded as the optimal conditions, and the reaction was examined with a variety of combinations of substrates (Table 2). Whereas only a moderate yield (57%) was obtained with methyl cyanoformate (entry 2), isopropyl and isobutyl cyanoformates gave results similar to that of ethyl cyanoformate (entries 3 and 4). The isoindole-forming reaction worked well with substrates having an electron-donating methoxy substituent on the aromatic ring of 1 (entries 5 and 6). On the other hand, lower yields were observed when the aromatic ring possessed an electron-withdrawing chloro substituent (entries 7 and 8), probably because protonolysis of the C—B linkage occurred more facilely with these substrates. Not only benzalacetone derivatives but also an analogous chalcone derivative gave the corresponding isoindole (entry 9).

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>2</th>
<th>R$^3$</th>
<th>3</th>
<th>Yield(%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2a</td>
<td>Et</td>
<td>3a</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2b</td>
<td>Me</td>
<td>3b</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2c</td>
<td>iPr</td>
<td>3c</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>Me</td>
<td>H</td>
<td>2d</td>
<td>iBu</td>
<td>3d</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>Me</td>
<td>4-MeO</td>
<td>2b</td>
<td>Et</td>
<td>3e</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>1c</td>
<td>Me</td>
<td>5-MeO</td>
<td>2b</td>
<td>Et</td>
<td>3f</td>
<td>69</td>
</tr>
<tr>
<td>7</td>
<td>1d</td>
<td>Me</td>
<td>4-Cl</td>
<td>2b</td>
<td>Et</td>
<td>3g</td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>1e</td>
<td>Me</td>
<td>5-Cl</td>
<td>2b</td>
<td>Et</td>
<td>3h</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>1f</td>
<td>Ph</td>
<td>H</td>
<td>2b</td>
<td>Et</td>
<td>3i</td>
<td>59</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield of 3.

Table 2. Synthesis of various 3-acylmethyl-2H-isoiindoles (3) from 1 and 2
Next, methyl cinnamate having a boronic ester group at the ortho position 5a was used in place of 1a (Table 3). The α,β-unsaturated ester moiety was less reactive as the conjugate acceptor than α,β-unsaturated ketones, and thus, hydrolysis of the N–Rh linkage of the iminorhodium intermediate occurred in competition with intramolecular conjugate addition to the α,β-unsaturated ester moiety. Hydrolysis of the iminorhodium intermediate gave an iminoester, which was further hydrolyzed to afford the keto ester 7. Formation of the keto ester 7 was suppressed by addition of an excessive amount of cyclooctadiene (COD). The isoindole 6a was formed in 79% NMR yield and was isolated in 59% yield when the reaction was carried out at 120 °C for 3 h in 1,3-dimethyl-2-imidazolidinone (DMI) in the presence of 10 equiv of COD and 3.5 mol % of [Rh(OH)(COD)]₂ (entry 5). It seems that the rhodium catalyst was deteriorated under the reaction conditions and that the presence of the excessive amount of COD caused its persistent coordination to rhodium, thereby retarding the deterioration of the catalyst.

Table 3. Optimization for the formation of 6a from 5a and 2a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Rh(OH)(cod)]₂</th>
<th>COD (equiv.)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Ratio²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5 mol %</td>
<td>none</td>
<td>80</td>
<td>12</td>
<td>83 : 24 : 9 : 7</td>
</tr>
<tr>
<td>2</td>
<td>2.5 mol %</td>
<td>1</td>
<td>80</td>
<td>12</td>
<td>60 : 24 : 9 : 7</td>
</tr>
<tr>
<td>3</td>
<td>2.5 mol %</td>
<td>10</td>
<td>80</td>
<td>12</td>
<td>23 : 49 : 16 : 12</td>
</tr>
<tr>
<td>4</td>
<td>2.5 mol %</td>
<td>10</td>
<td>120</td>
<td>12</td>
<td>23 : 63 : 5 : 9</td>
</tr>
<tr>
<td>5ᵇ</td>
<td>3.5 mol %</td>
<td>10</td>
<td>120</td>
<td>3</td>
<td>0 : 79 : 10 : 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(59 %)³</td>
</tr>
</tbody>
</table>

² Determined by °H NMR integral value of crude reaction mixture.
ᵇ DMI was employed as solvent.
ᶜ Isolated yield of 6a.
Other cinnamic ester derivatives were examined and moderate isolated yields ranging from 50% to 62% were observed (Table 4).

Table 4. Synthesis of various 3-alkoxycarbonylmethyl-2H-isoindoles (6) from 5 and 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>5</th>
<th>R1</th>
<th>R2</th>
<th>6</th>
<th>Yield(%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>Me</td>
<td>H</td>
<td>6a</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>Me</td>
<td>4-MeO</td>
<td>6b</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>Me</td>
<td>5-MeO</td>
<td>6c</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>5d</td>
<td>tBu</td>
<td>H</td>
<td>6d</td>
<td>50</td>
</tr>
</tbody>
</table>

a Isolated yield of 5.

Conclusion

Recently, isoindoles$^5, 6$ have attracted attention in materials science due to their interesting photophysical properties in fluorescence and electroluminescence.$^7$ In addition, isoindoles act as the highly reactive diene substrate in [4+2]-cycloaddition reactions employed for preparation of origoacenes.$^8$ The author has developed a new method to synthesize functionalized isoindole derivatives by the rhodium-catalyzed reaction of cyanoformates with ortho-borylbenzalacetone derivatives. The nitrogen atom of the cyanoformates is incorporated in the isoindole skeleton produced in this reaction.
Experimental Section

General. All reactions were carried out with standard Schlenk techniques under an argon atmosphere. IR measurements were performed on a Shimadzu FTIR-8100 spectrometer or a Horiba FT-720. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Gemini 2000 ($^1$H at 300 MHz and $^{13}$C at 75 MHz), a JNM-ECS 400 ($^1$H at 400 MHz and $^{13}$C at 100 MHz) or a Bruker AVANCE 500 ($^1$H at 500MHz and $^{13}$C at 125MHz) spectrometer using CHCl$_3$ ($^1$H, $\delta$ = 7.26) or tetramethylsilane ($^1$H, $\delta$ = 0.00) and CDCl$_3$ ($^{13}$C, $\delta$ = 77.0) or DMSO-d$_6$ ($^{13}$C, $\delta$ = 39.5) as an internal standard. High-resolution mass spectra were recorded on a JEOL JMS-SX102A, a JEOL JMS-HX110A, or a Thermo Scientific Exactive™ spectrometer. Flash column chromatography was performed with silica gel 60 N (Kanto). Preparative thin-layer chromatography was performed with silica gel 60 PF$_{254}$ (Merck).

Materials. The dehydrated N-methylpyrrolidone (NMP) and 1,3-dimethyl-2-imidazolidinone (DMI) were purchased and used without further purification. [Rh(OH)(cod)$_2$] was prepared according to the reported procedure. Boric acid (B(OH)$_3$) and cyclooctadiene (COD) were purchased from commercial sources and used without further purification. Ethyl cyanoformate was purchased and used after distillation. The ortho-borylbenzalacetone derivatives (1a, 1b, 1c, 1d, 1e, 1f, 5a, 5b, 5c and 5d) were prepared from the corresponding commercially available 2-formylarylboronic acids by the following procedure.

A representative procedure for the preparation of ortho-borylbenzalacetone derivatives 1 or 5.

To an oven-dried flask was added ortho-formylphenylboronic acid (10 g, 66.7 mmol), neopentylglycol (7.3 g, 70.0 mmol), MgSO$_4$ (2.50 g, 20.8 mmol) and benzene (200 mL). The reaction mixture was stirred at room temperature overnight. Then, MgSO$_4$ was removed by filtration. The filtrate was concentrated under reduced pressure to give crude ortho-formylphenylboronic neopentylglycolate (14.9 g, quant). The crude material (5.0 g, 22.9 mmol) was dissolved in toluene (35 ml). Then, 1-(triphenylphosphoranylidene)acetone (9.5 g, 29.8 mmol) was added and the mixture was heated at 90°C for 4.5 h. After cooling, the solvent was removed in vacuo and the residue suspended in ether and filtered to removed Ph$_3$P=O. The filtrate was concentrated and the residue purified by silica gel column chromatography (hexane:ethyl acetate =90:10 ~ 75:25) to give 1a (5.4 g, 92% ).
Chapter 2

\((E)-4-(2-(5, 5-Dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)but-3-en-2-one\) (1a)

\[
\begin{array}{c}
\text{MeO} \\
\text{B} \quad \text{O} \\
\text{O} \\
\end{array}
\]

IR (KBr): 2964, 2894, 1662, 1591, 1478, 1412, 1327, 1207, 1132, 1090, 1032 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.06\) (s, 6H), 2.39 (s, 3H), 3.83 (s, 4H), 6.57 (d, \(J = 16.2\) Hz, 1H), 7.33-7.45 (m, 2H), 7.63-7.66 (m, 1H), 7.86 (dd, \(J = 6.9\) Hz, 1.8 Hz, 1H), 8.47 (d, \(J = 16.2\) Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\), the boron-bound carbon was not detected due to quadrupolar relaxation): \(\delta = 22.0, 26.8, 31.9, 72.7, 126.1, 128.4, 129.2, 130.7, 135.7, 140.1, 146.1, 199.4\); HRMS (EI\(^+\)): Calcd for C\(_{15}\)H\(_{19}\)O\(_3\)B (M\(^+\)) 258.1427. Found m/z 258.1428.

\((E)-4-(2-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-5-methoxyphenyl)but-3-en-2-one\) (1b)

\[
\begin{array}{c}
\text{MeO} \\
\text{B} \quad \text{O} \\
\text{O} \\
\end{array}
\]

IR (KBr): 3094, 3077, 3006, 1671, 1624, 1593, 1553, 1478, 1443, 1426, 1402, 1377, 1179, 1132 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.05\) (s, 6H), 2.39 (s, 3H), 3.81 (s, 4H), 3.84 (s, 3H), 6.54 (d, \(J = 16.2\) Hz, 1H), 6.92 (dd, \(J = 8.7\) Hz, 2.7Hz, 1H), 7.14(d, \(J = 2.7\) Hz, 1H), 7.82 (d, \(J = 8.7\) Hz, 1H), 8.51 (d, \(J = 16.2\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), the boron-bound carbon was not detected due to quadrupolar relaxation): \(\delta = 21.8, 26.5, 31.7, 55.2, 72.4, 110.8, 115.2, 128.4, 137.4, 141.9, 146.0, 161.4, 199.5\); HRMS (EI\(^+\)): Calcd for C\(_{16}\)H\(_{21}\)O\(_4\)B (M\(^+\)) 288.1533. Found m/z 288.1533.

\((E)-4-(2-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-4-methoxyphenyl)but-3-en-2-one\) (1c)

\[
\begin{array}{c}
\text{MeO} \\
\text{B} \quad \text{O} \\
\text{O} \\
\end{array}
\]

32
IR (KBr): 2961, 1663, 1651, 1593, 1489, 1428, 1377, 1304, 1240, 1146, 1092 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.07\) (s, 6H), 2.36 (s, 3H), 3.83 (s, 4H), 3.85 (s, 3H), 6.51 (d, \(J = 16.2\) Hz, 1H), 6.96 (dd, \(J = 8.7\) Hz, 2.7Hz, 1H), 7.36 (d, \(J = 2.7\) Hz, 1H), 7.64 (d, \(J = 8.7\) Hz, 1H), 8.44 (d, \(J = 16.2\) Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\), the boron-bound carbon was not detected due to quadrupolar relaxation): \(\delta = 21.9, 26.5, 31.7, 55.3, 72.6, 116.9, 119.7, 126.3, 127.6, 132.3, 145.4, 160.4, 199.2\); HRMS (EI\(^+\)): Calcd for C\(_{16}\)H\(_{21}\)O\(_4\)B (M\(^+\)) 288.1533. Found m/z 288.1532.

\(\text{(E)-4-(5-Chloro-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)but-3-en-2-one} \) (1d)

\[
\begin{align*}
\text{Cl} & \quad \text{B} \\
\text{O} & \quad \text{O}
\end{align*}
\]

IR (ATR): 2962, 1668, 1624, 1577, 1541, 1471, 1419, 1290, 1257, 1230, 1126, 1105 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 1.05\) (s, 6H), 2.38 (s, 3H), 3.82 (s, 4H), 6.55 (d, \(J = 16.0\) Hz, 1H), 7.33 (dd, \(J = 8.5\) Hz, 2.7 Hz, 1H), 7.50 (d, \(J = 16.0\) Hz, 1H), 8.41 (d, \(J = 16.0\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), the boron-bound carbon was not detected due to quadrupolar relaxation): \(\delta = 21.8, 26.9, 31.7, 72.5, 125.9, 128.9, 129.0, 136.9, 137.0, 141.9, 144.2, 198.9\); HRMS (EI\(^+\)): Calcd for C\(_{15}\)H\(_{18}\)BClO\(_3\) (M\(^+\)) 292.1038. Found m/z 292.1033.

\(\text{(E)-4-(4-Chloro-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)but-3-en-2-one} \) (1e)

\[
\begin{align*}
\text{Cl} & \quad \text{B} \\
\text{O} & \quad \text{O}
\end{align*}
\]

IR (ATR): 2962, 1654, 1579, 1477, 1423, 1361, 1286, 1252, 1200, 1140, 1088 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.04\) (s, 6H), 2.37 (s, 3H), 3.81 (s, 4H), 6.53 (d, \(J = 16.5\) Hz, 1H), 7.31 (dd, \(J = 8.1\) Hz, 2.1 Hz, 1H), 7.58 (d, \(J = 2.1\) Hz, 1H), 7.79 (d, \(J = 8.1\) Hz, 1H), 8.40 (d, \(J = 16.5\) Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\), the boron-bound carbon was not detected due to quadrupolar relaxation): \(\delta = 21.8, 26.9, 31.7, 72.5, 125.8, 128.88, 128.92, 136.8, 137.0, 141.8, 144.2, 198.8\); HRMS (EI\(^+\)): Calcd for C\(_{15}\)H\(_{18}\)BClO\(_3\) (M\(^+\))
(E)-3-(2-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)-1-phenylprop-2-en-1-one (1f)

IR (KBr): 2959, 1657, 1606, 1578, 1564, 1475, 1412, 1375, 1336, 1304, 1279, 1244, 1213, 1132, 1091, 1036 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.03 \text{ (s, 6H)}, 3.80 \text{ (s, 4H)}, 7.33 \text{ (d, } J = 15.9 \text{ Hz, 1H)}, 7.38-7.59 \text{ (m, 6 H)}, 7.78 \text{ (d, } J = 7.8 \text{ Hz, 1H)}, 7.85 \text{ (dd, } J = 6.9 \text{ Hz, 1.5 Hz, 1H)}, 7.90-8.02 \text{ (m, 2 H)}, 8.59 \text{ (d, } J = 15.9 \text{ Hz, 1H}); \(^{13}\)C NMR (75 MHz, CDCl\(_3\), the boron-bound carbon was not detected due to quadrupolar relaxation): \(\delta = 22.1, 31.9, 72.7, 123.9, 126.2, 128.6, 128.9, 129.3, 130.6, 132.5, 135.6, 138.6, 140.4, 147.4, 192.3\); HRMS (EI\(^\dagger\)): Calcd for C\(_{20}\)H\(_{21}\)BO\(_3\) (M\(^{+}\)) 320.1584. Found m/z 320.1579.

(E)-Methyl 3-(2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)acrylate (5a)

IR (KBr): 2943, 1707, 1630, 1593, 1563, 1480, 1433, 1412, 1372, 1325, 1302, 1267, 1244, 1196, 1179, 1165, 1134 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.05 \text{ (s, 6H)}, 3.80 \text{ (s, 3H)}, 3.82 \text{ (s, 4H)}, 6.34 \text{ (d, } J = 15.9 \text{ Hz, 1H)}, 7.31-7.44 \text{ (m, 2 H)}, 7.61-7.66 \text{ (m, 1H)}, 7.80-7.84 \text{ (m, 1H)}, 8.54 \text{ (d, } J = 15.9 \text{ Hz, 1H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), the boron-bound carbon was not detected due to quadrupolar relaxation): \(\delta = 21.8, 31.6, 51.5, 72.4, 118.2, 125.9, 128.9, 130.3, 135.2, 139.7, 146.6, 167.8\); HRMS (EI\(^\dagger\)): Calcd for C\(_{15}\)H\(_{19}\)BO\(_4\) (M\(^{+}\)) 274.1376. Found m/z 274.1372.
(E)-Methyl 3-(2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-5-methoxyphenyl)acrylate (5b)

IR (KBr): 2957, 1700, 1632, 1597, 1480, 1335, 1302, 1250, 1229, 1177, 1132, 1024 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.03 (s, 6H), 3.80 (s, 7H), 3.84 (s, 3H), 6.32 (d, J = 15.9 Hz, 1H), 6.90 (dd, J = 8.4 Hz, 2.7 Hz, 1H), 7.13 (d, J = 2.7 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 8.58 (d, J = 15.9 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃, the boron-bound carbon was not detected due to quadrupolar relaxation): δ = 22.1, 31.9, 51.7, 55.3, 72.6, 111.2, 115.0, 118.5, 137.4, 141.9, 146.8, 161.4, 167.9; HRMS (EI⁺): Calcd for C₁₆H₂₁BO₅ (M⁺) 304.1482. Found m/z 304.1484.

(E)-Methyl 3-(2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-4-methoxyphenyl)acrylate (5c)

IR (KBr): 2963, 1701, 1622, 1593, 1491, 1445, 1426, 1331, 1242, 1211, 1144, 1092, 1042 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.05 (s, 6H), 3.78 (s, 3H), 3.82 (s, 4H), 3.84 (s, 3H), 6.26 (d, J = 15.9 Hz, 1H), 6.94 (dd, J = 8.7 Hz, 2.7 Hz, 1H), 7.32 (d, J = 2.7 Hz, 1H), 7.62 (d, J = 8.7 Hz, 1H), 8.50 (d, J = 15.9 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃, the boron-bound carbon was not detected due to quadrupolar relaxation): δ = 22.1, 31.9, 51.6, 55.5, 72.7, 116.1, 116.9, 119.4, 127.8, 132.4, 146.2, 160.4, 168.3; HRMS (EI⁺): Calcd for C₁₆H₂₁BO₅ (M⁺) 304.1482. Found m/z 304.1483.

(E)-tert-Butyl 3-(2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)acrylate (5d)
The rhodium-catalyzed reaction of cyanoformates with ortho-borylbenzalacetone Derivatives.

A typical procedure for the synthesis of 3-acetyl-2H-isoindole derivatives 3.

To a mixture of 1a (78.3 mg, 0.30 mmol), B(OH) 3 (55.6 mg, 0.90 mmol), and [Rh(OH)(cod)] 2 (3.5 mg, 7.7 μmol) under an argon atmosphere was added a solution of 2a (90.1 mg, 0.90 mmol) in NMP (0.3 mL). After the reaction mixture was stirred at room temperature for 30 min and then at 80 °C for 3 h, it was cooled and diluted with a mixed solvent of AcOEt and toluene (2 : 1, 5 mL) and H 2O (2 mL). The organic layer was separated and the aqueous layer was extracted with the mixed organic solvent (5 mL x 4). The combined extracts were more diluted with the mixed solvent (25 mL), washed with water (10 mL x 3) and with brine, and dried over Na 2SO 4. The solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (CHCl 3/AcOEt = 5/1) to afford 3a (56.1 mg, 75%).

Ethyl 3-(2-oxopropyl)-2H-isoindole-1-carboxylate (3a)

IR (KBr): 3214, 1717, 1651, 1471, 1291; 1H NMR (300 MHz, CDCl 3): δ = 1.47 (t, J = 7.2 Hz, 3H), 2.26 (s, 3H), 4.18 (s, 2H), 4.46 (q, J = 7.2 Hz, 2H), 7.11 (dd, J = 9.0 Hz, 6.9 Hz, 1H), 7.28 (dd, J = 8.7 Hz, 6.9 Hz, 1H), 7.57 (dd, J = 8.7 Hz, 0.6 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H), 11.05 (brs, 1H); 13C NMR (75 MHz, DMSO-d 6): δ = 19.1, 27.6, 29.4, 69.1, 108.9, 119.8, 120.5, 120.7, 124.2, 124.4, 125.1, 127.2, 160.7, 204.0; HRMS (FAB +): calcd. for C 14H 15NO 3, M + 245.1052. Found m/z 245.1052.
Methyl 3-(2-oxopropyl)-2H-isoindole-1-carboxylate (3b)

IR (ATR): 3219, 1720, 1653, 1473, 1315, 1292, 1209, 1159, 1088, 1014; $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 2.30$ (s, 3H), 3.98 (s, 3H), 4.17 (s, 2H), 7.08-7.14 (m, 1H), 7.25-7.30 (m, 1H), 7.53-7.58 (m, 1H), 8.06 (d, $J = 8.2$ Hz, 1H), 11.07 (brs, 1H); $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta = 29.5, 40.1, 50.7, 108.7, 119.9, 120.5, 120.8, 124.2, 124.4, 125.1, 127.5, 160.9, 204.2$; HRMS (ESI$^+$): calcd. for C$_{13}$H$_{14}$NO$_3$, [M+H]$^+$ 232.0968. Found m/z 232.0971.

Isopropyl 3-(2-oxopropyl)-2H-isoindole-1-carboxylate (3c)

IR (KBr): 3227, 1717, 1647, 1474, 1370, 1289, 1190, 1163, 1090, 1013; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 1.48$ (d, $J = 6.0$Hz, 6H), 2.21 (s, 3H), 4.19 (s, 2H), 5.36 (quint, $J = 6.0$Hz, 1H), 7.09-7.15 (m, 1H), 7.26-7.33 (m, 1H), 7.58 (d, $J = 8.7$ Hz, 1H), 8.09 (d, $J = 8.4$ Hz, 1H), 12.12 (brs, 1H); $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta = 22.2, 29.5, 40.1, 66.2, 109.3, 120.0, 120.4, 120.7, 124.1, 124.2, 125.0, 127.2, 160.2, 204.2$; HRMS (EI$^+$): calcd. for C$_{15}$H$_{17}$NO$_3$, [M]$^+$ 259.1208. Found m/z 259.1208.

Isobutyl 3-(2-oxopropyl)-2H-isoindole-1-carboxylate (3d)

IR (KBr): 3231, 1717, 1647, 1475, 1468, 1321, 1281, 1204, 1184, 1163, 1088; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta = 1.01$ (d, $J = 6.6$Hz, 6H), 1.95-2.08 (m, 1H), 2.17 (s, 3H), 4.08 (d, $J = 6.9$ Hz, 2H), 4.20 (s, 2H), 6.96-7.03 (m, 1H), 7.17-7.24 (m, 1H), 7.63 (d, $J = 8.7$ Hz, 1H), 7.91 (d, $J = 8.4$ Hz, 1H), 13.01 (brs, 1H); $^{13}$C NMR (75 MHz, DMSO-d$_6$):
δ = 19.1, 27.6, 29.4, 40.1, 69.1, 108.9, 119.8, 120.5, 120.7, 124.2, 124.4, 125.1, 127.2, 160.7, 204.0; HRMS (EI⁺): calcd. for C_{16}H_{19}NO_{3}, [M]+ 273.1365. Found m/z 273.1362.

**Ethyl 5-methoxy-3-(2-oxopropyl)-2H-isoindole-1-carboxylate (3e)**

\[
\text{IR (ATR): 3234, 1720, 1653, 1454, 1286, 1186, 1163, 1078, 1028; } ^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta = 1.45 (t, J = 7.2 Hz, 3H), 2.28 (s, 3H), 3.86 (s, 3H), 4.10 (s, 2H), 4.42 (q, J = 7.2 Hz, 2H), 6.74 (d, J = 2.2 Hz, 1H), 6.97 (dd, J = 9.2 Hz, 2.2 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 10.85 (brs, 1H); } ^{13}\text{C NMR (75 MHz, DMSO-d}_6\text{): } \delta = 14.7, 29.5, 40.1, 54.9, 59.1, 97.6, 109.2, 119.2, 121.3, 122.7, 123.4, 124.4, 154.3, 160.4, 204.3; \text{ HRMS (ESI}^⁺\text{): calcd. for } C_{15}H_{18}NO_{4}, [M+H]^+ 276.1230. \text{ Found m/z 276.1232.}
\]

**Ethyl 6-methoxy-3-(2-oxopropyl)-2H-isoindole-1-carboxylate (3f)**

\[
\text{IR (KBr): 3214, 1717, 1649, 1634, 1480, 1451, 1431, 1312, 1293, 1246, 1227, 1177, 1136, 1088, 1028; } ^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta = 1.44 (t, J = 7.1 Hz, 3H), 2.29 (s, 3H), 3.90 (s, 3H), 4.11 (s, 2H), 4.42 (q, J = 7.1 Hz, 2H), 6.79 (dd, J = 9.1 Hz, 2.3 Hz, 1H), 7.35 (brs, 1H), 7.43 (d, J = 9.1 Hz, 1H), 10.67 (brs, 1H); } ^{13}\text{C NMR (125 MHz, DMSO-d}_6\text{): } \delta = 14.7, 29.5, 40.2, 54.8, 58.9, 97.5, 108.3, 115.0, 120.2, 122.0, 124.8, 128.8, 157.7, 160.6, 204.2; \text{ HRMS (EI}^⁺\text{): calcd. for } C_{15}H_{17}NO_{4}, [M]^+ 275.1158. \text{ Found m/z 275.1158.}
\]

**Ethyl 5-chloro-3-(2-oxopropyl)-2H-isoindole-1-carboxylate (3g)**
Chapter 2

IR (ATR): 3224, 1718, 1651, 1498, 1290, 1203, 1161, 1103, 1049; ¹H NMR (500 MHz, CDCl₃): δ = 1.45 (t, J = 7.2 Hz, 3H), 2.32 (s, 3H), 4.13 (s, 2H), 4.43 (q, J = 7.2 Hz, 2H), 7.18 (dd, J = 9.0 Hz, 1.8 Hz, 1H), 7.53 (dd, J = 1.8 Hz, 0.6 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 11.15 (brs, 1H); ¹³C NMR (125 MHz, DMSO-d₆): δ = 14.6, 29.5, 39.9, 59.4, 109.7, 119.5, 122.0, 124.1, 124.6, 125.3, 125.5, 125.6, 160.4, 204.1; HRMS (ESI⁺): calcd. for C₁₄H₁₅ClNO₃, [M+H]⁺ 280.0735. Found m/z 280.0736.

Ethyl 6-chloro-3-(2-oxopropyl)-2H-isoindole-1-carboxylate (3h)

IR (ATR): 3213, 1714, 1649, 1498, 1464, 1425, 1288, 1186, 1161, 1092, 1057, 1030; ¹H NMR (500 MHz, CDCl₃): δ = 1.46 (t, J = 7.1 Hz, 3H), 2.31 (s, 3H), 4.15 (s, 2H), 4.44 (q, J = 7.1 Hz, 2H), 7.03 (dd, J = 9.0 Hz, 1.9 Hz, 1H), 7.48 (d, J = 9.0 Hz, 1H), 8.04 (brs, 1H), 11.10 (brs, 1H); ¹³C NMR (125 MHz, DMSO-d₆): δ = 14.6, 29.5, 40.0, 59.4, 108.9, 118.6, 121.5, 122.6, 122.9, 125.2, 127.3, 130.2, 160.3, 204.0; HRMS (ESI⁺): calcd. for C₁₄H₁₅ClNO₃, [M+H]⁺ 280.0735. Found m/z 280.0737.

Ethyl 3-(2-oxo-2-phenylethyl)-2H-isoindole-1-carboxylate (3i)

IR (KBr): 3227, 1686, 1482, 1468, 1287, 1204, 1184, 1084,1036; ¹H NMR (300 MHz, CDCl₃): δ = 1.41 (t, J = 6.9 Hz, 3H), 4.39 (q, J = 6.9 Hz, 2H), 4.92 (s, 2H), 6.99-7.11 (m, 1H), 7.21-7.32 (m, 1H), 7.56-7.68 (m, 2H), 7.68-7.80 (m, 2H), 8.01 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 7.8 Hz, 2H), 13.17 (brs, 1H); ¹³C NMR (75 MHz, DMSO-d₆): δ = 14.7, 36.0, 59.1, 109.1, 120.0, 120.6, 120.8, 124.3, 124.6, 125.0, 127.4, 128.3, 128.8, 133.5, 136.2, 160.6, 195.7; HRMS (EI⁺): calcd. for C₁₄H₁₅ClNO₃, [M]⁺ 307.1208. Found m/z 307.1210.

To a mixture of 5a (82.2 mg, 0.30 mmol), B(OH)$_3$ (55.6 mg, 0.90 mmol), and [Rh(OH)(cod)]$_2$ (4.9 mg, 10.7 μmol) under an argon atmosphere was added a solution of 2a (89.9 mg, 0.90 mmol) and COD (0.36 mL, 2.9 mmol) in DMI (1.0 mL). After the reaction mixture was stirred at room temperature for 30 min and then at 120 °C for 3 h, it was treated in a similar manner to that used for the synthesis of 3a. The obtained crude product was purified by preparative thin-layer chromatography (CHCl$_3$/AcOEt = 10/1) to afford 6a (46.3 mg, 59%).

**Ethyl 3-(2-methoxy-2-oxoethyl)-2H-isooindole-1-carboxylate (6a)**

\[
\text{\begin{tabular}{c}
\text{\includegraphics[width=0.2	extwidth]{structure6a.png}}
\end{tabular}}
\]

IR (KBr): 3206, 1742, 1663, 1482, 1313; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ = 1.36 (t, $J$ = 7.2 Hz, 3H), 3.63 (s, 3H), 4.15 (s, 2H), 4.27 (q, $J$ = 7.2 Hz, 2H), 7.02 (dd, $J$ = 6.9 Hz, 0.6 Hz, 1H), 7.22 (dd, $J$ = 6.9 Hz, 0.6 Hz, 1H), 7.77 (d, $J$ = 8.4 Hz, 1H), 7.93 (d, $J$ = 8.4 Hz, 1H), 13.1 (brs, 1H); $^{13}$C NMR (75 MHz, DMSO-d$_6$): $\delta$ = 14.6, 31.0, 52.0, 59.1, 109.0, 120.0, 120.4, 120.9, 123.0, 124.0, 125.0, 127.3, 160.5, 169.9; HRMS (EI$^+$): calcd. for C$_{14}$H$_{15}$NO$_4$, M$^+$ 261.1001, Found m/z 261.1002.

**Ethyl 5-methoxy-3-(2-methoxy-2-oxoethyl)-2H-isooindole-1-carboxylate (6b)**

\[
\text{\begin{tabular}{c}
\text{\includegraphics[width=0.2	extwidth]{structure6b.png}}
\end{tabular}}
\]

IR (ATR): 3232, 1734, 1653, 1541, 1471, 1433, 1288, 1217, 1167, 1078, 1018; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 1.44 (t, $J$ = 7.2Hz, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 4.02 (s, 2H), 4.42 (q, $J$ = 7.2 Hz, 2H), 6.77 (d, $J$ = 2.2 Hz, 1H), 6.96 (dd, $J$ = 9.2 Hz, 2.2 Hz, 1H), 7.95 (d, $J$ = 9.2 Hz, 1H), 10.55 (brs, 1H); $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ = 14.6, 30.9, 51.9, 54.9, 59.1, 97.6, 109.3, 119.3, 121.3, 121.5, 123.4, 124.3, 154.4, 160.5, 170.2; HRMS (ESI$^+$): calcd. for C$_{15}$H$_{18}$NO$_5$, [M+H]$^+$ 292.1179. Found m/z 292.1180.
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Ethyl 6-methoxy-3-(2-methoxy-2-oxoethyl)-2\(H\)-isoindole-1-carboxylate (6c)

![Chemical Structure of 6c]

IR (KBr): 3206, 1732, 1653, 1634, 1483, 1451, 1314, 1250, 1227, 1196, 1179, 1136, 1088, 1022, 1005; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 1.44\) (t, \(J = 7.1\) Hz, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 4.03 (s, 2H), 4.42 (q, \(J = 7.1\) Hz, 2H), 6.79 (dd, \(J = 9.1\) Hz, 2.3 Hz, 1H), 7.34 (brs, 1H), 7.46 (d, \(J = 9.1\) Hz, 1H), 10.55 (brs, 1H); \(^13\)C NMR (125 MHz, DMSO-d\(_6\)): \(\delta = 14.7, 31.1, 51.9, 54.8, 58.9, 97.5, 108.4, 115.2, 120.1, 121.9, 123.6, 128.7, 157.8, 160.6, 170.0\) HRMS (El\(^+\)): calcd. for C\(_{15}\)H\(_{17}\)NO\(_5\), [M]+ 291.1107. Found m/z 291.1111.

Ethyl 3-(2-tert-butoxy-2-oxoethyl)-2\(H\)-isoindole-1-carboxylate (6d)

![Chemical Structure of 6d]

IR (KBr): 3193, 1736, 1665, 1468, 1368, 1304, 1288, 1208, 1163, 1140, 1125, 1084, 1026; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.46\) (t, \(J = 7.2\) Hz, 3H), 1.48 (s, 9H), 4.01 (s, 2H), 4.46 (q, \(J = 7.2\) Hz, 2H), 7.05-7.13 (m, 1H), 7.23-7.30 (m, 1H), 7.60 (d, \(J = 8.4\) Hz, 1H), 8.06 (d, \(J = 8.7\) Hz, 1H), 11.28 (brs, 1H); \(^13\)C NMR (125 MHz, DMSO-d\(_6\)): \(\delta = 14.6, 27.7, 32.4, 59.1, 80.7, 108.8, 120.0, 120.5, 120.8, 123.6, 124.0, 125.0, 127.4, 160.6, 168.7\); HRMS (El\(^+\)): calcd. for C\(_{17}\)H\(_{21}\)NO\(_4\), M\(^+\) 303.1471, Found m/z 303.1463.
References and notes


4. The other boronic esters (esters with ethylene glycol, pinacol, catechol) or boronic acid itself failed to give satisfactory results.


Chapter 3

Reaction of 2-Alkynylbenzoyl Cyanides with Carboxylic Acids
Producing Functionalized Indenones

Abstract: 2-Alkynylbenzoyl cyanides react with carboxylic acids via a cyclic allene intermediate to produce 2-acylamino-3-acylindenones in good yield. The high reactivity of the 2-acylamino moiety of the product for a substitution reaction can be utilized for the synthesis of fused heterocycles.
**Introduction**

The cyanocarbonyl group is an interesting ambident electrophilic functionality; its cyano and carbonyl groups are both electrophilic enough to accept nucleophiles, and their electron-withdrawing nature reinforces the electrophilic reactivities.\(^1\), \(^2\) As an extension of the studies, which explained in chapter 1 and 2, on the rhodium-catalyzed reaction of cyanoformate with arylboronic acids,\(^3\) the author prepared 2-alkynylbenzoyl cyanide in order to develop a cascade reaction. Careful examination of its reactivity, however, disclosed an unexpected acid-mediated cyclization reaction. In this chapter, it is described the reaction of 2-alkynylbenzoyl cyanide with a carboxylic acid which furnishes a functionalized indenone as the cyclized product.

**Results and discussions**

2-(1-Hexyn-1-yl)benzoyl cyanide \(2a\) was readily prepared from 2-(1-hexyn-1-yl)benzoic acid \(1a\); treatment of \(1a\) with oxalyl chloride in the presence of DMF in \(\text{CH}_2\text{Cl}_2\) and subsequent removal of volatile compounds under reduced pressure afforded the corresponding acid chloride as the crude product. The crude acid chloride was directly reacted with CuCN in \(\text{CH}_3\text{CN}\) at 70 °C.\(^4\) Isolation by column chromatography on silica gel afforded the desired benzoyl cyanide \(2a\) in 79% yield (Equation 1).

![Chemical structure](image)

When 2-(1-hexyn-1-yl)benzoyl cyanide \(2a\) thus obtained was treated with 3-phenylpropylamine, the amino group attacked the carbonyl group of \(2a\), with the cyano group acting as a leaving group to afford the corresponding amide (\(3a\)) in 97% yield. The related reaction between 3-phenylpropanol and \(2a\) in the presence of \(\text{Et}_3\text{N}\) proceeded in a similar manner producing ester (\(3b\)) (Equation 2). Thus, relatively active nucleophiles attacked the carbonyl group of \(2a\) under basic conditions. In contrast, when \(2a\) was reacted with benzoic acid \(4a\), a cyclization reaction occurred to afford 2-benzozylamino-3-pentanoylindenone \(5aa\) as shown in Equation 3.\(^5\)
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\[
\begin{align*}
\text{CN} & \quad \text{O} \\
\text{PhCH}_{2}\text{CH}_{2}\text{NH}_{2} & \quad \text{(1.0 equiv)} \\
\text{or} & \\
\text{PhCH}_{2}\text{CH}_{2}\text{OH} & \quad \text{(1.0 equiv)} \\
\text{Et}_{3}\text{N} & \quad \text{(1.2 equiv)} \\
\text{dioxane} & \quad \text{r.t.} \\
1\text{h} & \\
\text{PhCH}_{2}\text{CH}_{2}\text{CH}_{2}\text{NH}_{2} & \quad \text{(1.0 equiv)} \\
\text{dioxane} & \quad \text{r.t.} \\
1\text{h} & \\
\text{X=NH} & \quad \text{3a (97%)} \\
\text{X=O} & \quad \text{3b (88%)} \\
\end{align*}
\]

In p-xylene, 140 °C, 24h 84%
In toluene, 100 °C, 48h 84%
In dioxane, 100 °C, 48h 87%

Table 1. Reaction of 2a with various carboxylic acids (4).

<table>
<thead>
<tr>
<th>entry</th>
<th>4</th>
<th>R²</th>
<th>product 5</th>
<th>yield(%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>Ph</td>
<td>5aa</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>4-MeO-C(_6)H(_4)</td>
<td>5ab</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>4-Cl-C(_6)H(_4)</td>
<td>5ac</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>4-Br-C(_6)H(_4)</td>
<td>5ad</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>4-MeO(_2)-C(_6)H(_4)</td>
<td>5ae</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>2-Pyridyl</td>
<td>5af</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>2-Thienyl</td>
<td>5ag</td>
<td>83</td>
</tr>
<tr>
<td>8</td>
<td>4h</td>
<td>(E)-PhCH=CH-</td>
<td>5ah</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td>4i</td>
<td>Me</td>
<td>5ai</td>
<td>92(^b)</td>
</tr>
<tr>
<td>10</td>
<td>4j</td>
<td>'Pr</td>
<td>5aj</td>
<td>83</td>
</tr>
<tr>
<td>11</td>
<td>4k</td>
<td>'Bu</td>
<td>5ak</td>
<td>87</td>
</tr>
</tbody>
</table>

\(^a\) isolated yield

\(^b\) reaction at 120 °C
The results obtained with other carboxylic acids (4) and 2a are summarized in Table 1. Not only substituted benzenecarboxylic acids (entries 1~5) but also heteroaromatic (entries 6 and 7), cinnamic (entry 8), and aliphatic (entries 9~11) carboxylic acids reacted with 2a to give the corresponding 2-acylamino-3-pentanoylindenone (5aa-5ak) in yields ranging from 60% to 92%. Thus, a wide range of carboxylic acids effectively mediated the cyclization reaction of 2a.

In order to further probe the scope of the reaction, benzoyl cyanides possessing other alkynyl groups were also examined. 2-Alkynylbenzoyl cyanide 2b having an isopropyl substituent was a suitable substrate (Equation 4). When the reaction of 2b with benzoic acid 4a was carried out at a lower temperature (100 °C), enol ester 6ba was isolated in 71% yield. Furthermore, on heating a mixture of 6ba and benzoic acid 4a at 120 °C, 2-acylaminoindene 5ba was produced in 65% yield (Scheme 1). Unlike 2a and 2b, 2-alkynylbenzoyl cyanides 2c, 2d, and 2e (Figure 1) failed to react with benzoic acid (4a), and 2c, 2d, 2e were recovered, suggesting the need for a hydrogen at the propargylic position in order for the cyclization reaction to occur. The attempted reaction of benzoyl cyanide 2f bearing a terminal alkyne resulted in the formation of a mixture of intractable compounds.

Scheme 1. Formation of 5ba from 2b and 4a via enol ester 6ba.

Figure 1. The substrate which failed to react with carboxylic acids.
In order to gain a further insight into the mechanism, it was treated 2a with acetic acid-d$_1$ 4i-D (5 equiv) in p-xylene at 120 °C for 7 h. Under these conditions, 5ai-D which incorporated a deuterium at the $\alpha$-position of the carbonyl group (67% D), was isolated in 83% yield (Equation 5). The deuterium incorporation also indicated the intermediacy of an enol ester such as 6ba. On the basis of these results, the author proposes the pathway shown in Scheme 2 to explain the formation of 2-acylamino-3-acylindenone (5) from 2. Initially, carboxylic acid (4) mediates isomerization of 2-alkynylbenzoyl cyanide (2) to cyclic allene (7). Then, carboxylic acid (4) attacks the sp-carbon of the allene moiety to form enol ester (6). Finally, the acyl group migrates to the amino group to afford 2-acylamino-3-acylindenone (5).

Scheme 2. Proposed mechanism for the formation of 5 from 2 and 4.
Next, the reactivities of the product were examined. Treatment of 5aa with a primary amine resulted in a facile substitution reaction of the acetyl amino group to give 2-alkylamino-3-pentanoylindenone (11) in high yield (Equation 6).\(^8\) The substitution reaction probably proceeds via an addition/elimination mechanism. The substitutive reactivity of the acylamino group with primary amines was next utilized for construction of heterocyclic structures.\(^9\) Treatment of 2-acetylamino-3-acylindenone (5ai and 5bi) with amidine hydrochlorides (8) in pyridine at 100 °C afforded the corresponding indenopyrimidine (9) as exemplified in Equation 7. When 5ai and 5bi were reacted with methylhydrazine, the primary amino group initially replaced the acetylamino group to furnish indenopyrazole derivatives (12) possessing a methyl group at the 2-position (Equation 8).\(^10\)
Conclusion

The indenone skeleton represents an important class of carbocyclic molecule, and many of these derivatives are found in important natural products. Some of indenone derivatives are also known to be pharmacologically active compounds. Due to their medicinal importance, the development of facile strategies to obtain such skeleton has become an attractive endeavor in synthetic organic and medicinal chemistry. The author has found that 2-alkynylbenzoyl cyanides possessing a propargylic hydrogen react readily with carboxylic acids to provide 2-acylamino-3-acylidenones. The reaction proceeds via a cyclic allenyl intermediate which is generated by assistance of the enhanced electrophilic nature of the cyano group. The produced 2-acylamino-3-acylidenones could be utilized for the synthesis of fused heterocycles with an indenone skeleton.
Experimental Section

General. All reactions were carried out with standard Schlenk techniques under an argon atmosphere. IR measurements were performed on a Shimadzu FTIR-8100 spectrometer or a Horiba FT-720. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Gemini 2000 ($^1$H at 300 MHz and $^{13}$C at 75 MHz), a JNM-ECS 400 ($^1$H at 400 MHz and $^{13}$C at 100 MHz) or a Bruker AVANCE 500 ($^1$H at 500MHz and $^{13}$C at 125MHz) spectrometer using CHCl$_3$ ($^1$H, $\delta = 7.26$) or tetramethylsilane ($^1$H, $\delta = 0.00$) and CDCl$_3$ ($^{13}$C, $\delta = 77.0$) as an internal standard. High-resolution mass spectra were recorded on a JEOL JMS-SX102A, a JEOL JMS-HX110A, or a Thermo Scientific Exactive™ spectrometer. Flash column chromatography was performed with silica gel 60 N (Kanto). Preparative thin-layer chromatography was performed with silica gel 60 PF$_{254}$ (Merck).

Materials. Acetonitrile was purchased and used without further purification. Dioxane, toluene and $p$-xylene were distilled from sodium-benzophenone ketyl before using for the reaction. All other commercially available materials were used without further purifications. 2-alkynylbenzoic acids $^2$ were prepared from the corresponding 2-alkynylbenzoyl cyanides 2 were prepared from the corresponding 2-alkynylbenzoic acids by the following procedure.

Representative procedure for the preparation of 2-alkynylbenzoic acids 2.

Oxalyl chloride (1.60 ml; 18.7 mmol) was added dropwise to a mixture of 2-(1-hexyn-1-yl) benzoic acid $^1$a (3.43 g; 17.0 mmol) and DMF (2 drops) in CH$_2$Cl$_2$ (35 ml). The reaction mixture was stirred for 1.5 h at room temperature. Then, volatile components were removed in vacuo to give crude acid chloride. A solution of the crude acid chloride in CH$_3$CN (20 ml) was added to a stirred suspension of CuCN (3.00 g; 33.5 mmol) in CH$_3$CN (20 ml) at room temperature. After the mixture was stirred for 1 h at 70 °C, the resulting clear solution was cooled to room temperature and concentrated in vacuo. The residue was washed with ether, filtrated and concentrated in vacuo again. The residue was purified rapidly by silica gel column chromatography (hexane and then hexane/Et$_2$O = 50/1) to afford $^2$a (2.83g, 79%).

2-(Hexyn-1-yl)benzoyl cyanide (2a)
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IR (neat): 2959, 2220, 1682, 1663, 1482, 1231 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.96 (t, J = 7.2 Hz, 3H), 1.42-1.58 (m, 2H), 1.58-1.72 (m, 2H), 2.51 (t, J = 7.2Hz, 2H), 7.42-7.52 (m, 1H), 7.54-7.67 (m, 2H), 8.05-8.12 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 13.8, 19.8, 22.2, 30.4, 77.9, 101.6, 113.5, 125.9, 127.9, 132.6, 133.7, 135.2 (two signals overlapping), 166.9; HRMS (EI⁺): m/z Calcd for C₁₄H₁₃NO [M]⁺: 211.0997; Found: 211.0997.

2-(3-Methylbutyn-1-yl)benzoyl cyanide (2b)

IR (ATR): 3066, 2933, 2873, 2222, 1680, 1591, 1558, 1479, 1279, 1226, 968 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.31 (d, J = 6.9 Hz, 6H), 2.87 (sept, J = 6.9 Hz, 1H), 7.44-7.51 (m, 1H), 7.55-7.66 (m, 2H), 8.05-8.09 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 21.8, 22.5, 77.1, 105.9, 113.5, 125.8, 127.9, 132.5, 133.7, 135.0, 135.1, 166.9; HRMS (EI⁺): m/z Calcd for C₁₃H₁₁NO[M⁺]: 197.0841; Found: 197.0843.

2-(3,3-Dimethylbutyn-1-yl)benzoyl cyanide (2c)

IR (ATR): 2968, 2359, 2218, 1668, 1589, 1552, 1471, 1360, 1290, 1227, 1203 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.37 (s, 9H), 7.42-7.50 (m, 1H), 7.54-7.66 (m, 2H), 8.04-8.09 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 28.5, 30.4, 76.4, 108.2, 113.5, 125.7, 127.8, 132.4, 133.6, 134.9, 135.0, 166.8; HRMS (EI⁺): m/z Calcd for C₁₄H₁₃NO [M⁺]: 211.0997; Found: 211.1001.
2-(Phenylethynyl)benzoyl cyanide (2d)

IR (ATR): 2362, 2210, 1672, 1552, 1491, 1273, 1230, 1020, 966 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.34-7.44\) (m, 3H), 7.52-7.59 (m, 1H), 7.61-7.69 (m, 2H), 7.69-7.77 (m, 2H), 8.14-8.21 (m, 1H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 86.5, 98.0, 113.3, 122.3, 124.8, 128.5\) (2 signals overlapping), 129.3, 132.0, 132.9, 133.3, 134.9, 135.2, 166.5; HRMS (EI\(^+\)): \(m/z\) Calcd for C\(_{16}\)H\(_{9}\)NO \([M]^+\): 231.0684; Found: 231.0682.

2-[(Trimethylsilyl)ethynyl]benzoyl cyanide (2e)

IR (ATR): 2958, 2360, 2218, 2156, 1676, 1591, 1560, 1477, 1234, 970, 843 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.29\) (s, 9H), 7.50-7.59 (m, 1H), 7.62-7.70 (m, 2H), 8.08-8.14 (m, 1H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = -0.5, 100.9, 105.0, 113.2, 124.3, 128.7, 132.6, 133.8, 135.0, 135.5, 166.5\); HRMS (EI\(^+\)): \(m/z\) Calcd for C\(_{13}\)H\(_{13}\)NOSi \([M]^+\): 227.0766; Found: 227.0767.

The preparation of 2-ethynylbenzoyl cyanides 2f.

Oxalyl chloride (0.92 ml; 10.69 mmol) was added dropwise to a mixture of 2-ethynylbenzoic acid (1.42 g; 9.72 mmol) and DMF (1 drop) in CH\(_2\)Cl\(_2\) (15 ml). The reaction mixture was stirred for 2 h at room temperature. Then, volatile components were removed in vacuo, and then the residue was washed with hexane to give crude acid chloride (0.81 g, crude 51%). To a stirred solution of the crude acid chloride and cyanotrimethylsilane (0.74 ml, 5.90 mmol) in CH\(_2\)Cl\(_2\) (20 ml) was added tin(IV) chloride (0.056 ml, 0.49 mmol) under nitrogen at 0 °C. After the mixture was stirred for 2 h at 0 °C, furthermore, cyanotrimethylsilane (0.49 ml, 3.94 mmol) and tin(IV) chloride (0.056 ml, 0.49 mmol) were added to this mixture. After the mixture was additional stirred for 30 min at 0 °C, it was quenched with ice-cold water and extracted.
with CH₂Cl₂. The organic layer was washed with water and brine, dried with magnesium sulfate, and evaporated. The residue was purified rapidly by silica gel column chromatography (toluene) to afford 2f (0.25g, 17% from 2-ethynylbenzoic acid).

2-Ethynylbenzoyl cyanide (2f)

\[
\text{CN}
\]

IR (ATR): 3276, 2360, 2102, 1672, 1589, 1556, 1475, 1302, 1236, 968 cm⁻¹; \text{¹H NMR (300 MHz, CDCl₃)}: δ = 3.56 (s, 1H), 7.58-7.65 (m, 1H), 7.67-7.76 (m, 2H), 8.17-8.22 (m, 1H); \text{¹³C NMR (125 MHz, CDCl₃)}: δ = 80.2, 85.7, 112.9, 123.2, 129.2, 133.3, 133.9, 135.2, 136.1, 166.3; HRMS (EI⁺): \text{m/z Calcd for C}_{10}\text{H}_5\text{NO} [M]⁺: 155.0371; Found: 155.0371.

Reaction of 2-Alkynylbenzoyl Cyanides 2 with nucleophiles.

**Representative procedure for the reaction of 2a with an amine and an alchol.**

To a solution of 2a (85.0 mg, 0.40 mmol) in dioxane (1 ml) under an argon atmosphere was added a solution of 3-phenyl-1-propylamine (54.1 mg, 0.40 mmol) in dioxane (1 mL) and subsequently added triethylamine (0.067ml, 0.48ml). After the reaction mixture was stirred at room temperature for 1 h, the reaction was quenched by sat.NaHCO₃aq. The mixture was extracted with ethyl acetate. The combined extracts were washed with water and with brine, and dried over Na₂SO₄. The solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 9/1) to afford 3a (123.9 mg, 97%).

2-(Hexyn-1-yl)-N-(3-phenylpropan-1-yl)benzamide (3a)

\[
\text{O}
\]

IR (ATR): 3269, 2949, 2870, 2227, 1635, 1545, 1429, 1358, 1309, 1236, 1173 cm⁻¹; \text{¹H NMR (300 MHz, CDCl₃)}: δ = 0.92 (t, \text{J} = 7.5 \text{ Hz}, 3\text{H}), 1.37-1.52 (m, 2\text{H}), 1.52-1.65 (m, 2\text{H}), 1.90-2.05 (m, 2\text{H}), 2.45 (t, \text{J} = 7.2\text{Hz}, 2\text{H}), 2.74 (t, \text{J} = 7.5\text{Hz}, 2\text{H}), 3.47-3.57 (m,
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2H), 7.15-7.23 (m, 3H), 7.24-7.32 (m, 2H), 7.34-7.42 (m, 2H), 7.43-7.50 (m, 1H), 7.61 (brs, 1H), 8.01-8.09 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 13.7, 19.5, 22.3, 30.8, 31.4, 33.5, 39.7, 79.7, 97.4, 120.3, 126.1, 128.3, 128.4, 128.5, 130.0, 130.4, 133.8, 135.3, 141.5, 166.4; HRMS (ESI$^+$): m/z Calcd for C$_{22}$H$_{26}$NO $[$M+H$]^+$: 320.2009; Found: 320.2010.

3-Phenylpropan-1-yl 2-(hexyn-1-yl)benzoate (3b)

IR (ATR): 2956, 2931, 2866, 2229, 1726, 1711, 1483, 1450, 1288, 1244, 1130, 1078 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 0.95$ (t, $J = 7.4$ Hz, 3H), 1.42-1.56 (m, 2H), 1.52-1.70 (m, 2H), 2.06-2.19 (m, 2H), 2.47 (t, $J = 7.1$Hz, 2H), 2.81 (t, $J = 7.7$Hz, 2H), 4.37 (t, $J = 6.7$ Hz, 2H), 7.16-7.26 (m, 3H), 7.26-7.35 (m, 3H), 7.43 (dt, $J = 1.5$ Hz, 7.2 Hz, 1H), 7.53 (dd, $J = 8.1$ Hz, 1.2 Hz, 1H), 7.88 (dd, $J = 8.0$ Hz, 1.2 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 13.8, 19.7, 22.2, 30.4, 30.9, 32.4, 64.6, 79.5, 96.1, 124.5, 126.1, 127.2, 128.50, 128.54, 130.2, 131.5, 132.2, 134.4, 141.3, 166.6; HRMS (ESI$^+$): m/z Calcd for C$_{22}$H$_{25}$NO$_2$ $[$M+H$]^+$: 321.1849; Found: 321.1852.

Representative procedure for the cyclization reaction of 2 with carboxylic acids 4.

A mixture of 2-(1-hexyn-1-yl)benzoyl cyanide 2a (42.3 mg; 0.20 mmol) and benzoic acid 4a (48.8 mg; 0.40 mmol) in p-xylene (1.0 ml) was stirred at 140 °C for 24 h under an argon atmosphere, and then the solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (toluene/AcOEt = 10/1) to afford 5aa (55.9 mg, 84%).

2-Benzoylamino-3-pentanoylindenone (5aa)

IR (KBr): 3312, 2959, 1726, 1678, 1662, 1512, 1277 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 0.91$ (t, $J = 7.2$ Hz, 3H), 1.38 (pseudo sextet, $J = 7.5$ Hz, 2H), 1.74 (pseudo quintet, $J = 7.5$ Hz, 2H), 2.75 (t, $J = 7.5$ Hz, 2H), 7.14 (t, $J = 7.5$ Hz, 2H), 7.35 (dt, $J =
1.2 Hz, 7.5 Hz, 1H), 7.44-7.56 (m, 3H), 7.56-7.64 (m, 1H), 7.87-7.94 (m, 2H), 8.40 (brs, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 14.1, 22.6, 25.8, 44.1, 121.9, 124.4, 126.8, 127.3, 127.6, 127.9, 129.1, 132.5, 132.7, 133.0, 135.6, 145.5, 164.9, 193.0, 201.1; HRMS (EI$^+$): m/z Calcd for C$_{21}$H$_{19}$NO$_3$ [M]$^+$: 333.1365; Found: 333.1361.

2-(4-Methoxybenzoyl)amino-3-pentanoylindenone (5ab)

IR (ATR): 3280, 2956, 1720, 1672, 1604, 1533, 1502, 1458, 1309, 1248, 1173, 1124, 1080, 1020 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.91 (t, $J$ = 7.5 Hz, 3H), 1.37 (pseudo sext, $J$ = 7.5 Hz, 2H), 1.73 (pseudo quint, $J$ = 7.5 Hz, 2H), 2.74 (t, $J$ = 7.5 Hz, 2H), 3.88 (s, 3H), 6.95-7.02 (m, 2H), 7.08-7.16 (m, 2H), 7.30-7.38 (m, 1H), 7.42-7.48 (m, 1H), 7.83-7.92 (m, 2H), 8.34 (brs, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ = 13.7, 22.4, 25.6, 43.8, 55.5, 114.1, 121.7, 124.2, 124.5, 126.7, 127.55, 127.58, 129.5, 132.0, 135.4, 145.5, 163.3, 164.3, 193.0, 201.1; HRMS (EI$^+$): m/z Calcd for C$_{22}$H$_{21}$NO$_4$ [M]$^+$: 363.1471; Found: 363.1473.

2-(4-Chlorobenzoyl)amino-3-pentanoylindenone (5ac)

IR (ATR): 3290, 2958, 1722, 1657, 1516, 1456, 1271, 1088, 1009 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 0.91 (t, $J$ = 7.2 Hz, 3H), 1.38 (pseudo sext, $J$ = 7.2 Hz, 2H), 1.66-1.80 (m, 2H), 2.75 (t, $J$ = 7.7 Hz, 2H), 7.10-7.19 (m, 2H), 7.32-7.40 (m, 1H), 7.44-7.52 (m, 3H), 7.81-7.88 (m, 2H), 8.40 (brs, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 14.1, 22.6, 25.7, 44.1, 121.9, 124.5, 126.8, 127.3, 128.0, 129.0, 129.3, 130.8, 133.0, 135.6, 139.4, 145.2, 163.9, 192.7, 201.0; HRMS (EI$^+$): m/z Calcd for C$_{21}$H$_{18}$ClNO$_3$ [M]$^+$: 367.0975; Found: 367.0977.
2-(4-Bromobenzoyl)amino-3-pentanoylindenone (5ad)

![Structural formula](image)

IR (ATR): 3282, 2956, 2870, 1724, 1660, 1522, 1458, 1298, 1178, 1070, 1007 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.94\) (t, \(J = 7.5\) Hz, 3H), 1.39 (pseudo sext, \(J = 7.5\) Hz, 2H), 1.65-1.80 (m, 2H), 2.75 (t, \(J = 7.5\) Hz, 2H), 7.09-7.19 (m, 2H), 7.36 (dt, \(J = 1.2\) Hz, 7.5 Hz, 1H), 7.46 (d, \(J = 7.5\)Hz, 1H), 7.61-7.68 (m, 2H), 7.74-7.80 (m, 2H), 8.40 (brs, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 14.1, 25.6, 25.7, 44.0, 121.9, 124.4, 126.7, 127.3, 127.9\) (2 signals were overlapping), 129.1, 131.3, 132.3, 133.1, 135.6, 145.1, 164.0, 192.7, 201.0; HRMS (EI\(^{+}\)): \(m/z\) Calcd for C\(_{21}\)H\(_{18}\)BrNO\(_3\) [M\(^+\)]: 411.0470; Found: 411.0472.

2-(4-Methoxycarbonylbenzoyl)amino-3-pentanoylindenone (5ae)

![Structural formula](image)

IR (ATR): 3303, 2956, 1720, 1678, 1520, 1458, 1433, 1279, 1111 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.92\) (t, \(J = 7.2\) Hz, 3H), 1.39 (pseudo sext, \(J = 7.2\) Hz, 2H), 1.68-1.80 (m, 2H), 2.76 (t, \(J = 7.7\) Hz, 2H), 3.96 (s, 3H), 7.10-7.19 (m, 2H), 7.36 (dt, \(J = 1.2\) Hz, 7.5 Hz, 1H), 7.47 (d, \(J = 6.9\) Hz, 1H), 7.92-7.99 (m, 2H), 8.13-8.19 (m, 2H), 8.46 (brs, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 14.1, 25.6, 25.7, 44.1, 52.7, 122.0, 124.5, 126.8, 127.0, 127.7, 128.0, 130.2, 133.4, 134.0, 135.6, 136.2, 145.2, 164.1, 166.0, 192.7, 201.0); HRMS (EI\(^{+}\)): \(m/z\) Calcd for C\(_{23}\)H\(_{21}\)NO\(_5\) [M\(^+\)]: 391.1420; Found: 391.1417.

2-(2-Pyridinecarbonyl)amino-3-pentanoylindenone (5af)

![Structural formula](image)

IR (ATR): 3315, 2954, 1718, 1691, 1597, 1508, 1456, 1173, 1117, 1068 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.91\) (t, \(J = 7.2\) Hz, 3H), 1.38 (pseudo sext, \(J = 7.2\) Hz, 2H), 1.68-1.82 (m, 2H), 2.76 (t, \(J = 7.5\) Hz, 2H), 7.09-7.18 (m, 2H), 7.35 (dt, \(J = 1.2\) Hz, 7.7 Hz, 1H), 7.48 (d, \(J = 6.9\) Hz, 1H), 7.53 (ddd, \(J = 7.8\) Hz, 4.8 Hz, 1.2 Hz, 1H), 7.90 (dt, \(J = 8.4\) Hz, 1H)
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= 1.8 Hz, 7.5 Hz, 1H), 8.17-8.23 (m, 1H), 8.65-8.71 (m, 1H), 10.30 (brs, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 14.1, 22.6, 25.9, 44.3, 121.8, 123.0, 124.3, 126.3, 126.8, 127.4, 127.9, 133.4, 135.4, 137.8, 145.6, 148.2, 148.6, 162.5, 193.0, 201.4; \(m/z\) HRMS (EI\(^{+}\)): Calcd for \(\text{C}_{20}\text{H}_{18}\text{N}_{2}\text{O}_{3}\) [M]\(^{+}\): 334.1317; Found: 334.1312.

2-(2-Thiophenecarbonyl)amino-3-pentanoylindenone (5ag)

IR (ATR): 3294, 3087, 2868, 1724, 1651, 1510, 1454, 1415, 1358, 1282, 1176, 1082, 1047 cm\(^{-1}\); \(^{1}\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.92\) (t, \(J = 7.2\) Hz, 3H), 1.38 (pseudo sext, \(J = 7.2\) Hz, 2H), 1.66-1.79 (m, 2H), 2.75 (t, \(J = 7.7\) Hz, 2H), 7.09-7.19 (m, 3H), 7.35 (dt, \(J = 1.2\) Hz, 7.5 Hz, 1H), 7.46 (d, \(J = 7.5\) Hz, 1H), 7.62 (dd, \(J = 5.1\) Hz, 1.2 Hz, 1H), 7.72 (dd, \(J = 3.6\) Hz, 0.9 Hz, 1H), 8.29 (brs, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 14.0, 22.6, 25.8, 44.0, 121.9, 124.4, 126.7, 127.3, 127.8, 128.2, 130.2, 132.6, 132.7, 135.6, 137.0, 145.3, 159.3, 192.6, 201.0; \(m/z\) HRMS (EI\(^{+}\)): Calcd for \(\text{C}_{19}\text{H}_{17}\text{NO}_{3}\text{S}\) [M]\(^{+}\): 339.0929; Found: 339.0931.

2-Cinnamoylamino-3-pentanoylindenone (5ah)

IR (ATR): 3334, 2954, 2866, 1722, 1684, 1628, 1520, 1452, 1342, 1198, 1157, 1124, 1070 cm\(^{-1}\); \(^{1}\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.93\) (t, \(J = 7.2\) Hz, 3H), 1.39 (pseudo sext, \(J = 7.2\) Hz, 2H), 1.67-1.80 (m, 2H), 2.74 (t, \(J = 7.5\) Hz, 2H), 6.59 (dd, \(J = 15.6\) Hz, 1.2 Hz, 1H), 7.06-7.16 (m, 2H), 7.34 (dt, \(J = 0.9\) Hz, 7.5 Hz, 1H), 7.37-7.48 (m, 4H), 7.52-7.58 (m, 2H), 7.76 (d, \(J = 15.6\) Hz, 1H), 7.85 (brs, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 14.1, 22.6, 25.8, 44.2, 118.6, 121.8, 124.3, 126.65, 126.68, 127.8, 128.3, 129.1, 130.7, 133.0, 134.2, 135.6, 144.8, 145.7, 163.7, 193.2, 201.1; \(m/z\) HRMS (EI\(^{+}\)): Calcd for \(\text{C}_{23}\text{H}_{21}\text{NO}_{3}\) [M]\(^{+}\): 359.1521; Found: 359.1520.
2-Acetylamino-3-pentanoylindenone (5ai)

IR (ATR): 3332, 2931, 2868, 1720, 1699, 1604, 1516, 1454, 1369, 1244, 1082, 1043 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.92\) (t, \(J = 7.5\) Hz, 3H), 1.37 (pseudo sext, \(J = 7.5\) Hz, 2H), 1.70 (pseudo quint, \(J = 7.5\) Hz, 2H), 2.20 (s, 3H), 2.68 (t, \(J = 7.5\) Hz, 2H), 7.04 (d, \(J = 7.5\) Hz, 1H), 7.08-7.15 (m, 1H), 7.28-7.36 (m, 1H), 7.41 (dd, \(J = 7.2\) Hz, 0.6 Hz, 1H), 7.66 (brs, 1H); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 14.1, 22.6, 25.7, 44.0, 121.7, 124.3, 126.2, 126.5, 127.8, 133.1, 135.6, 145.5, 168.2, 193.1, 201.0; HRMS (EI\(^+\)): m/z Calcd for C\(_{16}\)H\(_{17}\)NO\(_3\) [M]\(^+\): 271.1208; Found: 271.1208.

2-(Propan-2-ylcarbonyl)amino-3-pentanoylindenone (5aj)

IR (ATR): 3288, 2960, 2927, 2871, 1726, 1678, 1512, 1458, 1379, 1200, 1124, 1086 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.91\) (t, \(J = 7.5\) Hz, 3H), 1.23 (d, \(J = 7.2\) Hz, 6H), 1.36 (pseudo sext, \(J = 7.5\) Hz, 2H), 1.60-1.75 (m, 2H), 2.52-2.68 (m, 3H), 7.07-7.14 (m, 2H), 7.28-7.35 (m, 1H), 7.39-7.44 (m, 1H), 7.61 (brs, 1H); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 14.0, 19.4, 22.6, 25.7, 36.1, 43.7, 121.8, 124.2, 126.6, 126.8, 127.7, 132.8, 135.5, 145.5, 175.1, 193.4, 200.8; HRMS (EI\(^+\)): m/z Calcd for C\(_{18}\)H\(_{21}\)NO\(_3\) [M]\(^+\): 299.1521; Found: 299.1523.

2-Pivaloylamino-3-pentanoylindenone (5ak)

IR (ATR): 3354, 2958, 2931, 2870, 1724, 1678, 1500, 1454, 1369, 1184, 1140, 1080 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.91\) (t, \(J = 7.5\) Hz, 3H), 1.30 (s, 9H), 1.36 (pseudo sext, \(J = 7.5\) Hz, 2H), 1.69 (pseudo quint, \(J = 7.5\) Hz, 2H), 2.60 (t, \(J = 7.5\) Hz, 2H), 7.07-7.14 (m, 2H), 7.28-7.36 (m, 1H), 7.40-7.45 (m, 1H), 7.84 (brs, 1H); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 14.0, 22.6, 25.7, 27.4, 39.8, 43.8, 121.9, 124.2, 126.7, 127.1,
127.7, 132.4, 135.5, 145.5, 176.6, 193.4, 200.8; HRMS (El⁺): m/z Calcd for C₁₉H₂₃NO₃ [M⁺]: 313.1678; Found: 313.1676.

**2-Benzoylamino-3-(propan-2-ylcarbonyl)indenone (5ba)**

IR (ATR): 3323, 1722, 1666, 1510, 1454, 1271, 1178, 1065 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.21 (d, J = 7.2 Hz, 6H), 2.97 (sept, J = 7.2 Hz, 1H), 7.04-7.08 (m, 1H), 7.10-7.17 (m, 1H), 7.31-7.38 (m, 1H), 7.43-7.54 (m, 3H), 7.56-7.64 (m, 1H), 7.87-7.93 (m, 2H), 8.32 (brs, 1H); ¹³C NMR (125 MHz, CDCl₃): δ = 17.3, 41.9, 121.9, 124.2, 126.4, 126.5, 127.4, 127.7, 129.0, 132.3, 132.4, 132.9, 135.6, 146.1, 164.7, 193.0, 204.0; HRMS (El⁺): m/z Calcd for C₂₀H₁₇NO₃ [M⁺]: 319.1208; Found: 319.1208.

**2-Acetylamino-3-(propan-2-ylcarbonyl)indenone (5bi)**

IR (ATR): 3327, 1724, 1691, 1606, 1520, 1456, 1371, 1242, 1063 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.17 (d, J = 7.2 Hz, 6H), 2.20 (s, 3H), 2.88 (sept, J = 7.2 Hz, 1H), 6.98 (d, J = 7.5 Hz, 1H), 7.07-7.14 (m, 1H), 7.28-7.35 (m, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.63 (brs, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 17.4, 23.7, 41.9, 121.9, 124.1, 125.9, 126.3, 127.8, 132.6, 135.7, 146.2, 168.1, 193.2, 204.0; HRMS (El⁺): m/z Calcd for C₁₅H₁₅NO₃ [M⁺]: 257.1052; Found: 257.1049.

**2-Amino-3-(1-benzoyloxy-2-methyl-propen-1-yl)indenone (6ba)**
IR (ATR): 3464, 3361, 2920, 1720, 1639, 1606, 1454, 1277, 1244, 1176, 1107 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 1.81 (s, 3H), 1.82 (s, 3H), 4.27 (brs, 2H), 6.79-6.86 (m, 2H), 7.12-7.23 (m, 2H), 7.43-7.50 (m, 2H), 7.55-7.63 (m, 1H), 8.07-8.13 (m, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 17.9, 19.8, 115.6, 118.7, 123.0, 124.7, 126.5, 128.2, 128.7, 129.5, 130.1, 133.5, 134.2, 135.2, 138.6, 148.7, 165.4, 193.5\); HRMS (EI\(^+\)): \(m/z\) Calcd for C\(_{20}\)H\(_{17}\)NO\(_3\) [M]\(^+\): 319.1208; Found: 319.1212.

2-(3-Phenylpropan-1-yl)amino-3-pentanoylindenone (11aaa)

IR (ATR): 2922, 2858, 1714, 1599, 1558, 1464, 1261, 1049 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.98 (t, J = 7.5 Hz, 3H), 1.45 \) (pseudo sext, \(J = 7.5 \) Hz, 2H), 1.62-1.76 (m, 2H), 1.90-2.03 (m, 2H), 2.66 (t, \(J = 7.5\) Hz, 2H), 2.72 (t, \(J = 7.5\) Hz, 2H), 3.84 (q, \(J = 6.9\) Hz, 2H), 6.86-6.94 (m, 1H), 7.08 (d, \(J = 7.5\) Hz, 1H), 7.15-7.23 (m, 3H), 7.24-7.41 (m, 4H), 10.30-10.50 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 14.2, 22.8, 26.3, 32.2, 33.1, 41.8, 42.7, 110.0, 119.6, 123.6, 124.9, 126.2, 127.2, 128.5, 128.6, 136.8, 141.0, 148.2, 152.0, 192.7, 196.7\); HRMS (EI\(^+\)): \(m/z\) Calcd for C\(_{23}\)H\(_{25}\)NO\(_2\) [M]\(^+\): 347.1885; Found: 347.1888.

2-(1-Phenylethan-1-yl)amino-3-pentanoylindenone (11aab)

IR (ATR): 2956, 2868, 1716, 1606, 1558, 1458, 1371, 1263, 1078, 1022 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 0.98 (t, J = 7.5 \) Hz, 3H), 1.45 \) (pseudo sext, \(J = 7.5 \) Hz, 2H), 1.58 (d, \(J = 6.9 \) Hz, 3H), 1.64-1.76 (m, 2H), 2.67 (t, \(J = 7.5\) Hz, 2H), 5.83-5.96 (m, 1H), 6.84-6.92 (m, 1H), 7.08 (d, \(J = 7.5\) Hz, 1H), 7.21-7.39 (m, 7H), 10.69 (d, \(J = 9.0 \) Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 14.2, 22.8, 24.5, 26.2, 41.9, 52.0, 110.6, 119.7, 123.8, 125.0, 126.1, 127.2, 127.5, 128.9, 136.7, 143.7, 147.9, 150.8, 192.4, 197.0\); HRMS (EI\(^+\)): \(m/z\) Calcd for C\(_{22}\)H\(_{23}\)NO\(_2\) [M]\(^+\): 333.1729; Found: 333.1731.
Representative procedure for the synthesis of indenopyrimidine

A mixture of 5ai (27.2 mg; 0.10 mmol) and benzamidine hydrochloride 8a (38.5 mg; 0.20 mmol) in pyridine (1.0 ml) was stirred at 100 °C for 24 h under an argon atmosphere, and then the reaction mixture was cooled and diluted with AcOEt (5 ml) and H2O (5 ml). The organic layer was separated and the aqueous layer was extracted with AcOEt (3 ml x 3). The combined extracts were washed with water and brine, and dried over MgSO4. The solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (toluene/AcOEt = 20/1) to afford 9aia (28.1 mg, 89 %)

4-Butyl-2-phenyl-9H-indeno[2,1-d]pyrimidin-9-one (9aia)

IR (KBr): 2959, 1730, 1572, 1458, 1390, 1186 cm^-1; ^1H NMR (300 MHz, CDCl3): δ = 1.04 (t, J = 7.5 Hz, 3H), 1.45-1.65 (m, 2H), 1.92 (quintet, J = 7.7 Hz, 2H), 3.13 (t, J = 7.5 Hz, 1H), 7.33-7.47 (m, 1H), 7.47-7.57 (m, 3H), 7.57-7.69 (m, 2H), 7.82 (d, J = 7.5 Hz, 1H), 8.47-8.62 (m, 2H); ^13C NMR (75 MHz, CDCl3): δ = 14.2, 22.8, 29.4, 35.9, 123.7, 125.6, 128.6, 128.7, 129.7, 131.17, 131.23, 131.9, 136.3, 137.1, 141.8, 160.3, 165.3, 165.5, 193.4; HRMS (EI+): m/z Calcd for C_{21}H_{18}N_{2}O (M+): 314.1419; Found: 314.1422.

4-Butyl-2-methyl-9H-indeno[2,1-d]pyrimidin-9-one (9aib)

IR (ATR): 2951, 2866, 1730, 1601, 1574, 1400, 1373, 1182, 1101 cm^-1; ^1H NMR (300 MHz, CDCl3): δ = 1.01 (t, J = 7.2 Hz, 3H), 1.53 (pseudo sext, J = 7.2 Hz, 2H), 1.73-1.86 (m, 2H), 2.81 (s, 3H), 2.99-3.08 (m, 2H), 7.40 (ddd, J = 7.8 Hz, 6.6 Hz, 2.4 Hz, 1H), 7.57-7.65 (m, 2H), 7.78-7.82 (m, 1H); ^13C NMR (75 MHz, CDCl3): δ = 14.1, 23.0, 26.1, 30.0, 36.1, 123.5, 125.6, 129.7, 130.6, 131.6, 136.3, 141.8, 160.0, 165.6, 169.4, 193.4; HRMS (EI+): m/z Calcd for C_{16}H_{16}N_{2}O [M]+: 252.1263; Found: 252.1264.
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4-(2-Propyl)-2-phenyl-9H-indeno[2,1-d]pyrimidin-9-one (9bia)

IR (ATR): 2970, 2929, 2868, 1726, 1599, 1564, 1458, 1383, 1298, 1180 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 1.51 (d, J = 6.9 Hz, 6H), 3.58 (sept, J = 6.9 Hz, 1H), 7.41 (dt, J = 0.9 Hz, 7.8 Hz, 1H), 7.47-7.54 (m, 3H), 7.63 (dt, J = 0.9 Hz, 7.5 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 8.56-8.65 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ = 20.6, 33.4, 123.9, 125.6, 128.6, 128.7, 129.6, 130.4, 131.2, 132.0, 136.3, 137.2, 141.7, 160.4, 165.3, 169.8, 193.5; HRMS (EI⁺): m/z Calcd for C₂₀H₁₆N₂O [M⁺]: 300.1263; Found: 300.1263.

Representative procedure for the synthesis of indenopyrazole

To a stirred solution of 5ai (27.2 mg; 0.10 mmol) in 1,4-dioxane (0.5 ml) under an argon atmosphere was added a solution of methylhydrazine (5.5 mg; 0.12 mmol) in 1,4-dioxane (0.5 ml) at 60 °C over 5 min. After being stirred for 3 h, the reaction mixture was cooled and diluted with AcOEt (5 ml) and H₂O (5 ml). The organic layer was separated and the aqueous layer was extracted with AcOEt (3 ml x 4). The combined extracts were washed with water and brine, and dried over MgSO₄. The solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography (CHCl₃/AcOEt = 10/1) to afford 12ai (12.4 mg, 52%).

3-Butyl-2-methyl-8H-indeno[2,1-c]pyrazol-8-one (12ai)

IR (KBr): 2939, 1714, 1603, 1491, 1317, 1169 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.97 (t, J = 7.3 Hz, 3H), 1.39-1.49 (m, 2H), 1.63-1.73 (m, 2H), 2.74 (t, J = 7.5 Hz, 2H), 3.83 (s, 3H), 7.09 - 7.14 (m, 2H), 7.35 (dt, J = 1.1 Hz, 7.5 Hz, 1H), 7.52 (dd, J = 1.3 Hz, 7.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 13.8, 22.3, 25.0, 30.7, 37.1, 120.2, 124.7,
126.8, 129.6, 134.4, 137.5, 138.0, 138.4, 152.3, 186.2; HRMS (EI\(^+\)): \textit{m/z} Calcd for C\(_{15}\)H\(_{16}\)N\(_2\)O [M]\(^+\): 240.1263; Found: 240.1260.

3-(2-Propyl)-2-methyl-8\textit{H}-inden[2,1-\textit{c}]pyrazol-8-one (12bi)

![Chemical Structure](image)

IR (ATR): 2970, 1712, 1603, 1481, 1371, 1317, 1167, 1090, 1007 cm\(^{-1}\); \textsuperscript{1}H NMR (500 MHz, CDCl\(_3\)): \(\delta = 1.42\) (d, \(J = 7.0\) Hz, 6H), 3.11 (sept, \(J = 7.0\) Hz, 1H), 3.88 (s, 3H), 7.13 (t, \(J = 7.5\) Hz, 1H), 7.24 (d, \(J = 7.5\) Hz, 1H), 7.38 (dt, \(J = 1.2\) Hz, 7.5 Hz, 1H), 7.55 (d, \(J = 7.5\) Hz, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\(_3\)): \(\delta = 21.7, 25.5, 37.7, 122.0, 124.7, 126.8, 127.6, 134.5, 138.1, 138.4, 144.1, 152.6, 186.3\); HRMS (EI\(^+\)): \textit{m/z} Calcd for C\(_{14}\)H\(_{14}\)N\(_2\)O [M]\(^+\): 226.1106; Found: 226.1108.
References and notes


5. No reaction occurred at room temperature.


7. When 5ai was exposed to same reaction conditions, a deuterium was incorporated only in 17% at the α-position of the carbonyl group.

8. No reaction occurred with secondary amines such as a piperidine and N-benzylmethylamine.


Chapter 3
Stereoselective Synthesis of Vinyl-Substituted (Z)-Stilbenes
by Rhodium-Catalysed Addition of Arylboronic Acids
to Allenic Alcohols

Abstract: Vinyl-substituted (Z)-stilbenes are stereoselectively synthesised on treatment of 4-arylbuta-2,3-dien-1-ols with arylboronic acids in the presence of a rhodium(I) catalyst. The reaction proceeds through the regioselective addition of organorhodium(I) species across the aryl-substituted carbon–carbon double bond of the allene moiety and subsequent δ-elimination of Rh(I)–OH.
**Introduction**

The rhodium-catalysed addition reactions of organoboronic acids to unsaturated functionalities have rapidly expanded as a powerful tool for the construction of carbon–carbon bonds. Mechanistically, an organorhodium(I) species is generated by transmetalation between Rh(I)–OR species (OR = hydroxy or alkoxy) and organoboronic acids. It undergoes intermolecular addition to various unsaturated organic compounds and, for the next catalytic cycle, the Rh(I)–OR species is regenerated typically by two types of termination steps. One is protodemetallation with H₂O or ROH, and the other is β-elimination with an OR group located β to rhodium(I) of an organorhodium(I) intermediate. Murakami et al have developed a variety of rhodium-catalysed reactions which proceed through a sequential addition/β-OR elimination pathway. For example, the addition reaction of arylboroxines onto cis-allylic diols gave 2-aryllalk-3-en-1-ols. In this chapter, the author describes a new addition reaction of organoboronic acids to allenic alcohols, in which δ-elimination of an Rh(I)–OH species occurs with an organorhodium(I) adduct to give vinyl-substituted (Z)-stilbenes stereoselectively.

**Results and discussions**

A solution of 4-phenylbuta-2,3-dien-1-ol (1a), o-tolylboronic acid (2a, 1.0 equiv.) and a catalytic amount of [Rh(OH)(cod)]₂ (5 mol% Rh, cod = cycloocta-1,5-diene) in MeOH (0.1 M) was stirred for 3 h at room temperature. The allenic alcohol 1a was consumed and chromatographic isolation afforded (Z)-vinyl-(2'-methyl)stilbene (3aa) in 61% yield with high stereoselectivity (Z/E = 99:1, eqn 1). The stereochemistry of the double bond was confirmed by a difference NOE study. When the reaction was carried out in the presence of ten equivalents of B(OH)₃ as an additive, the yield of 3aa was improved to 71%. Of interest was that the stereochemical outcome is opposite to that of the reaction of 1a with 2a using a palladium catalyst; (E)-isomer 3aa was selectively produced in the presence of Pd(PPh₃)₄.
The stereoselective formation of \((Z)\)-isomer 3aa can be explained by assuming the reaction pathway involving \(\delta\)-elimination of Rh(I)–OH, as depicted in Scheme 1.\(^\text{10}\) Initially, \(o\)-tolylrhodium(I) species A is generated by transmetalation between Rh(I)–OH and 2a. Regioselective \(\text{syn}\) addition of A across the phenyl-substituted carbon–carbon double bond of 1a occurs from the less-hindered side (\(a\)-side) to give the alkylrhodium(I) intermediate B.\(^\text{11}\) We assume that attachment of rhodium(I) to the benzylic position is favoured for the carborhodation of A, as with the case of the rhodium-catalysed hydroarylation of styrene.\(^\text{12}\) Then, intramolecular coordination of the hydroxy group to rhodium(I) forms a six-membered ring rhodium(I) intermediate, for which two half-chair conformations (C and D) are available. The intermediate C having the phenyl substituent at the pseudo-equatorial position is more stable than the other conformer D. The more stable conformer C undergoes \(\delta\)-elimination of Rh(I)–OH with a double bond shift to afford \((Z)\)-isomer 3aa together with the catalytically active Rh(I)–OH species.

Scheme 1. Proposed reaction pathway.
A variety of aryl- and alkenylboronic acids 2 were subjected to the addition reaction to 1a (Table 1). The two other isomeric tolylboronic acids 2b and 2c both afforded the corresponding vinylstilbenes 3ab–3ac with high stereoselectivities (Z/E = >95:5, entries 1 and 2). Not only electron-donating and -withdrawing arylboronic acids 2e–2h but also heteroarylboronic acids 2i and 2j were suitably reactive (entries 4–9). In addition, even alkenylboronic acids 2k and 2l could participate in the addition reaction (entries 10 and 11).

Table 1. Rh(I)-catalysed addition of aryl- and alkenylboronic acids 2 to 1a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2</th>
<th>R</th>
<th>3</th>
<th>Yield/%b</th>
<th>Z/Ec</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b</td>
<td>m-Tol</td>
<td>3ab</td>
<td>68</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>2</td>
<td>2c</td>
<td>p-Tol</td>
<td>3ac</td>
<td>77</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>Ph</td>
<td>3ad</td>
<td>68</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>2e</td>
<td>o-MeO–C₆H₄</td>
<td>3ae</td>
<td>76</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>5</td>
<td>2f</td>
<td>p-MeO–C₆H₄</td>
<td>3af</td>
<td>68</td>
<td>92:8</td>
</tr>
<tr>
<td>6</td>
<td>2g</td>
<td>p-Br–C₆H₄</td>
<td>3ag</td>
<td>71</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>7</td>
<td>2h</td>
<td>p-MeO₂C–C₆H₄</td>
<td>3ah</td>
<td>73</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>8</td>
<td>2i</td>
<td>2-thienyl</td>
<td>3ai</td>
<td>61</td>
<td>93:7d</td>
</tr>
<tr>
<td>9</td>
<td>2j</td>
<td>3-thienyl</td>
<td>3aj</td>
<td>71</td>
<td>94:6d</td>
</tr>
<tr>
<td>10</td>
<td>2k</td>
<td>b-styryl</td>
<td>3ak</td>
<td>52</td>
<td>89:11</td>
</tr>
<tr>
<td>11</td>
<td>2l</td>
<td>(E)-hexenyl</td>
<td>3al</td>
<td>68</td>
<td>90:10</td>
</tr>
</tbody>
</table>

a Reaction conducted on a 0.2 mmol scale.
b Isolated yield.
c Determined by ¹H NMR.
d In the absence of B(OH)₃

The use of other allenic alcohols 1 was also examined in the rhodium-catalysed addition reaction of 2a (Table 2). Trisubstituted allenic alcohol 1b reacted to produce 3ba with high stereoselectivity, albeit in low yield (Z/E = >95:5, entry 1). Dimethyl-substituted substrate 1c was also converted to the product 3ca in 62% yield (Z/E = 91:9, entry 2). Both chloro and methoxy substituents were tolerated on the aryl substituent of 1 (entries 3 and 4). The chloro-substituted allenic alcohol 1d exhibited a higher stereoselectivity than the methoxy-substituted allenic alcohol 1e.
Table 2. Rh(I)-catalyzed addition of o-tolyboronic acid (2a) to a-allenols 1a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>3</th>
<th>Yield/%b</th>
<th>Z/Ec</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph=CH·=CH·OH</td>
<td>Ph=CH·=CH·O-Tol 3ba</td>
<td>46</td>
<td>&gt;95:5d</td>
</tr>
<tr>
<td>2</td>
<td>Ph=CH·=CH·OH</td>
<td>Ph=CH·=CH·O-TolMe 3ca</td>
<td>62</td>
<td>91:9d</td>
</tr>
<tr>
<td>3</td>
<td>1d Ar = p-Cl–C6H4</td>
<td>3da</td>
<td>68</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td>4</td>
<td>1e Ar = p-MeO–C6H4</td>
<td>3ea</td>
<td>61</td>
<td>86:14</td>
</tr>
</tbody>
</table>

a The reaction conditions were the same as those in Table 1.
b Isolated yield.
c Determined by 1H NMR.
d Using 2.5 equiv. of o-TolB(OH)2 for 24 h.

For comparison, the reaction was carried out using alkyl-substituted allene alcohols 4. Much to our surprise, (E)-isomers 5 having an opposite stereochemistry was predominantly formed (eqn. 2). The inversion of the stereochemistry is explained by assuming that o-tolylrhodium(I) species A prefers addition to the hydroxymethyl-substituted carbon–carbon double bond rather than to the cyclohexyl- or n-butyl-substituted double bond.13 Syn addition of A across the hydroxymethyl-substituted carbon–carbon double bond occurs from the less-hindered side (d-side) and β-elimination of Rh(I)–OH immediately follows to give (E)-5.

\[
\begin{align*}
\text{R–}=\text{CH·}=\text{CH·OH} & + \text{O-TolB(OH)2} \\
\text{2a} & \xrightarrow{\text{2.5 mol\% [Rh(OH)(cod)]2 Br(OH)3 (10 equiv.)}} \text{MeOH, rt, 3–6 h} \\
\text{4a R = Cy} & \rightarrow \text{5aa 65\% (E/Z = >95/5)} \\
\text{4b R = n-Bu} & \rightarrow \text{5ba 56\% (E/Z = 91/9)} \\
\end{align*}
\]
Conclusion

In summary, the author has developed a rhodium-catalysed addition reaction of arylboronic acids to allenic alcohols, allowing the stereoselective formation of vinyl-substituted (Z)-stilbenes. This catalytic process presents a rare example of δ-elimination of Rh(I)–OH.
Experimental Section

General. Infrared spectra were recorded on a Shimadzu FTIR-8100 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Gemini 2000 ($^1$H at 300 MHz and $^{13}$C at 75 MHz), a JNM-ECS 400 ($^1$H at 400 MHz and $^{13}$C at 100 MHz) or a Bruker AVANCE 500 ($^1$H at 500MHz and $^{13}$C at 125MHz) spectrometer using CHCl$_3$ ($^1$H, $\delta$ = 7.26) and CDCl$_3$ ($^{13}$C, $\delta$ = 77.0) as an internal standard. High-resolution mass spectra were recorded on a JEOL JMS-SX102A (EI) or a JEOL JMS-HX110A (FAB) spectrometer. All reactions were carried out under an argon atmosphere unless otherwise noted. Flash column chromatography was performed with basic silica gel NH-DM1020 (Fuji Silysia Chemical Ltd) or silica gel 60 N (Kanto). Preparative thin-layer chromatography was performed with silica gel 60 PF254 (Merck).

Materials. Unless otherwise noted, all chemicals were obtained from commercial suppliers and used as received. Anhydrous MeOH (Nacalai) was purchased and distilled from magnesium. [Rh(OH)(cod)$_2$] was prepared according to the literature procedure.$^1$ Allenic alcohols ($1a$, $1c$, $1d$, $1e$ and $4b$) were prepared from the corresponding propargyl alcohols by the literature procedures.$^{2,3}$ Allenic alcohols ($1b$ and $4a$) were prepared from the corresponding allenic esters$^4$ according to the reported procedure.$^5$ The analytical data of compounds ($1a$, $1b$, $3ac$, $3ad$, $4a$, and $4b$) have been already reported.

2-Methyl-5-phenylpenta-3,4-dien-2-ol (1c)

\[
\text{IR (neat): 3397, 3032, 2930, 1950, 1703, 1599, 1495, 1456, 1375, 1152 cm}^{-1}; \quad ^1\text{H NMR (300 MHz, CDCl}_3\text{): } \delta = 1.44 \text{ (6H, s), 5.79 \text{ (1H, d, } J = 6.6 \text{ Hz), 6.33 \text{ (1H, d, } J = 6.6 \text{ Hz), 7.13–7.25 \text{ (1H, m), 7.25–7.35 \text{ (4H, m); }} \quad ^{13}\text{C NMR (75 MHz, CDCl}_3\text{): } \delta = 30.4, 70.5, 98.2, 105.3, 126.8, 127.3, 128.8, 134.2, 202.1; HRMS (EI$^+$): Calcd for C$_{12}$H$_{14}$O, M$^+$ 174.1045. Found m/z 174.1047.}

4-(4-Chlorophenyl)buta-2,3-dien-1-ol (1d)

\[
\text{IR (neat): 3347, 2930, 2874, 1952, 1491, 1092, 1013 cm}^{-1}; \quad ^1\text{H NMR (300 MHz, CDCl}_3\text{):}
\]
\[ \delta = 4.20-4.33 \ (2H, m), \ 5.73-5.85 \ (1H, m), \ 6.23-6.33 \ (1H, m), \ 7.17-7.35 \ (4H, m); \ \text{^13C} \ \text{NMR (75 MHz, CDCl}_3): \ \delta = 60.4, \ 96.4, \ 96.5, \ 128.2, \ 129.0, \ 132.5, \ 133.0, \ 204.5; \ \text{HRMS (EI\textsuperscript{+}): Calcd for C}_{10}H_{9}ClO, M\textsuperscript{+} 180.0342. \ \text{Found m/z} \ 180.0345. \]

4-(4-Methoxyphenyl)buta-2,3-dien-1-ol (1e)

\[
\begin{align*}
\text{IR (neat):} & \ 3386, \ 2838, \ 1948, \ 1607, \ 1444, \ 1300, \ 1248, \ 1173, \ 1032 \ cm^{-1}; \ \text{^1H} \ \text{NMR (300 MHz, CDCl}_3): \ \delta = 3.80 \ (3H, s), \ 4.18-4.32 \ (2H, m), \ 5.73-5.82 \ (1H, m), \ 6.26-6.34 \ (1H, m), \ 6.80-6.90 \ (2H, m), \ 7.19-7.30 \ (2H, m); \ \text{^13C} \ \text{NMR (75 MHz, CDCl}_3): \ \delta = 55.5, \ 60.7, \ 96.0, \ 97.0, \ 114.4, \ 126.2, \ 128.1, \ 159.2, \ 203.7; \ \text{HRMS (EI\textsuperscript{+}): Calcd for C}_{11}H_{12}O_{2}, M\textsuperscript{+} 176.0837. \ \text{Found m/z} \ 176.0836.
\end{align*}
\]

Typical procedure for the rhodium-catalysed reaction of arylboronic acids to allenic alcohols.

An oven-dried flask was charged with 2a (27.1 mg, 0.20 mmol), B(OH)_3 (123.6 mg, 2.0 mmol) and a solution of 1a (29.4 mg, 0.20 mmol) in MeOH (2.0 mL). Then, [Rh(OH)(cod)]_2 (2.3 mg, 5.0 \mu mol) was added and the flask was flushed with argon. After stirred at room temperature for 3 h, the reaction mixture was diluted with ethyl acetate (10 mL) and passed through a pad of basic silica gel (Fuji Silysia Chemical Ltd., NH-DM1020). The filtrate was concentrated under reduced pressure and the residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate 50:1) to give the product 3aa as a colorless oil (31.6 mg, 0.14 mmol, 71%, Z/E = 98:2).

(Z)-2-(2-Methylphenyl)-1-phenylbuta-1,3-diene (3aa)

\[
\begin{align*}
\text{IR (neat):} & \ 3061, \ 3022, \ 2922, \ 1601, \ 1493, \ 1447 \ cm^{-1}; \ \text{^1H} \ \text{NMR (300 MHz, CDCl}_3): \ \delta = 2.10 \ (3H, s), \ 4.67 \ (1H, d, J = 17.1Hz), \ 5.10 \ (1H, d, J = 10.5 \ Hz), \ 6.63 \ (1H, s), \ 6.73 \ (1H, s), \ 7.13-7.23 \ (2H, m);
\end{align*}
\]

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dd, \(J = 17.1, 10.5\) Hz), 6.81–6.92 (2H, m), 7.00–7.15 (4H, m), 7.15–7.35 (3H, m); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 19.2, 115.9, 126.3, 127.0, 127.5, 128.1, 128.9, 129.4, 130.3, 131.5, 136.2, 136.8, 137.3, 141.1\); HRMS (EI\(^{+}\)): Calcd for C\(_{17}H_{16}\), M\(^{+}\) 220.1252; Found m/z 220.1251.

(Z)-2-(3-Methylphenyl)-1-phenylbuta-1,3-diene (3ab)

IR (KBr): 3029, 2921, 1599, 1493, 1445, 1408, 1076 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 2.35 (3H, s), 4.85 (1H, d, \(J = 17.1\) Hz), 5.15 (1H, d, \(J = 10.5\) Hz), 6.58 (1H, s), 6.73 (1H, dd, \(J = 17.1, 10.5\) Hz), 6.87–7.00 (4H, m), 7.05–7.20 (4H, m), 7.23–7.33 (1H, m); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 21.7, 116.5, 126.7, 127.0, 128.1, 128.2, 128.8, 129.6, 130.2, 131.5, 136.9, 137.9, 138.5, 142.0\); HRMS (EI\(^{+}\)): Calcd for C\(_{17}H_{16}\), M\(^{+}\) 220.1252. Found m/z 220.1254.

(Z)-2-(4-Methylphenyl)-1-phenylbuta-1,3-diene (3ac)

IR (KBr): 2919, 1599, 1512, 1445, 1109 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 2.40 (3H, s), 4.87 (1H, d, \(J = 17.1\) Hz), 5.15 (1H, d, \(J = 10.5\) Hz), 6.59 (1H, s), 6.73 (1H, dd, \(J = 17.1, 10.5\) Hz), 6.88–6.98 (2H, m), 7.13–7.15 (5H, m), 7.16–7.24 (2H, m); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 21.5, 116.4, 127.0, 128.1, 129.60, 129.64, 131.5, 134.9, 137.0, 141.9, 142.1\); HRMS (EI\(^{+}\)): Calcd for C\(_{17}H_{16}\), M\(^{+}\) 220.1252. Found m/z 220.1254.

(Z)-2-(2-Methoxylphenyl)-1-phenylbuta-1,3-diene (3ae)

IR (neat): 3084, 2834, 1597, 1491, 1248, 1097 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 3.73 (3H, s), 4.83 (1H, d, \(J = 17.1\) Hz), 5.16 (1H, d, \(J = 9.6\) Hz), 6.75 (1H, s), 6.80 (1H,
dd, $J = 17.1, 10.2$ Hz), 6.95–7.20 (8H, m), 7.35–7.45 (1H, m); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 55.9, 111.6, 115.5, 121.3, 126.8, 127.0, 128.1, 129.0, 129.7, 131.1, 132.2, 137.1, 138.5, 141.0, 157.2$; HRMS (EI$^+$): Calcd for C$_{17}$H$_{16}$O, M$^+$ 236.1201. Found m/z 236.1202.

**(Z)-2-(4-Methoxylphenyl)-1-phenylbuta-1,3-diene (3af)**

![Chemical structure of (Z)-2-(4-Methoxylphenyl)-1-phenylbuta-1,3-diene (3af)](attachment:image)

IR (KBr): 3017, 2934, 1603, 1509, 1441, 1287, 1244, 1183, 1173, 1030 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 3.85$ (3H, s), 4.89 (1H, dd, $J = 17.4$ Hz), 5.15 (1H, dd, $J = 11.1$ Hz), 6.59 (1H, s), 6.73 (1H, dd, $J = 17.1, 10.5$ Hz), 6.89–6.99 (4H, m), 7.05–7.15 (5H, m); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 55.4, 114.4, 116.4, 127.0, 128.1, 129.6, 130.1, 130.9, 131.6, 137.0, 141.5, 142.2, 159.0$; HRMS (EI$^+$): Calcd for C$_{17}$H$_{16}$O, M$^+$ 236.1201. Found m/z 236.1202.

**(Z)-2-(4-Bromophenyl)-1-phenylbuta-1,3-diene (3ag)**

![Chemical structure of (Z)-2-(4-Bromophenyl)-1-phenylbuta-1,3-diene (3ag)](attachment:image)

IR (KBr): 3092, 3046, 1597, 1485, 1445, 1406, 1389, 1069 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 4.83$ (1H, d, $J = 17.4$ Hz), 5.17 (1H, d, $J = 10.5$ Hz), 6.63 (1H, s), 6.73 (1H, dd, $J = 16.5, 10.5$ Hz), 6.85–6.98 (2H, m), 7.03–7.20 (5H, m), 7.50–7.59 (2H, m); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 116.6, 121.5, 127.3, 128.2, 129.5, 131.6, 132.1, 132.2, 136.4, 136.9, 140.5, 141.4$; HRMS (EI$^+$): Calcd for C$_{16}$H$_{15}$Br, M$^+$ 284.0201. Found m/z 284.0203.
(Z)-2-(4-Methoxycarbonylphenyl)-1-phenylbuta-1,3-diene (3ah)

IR (neat): 2951, 1723, 1607, 1435, 1277, 1103 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 3.94 (3H, s), 4.79 (1H, d, J = 17.1 Hz), 5.17 (1H, dd, J = 10.5 Hz), 6.65 (1H, s), 6.74 (1H, dd, J = 17.1, 10.5 Hz), 6.85–6.95 (2H, m), 7.05–7.15 (3H, m), 7.24–7.32 (2H, m), 8.04–8.12 (2H, m); ¹³C NMR (75 MHz, CDCl₃): δ = 52.3, 116.7, 127.3, 128.2, 129.3, 129.5, 130.0, 130.2, 132.1, 136.3, 140.8, 141.2, 143.3, 167.1; HRMS (EI⁺): Calcd for C₁₈H₁₆O₂, M⁺ 264.1150. Found m/z 264.1151.

(Z)-1-Phenyl-2-(2-thienyl)buta-1,3-diene (3ai)

IR (neat): 3075, 2926, 1599, 1491, 1449, 1225 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 5.14 (1H, d, J = 16.5 Hz), 5.24 (1H, d, J = 10.2 Hz), 6.73 (1H, s), 6.76 (1H, dd, J = 16.8, 10.5 Hz), 6.86–6.92 (1H, m), 6.99–7.21 (6H, m), 7.34–7.42 (1H, m); ¹³C NMR (100 MHz, CDCl₃): δ = 116.5, 126.0, 127.28, 127.34, 127.35, 128.0, 129.4, 133.9, 134.1, 136.3, 137.9, 141.2; HRMS (EI⁺): Calcd for C₁₄H₁₂S, M⁺ 212.0660. Found m/z 212.0663.

(Z)-1-Phenyl-2-(3-thienyl)buta-1,3-diene (3aj)

IR (KBr): 3102, 2924, 1597, 1489, 1444, 997 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 5.01 (1H, d, J = 17.1 Hz), 5.18 (1H, d, J = 9.6 Hz), 6.64 (1H, s), 6.72 (1H, dd, J = 17.1, 11.4 Hz), 6.85–7.05 (3H, m), 7.05–7.23 (3H, m), 7.23–7.43 (1H, m); ¹³C NMR (75 MHz, CDCl₃): δ = 116.3, 123.7, 125.9, 127.2, 128.2, 129.1, 129.4, 132.5, 136.7, 136.9, 137.6, 141.4; HRMS (EI⁺): Calcd for C₁₄H₁₂S, M⁺ 212.0660. Found m/z 212.0664.
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(Z)-1-Phenyl-2-[(E)-styryl]buta-1,3-diene (3ak)

![Structure](image)

IR (neat): 3024, 2926, 1599, 1493, 1449 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 5.19\) (1H, d, \(J = 10.8\) Hz), 5.52 (1H, d, \(J = 17.1\) Hz), 6.58 (1H, dd, \(J = 17.1, 10.8\) Hz), 6.65 (1H, s), 6.72 (1H, d, \(J = 16.5\) Hz), 7.06 (1H, d, \(J = 16.5\) Hz), 7.10–7.43 (10H, m); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 116.7, 125.9, 126.7, 127.3, 127.8, 128.3, 128.4, 128.8, 130.0, 132.6, 137.5, 137.6, 137.8, 138.2\); HRMS (EI\(^+\)): Calcd for C\(_{18}\)H\(_{16}\), M\(^+\) 232.1252. Found m/z 232.1254.

(Z)-2-[(E)-Hex-1-en-1-yl]-1-phenylbuta-1,3-diene (3al)

IR (neat): 3023, 2957, 2926, 2857, 1597, 1491, 1466, 1445, 1379, 1076, 1030 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.92\) (3H, t, \(J = 7.2\) Hz), 1.27–1.56 (4H, m), 2.05–2.24 (2H, m), 5.17 (1H, d, \(J = 11.1\) Hz), 5.50 (1H, d, \(J = 17.1\) Hz), 5.91 (1H, dt, \(J = 15.9, 7.2\) Hz), 6.36 (1H, d, \(J = 15.6\) Hz), 6.53 (1H, s) 6.54 (1H, dd, \(J = 17.1, 10.8\) Hz), 7.16–7.42 (5H, m); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 14.2, 22.5, 31.6, 33.1, 115.8, 126.5, 126.9, 128.1, 128.2, 129.8, 135.8, 137.7, 138.1, 139.1\); HRMS (EI\(^+\)): Calcd for C\(_{16}\)H\(_{20}\), M\(^+\) 212.1565. Found m/z 212.1567.

(Z)-3-Methyl-2-(2-methylphenyl)-1-phenylbuta-1,3-diene (3ba)

![Structure](image)

IR (neat): 3020, 2923, 1603, 1491, 1445, 1369 cm\(^{-1}\); \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta = 2.08\) (3H, s), 2.17 (3H, d, \(J = 0.7\)Hz), 4.55 (1H, d, \(J = 1.9\) Hz), 5.05-5.07 (1H, m), 6.75 (1H, s), 6.82–6.84 (2H, m), 7.02 (1H, dd, \(J = 7.4, 1.4\)Hz), 7.05-7.11(3H, m), 7.18–7.27
(Z)-4-Methyl-2-(2-methylphenyl)-1-phenylpenta-1,3-diene (3ca)

IR (neat): 3060, 2923, 1599, 1489, 1447, 1375 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 1.46 (3H, s), 1.83 (3H, s), 2.15 (3H, s), 5.96–6.00 (1H, m), 6.50 (1H, s), 6.82–6.86 (2H, m), 7.02–7.11 (4H, m), 7.15–7.26 (3H, m); ¹³C NMR (100 MHz, CDCl₃): δ = 18.8, 19.4, 27.9, 126.3, 126.4, 127.3, 128.0, 128.3, 128.5, 129.0, 129.8, 130.2, 135.3, 135.9, 137.5, 140.2, 140.4; HRMS (EI⁺): Calcd for C₁₉H₂₀, M⁺ 248.1565. Found m/z 248.1564.

(Z)-1-(4-Chlorophenyl)-2-(2-methylphenyl)buta-1,3-diene (3da)

IR (KBr): 3002, 2921, 1584, 1487, 1455, 1090 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 2.09 (3H, s), 4.70 (1H, d, J = 17.1 Hz), 5.14 (1H, d, J = 11.1 Hz), 6.58 (1H, s), 6.71 (1H, dd, J = 17.1, 10.2 Hz), 6.73–6.82 (2H, m), 7.00–7.10 (3H, m), 7.19–7.35 (3H, m); ¹³C NMR (75 MHz, CDCl₃): δ = 19.3, 116.7, 126.6, 127.9, 128.5, 129.5, 130.2, 130.3, 130.6, 132.8, 135.5, 136.2, 137.1, 140.9, 141.9; HRMS (EI⁺): Calcd for C₁₇H₁₅Cl, M⁺ 254.0862. Found m/z 254.0860.

(Z)-1-(4-Methoxyphenyl)-2-(2-methylphenyl)buta-1,3-diene (3ea)
Hz), 6.58 (1H, s), 6.60–6.84 (5H, m), 7.06 (1H, d, $J = 6.6$ Hz), 7.18–7.30 (3H, m); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 19.1$, 55.1, 113.6, 114.7, 126.3, 127.4, 129.5, 129.6, 130.1, 130.2, 131.0, 136.3, 137.5, 139.0, 141.2, 158.6; HRMS (EI$^+$): Calcd for C$_{18}$H$_{18}$O, M$^+$ 250.1358. Found m/z 250.1356.

**$(E)$-1-Cyclohexyl-2-(2-methylphenyl)buta-1,3-diene (5aa)**

![Diagram](image)

IR (neat): 2924, 2850, 1631, 1592, 1487, 1448, 986, 909 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 1.03$–1.28 (3H, m), 1.28–1.42 (2H, m), 1.64–1.72 (1H, m), 1.72–1.80 (4H, m), 2.17 (3H, s), 2.55–2.65 (1H, m), 4.64 (1H, d, $J = 17.5$ Hz), 5.09 (1H, d, $J = 10.6$ Hz), 5.24 (1H, d, $J = 9.4$ Hz), 6.91 (1H, dd, $J = 17.2$, 10.6 Hz), 7.05 (1H, d, $J = 7.1$ Hz), 7.12–7.23 (3H, m); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 19.5$, 25.9, 26.0, 33.3, 36.6, 116.2, 125.3, 126.8, 129.6, 130.0, 133.0, 136.3, 137.6, 139.1, 141.1; HRMS (EI$^+$): Calcd for C$_{17}$H$_{22}$, M$^+$ 226.1722. Found m/z 226.1704.

**$(E)$-3-(2-Methylphenyl)octa-1,3-diene (5ba)**

![Diagram](image)

IR (neat): 3015, 2957, 1593, 1487, 1456, 1379, 1044 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 0.95$ (3H, t, $J = 7.1$ Hz), 1.35–1.51 (4H, m), 2.19 (3H, s), 2.31–2.38 (2H, m), 4.66 (1H, d, $J = 17.2$, Hz), 5.10 (1H, d, $J = 10.6$ Hz), 5.41 (1H, t, $J = 7.7$ Hz), 6.91 (1H, d, $J = 17.2$, 10.6 Hz), 7.06 (1H, d, $J = 7.1$ Hz), 7.13–7.24 (3H, m); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 14.2$, 19.8, 22.6, 27.5, 32.1, 116.4, 125.5, 127.0, 129.8, 130.2, 133.0, 133.5, 136.5, 139.6, 141.4; HRMS (EI$^+$): Calcd for C$_{15}$H$_{20}$, M$^+$ 200.1565. Found m/z 200.1572.
References and Notes


10. An alternative mechanism involving allylic 1,3-migration of rhodium with the intermediate B and subsequent b-elimination of Rh(I)–OH is also conceivable. However, it is difficult to rationalise the stereoselective formation of (Z)-isomer with this alternative mechanism.

11. For regioselective carbopalladation onto an allene moiety from the less-hindered


Rhodium-Catalyzed Reaction of 1-Alkenylboronates with Aldehydes Leading to Allylation Products

Abstract: 1-Alkenylboronates perform the role of an allylating reagent. Their reaction with aldehydes in the presence of a cationic rhodium(I)/dppm catalyst results in a highly diastereoselective production of anti-configured homoallylic alcohols.
**Introduction**

An allylation reaction of carbonyl compounds with $\gamma$-substituted allylboron reagents is one of the most reliable procedures for the regio- and diastereoselective synthesis of homoallylic alcohols, and hence, is widely used in organic synthesis.\(^1\) Since the stereochemistry of the C–C double bond of a substituted allylboron reagent dictates the stereochemistry of the resultant homoallylic alcohols, it is crucial to obtain stereochemically defined $\gamma$-substituted allylboron reagents. Conventional preparative methods of allylboron reagents include 1) the substitution reaction of boron compounds with allylmetal reagents and 2) the substitution reaction of halomethylboron compounds with alkenylmetal reagents. Recently, different approaches\(^2\)–\(^7\) have been developed to address the issue associated with the lability of allylboron reagents towards hydrolysis, which often hamper chromatographic isolation of isomers; a substituted allylboron reagent is generated *in situ* and is immediately subjected to a reaction with a carbonyl compound. For example, a ruthenium(IV)-catalyzed cross-metathesis reaction of 2-propenylboronate and an alkene generates a (E)-$\gamma$-substituted allylboronate and the following addition of an aldehyde to the reaction mixture prompts an allylation reaction to furnish a homoallylic alcohol with moderate to high *anti* selectivity.\(^3\) A palladium(0)-catalyzed substitution reaction of an allylic alcohol with diboronic acid generates a (E)-$\gamma$-substituted allylboronic acid, which reacts with a coexisting aldehyde to give a homoallylic alcohol with high *anti* selectivity.\(^4\) Hydroboration of an allene with Soderquist borane (10-TMS-9-BBD-H) generates a (Z)-$\gamma$-substituted allylborane and the following addition of an aldehyde produces a homoallylic alcohol with moderate to high *syn* selectivity.\(^5\) The author envisaged that an alkene isomerization reaction\(^8\) could be utilized for generation of $\gamma$-substituted allylboronates (2-alkenylboronates) from 1-alkenylboronates, which were readily accessible by hydroboration of terminal alkynes. Iridium(III) and nickel(0) complexes are known to catalyze such isomerization reactions.\(^9\) However, the substrates have been limited to 3-alkoxy- or 3-siloxy-1-alkenylboronates, and it is supposed that the oxygen substituent at the 3-position directs the isomerization, as is the case with allylic ether/vinyl ether isomerization. There has been no report about the use of simple 1-alkenylboron compounds as the surrogate for 2-alkenylboron reagents. In this chapter, it is described a one-pot allylation reaction of aldehydes with 1-alkenylboronates, which provides a convenient and straightforward synthetic method of stereo-defined homoallylic alcohols from terminal alkynes and aldehydes.
Results and discussions

A reaction of 4-chlorobenzaldehyde (1a) with (E)-1-pentenyloboronic acid (2a) was initially examined in the presence of a rhodium(I) catalyst (Figure 1). As reported by Miyaura et al.,10 4-chlorophenyl penty ketone (4aa) was isolated in 80% yield when 1a (1.0 equiv) was treated with (E)-2a (1.5 equiv) in the presence of [Rh(OH)(cod)]2 (2.5 mol%) and dppf (5 mol%) in 1,4-dioxane/H2O (6:1, 2ml) for 12 h at 100 °C. An alkenylrhodium(I) species, generated in situ by transmetallation between the rhodium(I) complex and (E)-2a, adds to the aldehyde 1a to give the allylic alcohol I. Next, alkene isomerization and keto/enol tautomerization follow to afford 4aa.

It was further investigated reaction conditions in detail using (E)-1-pentenyloboronic acid (2a) or its ester (E)-3a to find reaction conditions under which a different product, homoallylic alcohol 5aa, was selectively obtained as the C–C bond forming product. When 1a (1.0 equiv) was treated with (E)-1-pentenyloboronic pinacolate (3a, 1.5 equiv) in the presence of [Rh(nbd)(CH3CN)]SbF6 (5 mol%) and dppm (5 mol%)11 in 1,2-dichloroethane at 90 °C for 12 h (conditions B), 1-(4-chlorophenyl)-2-ethylbut-3-en-1-ol (5aa) was isolated in 86% yield with fair diastereoselectivity (anti/syn = 85:15). The formation of the homoallylic alcohol 5aa is accounted for by the following pathway (Figure 1, bottom). The rhodium(I) catalyst promotes alkene isomerization of (E)-3a rather than transmetallation from boron to rhodium, generating 2-pentenyloborinate II. Then, addition of II to 1a spontaneously occurs via a six-membered chair-like transition state to produce 5aa. The anti selectivity observed with 5aa suggests the preferential formation of the (E)-isomer of
2-pentenylboronate II in the isomerization process or the preferential carbonyl addition of the (E)-isomer over the (Z)-isomer of II (vide infra).\textsuperscript{13} Whereas the transmetallation/carbonyl addition precede alkene isomerization under conditions A using the hydroxorhodium(I) species in protic media, alkene isomerization precedes the carbonyl addition under conditions B. We assume that, under conditions B lacking a hydroxide ligand on rhodium and nucleophilic H\textsubscript{2}O in the media, transmetallation is retarded and isomerization is facilitated on a cationic rhodium center.

Thus, it proved that simple 1-alkenylboronates could act as the surrogate for 2-alkenylboron reagents. The (E)-isomers of other 1-alkenylboronates 3b–e, which were readily accessible by simple cis-hydroboration of terminal alkynes with pinacolborane,\textsuperscript{14} were subjected to the rhodium(I)-catalyzed allylation reaction of 1a (Table 1). (E)-1-Butenylboronate 3b and (E)-3-cyclopentyl-1-propenylboronates 3c gave the corresponding homoallylic alcohols 5ab and 5ac, respectively, with good

---

**Table 1. Allylation reaction of 1a with alkenylboronates 3b–h.\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textsuperscript{2}</th>
<th>t (h)</th>
<th>Yield (%)\textsuperscript{b}</th>
<th>anti/syn\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(E)-3b Me</td>
<td>12</td>
<td>71</td>
<td>89:11</td>
</tr>
<tr>
<td>2</td>
<td>(E)-3c c-Pent</td>
<td>24</td>
<td>89\textsuperscript{d}</td>
<td>88:12</td>
</tr>
<tr>
<td>3</td>
<td>(E)-3d i-Pr</td>
<td>24</td>
<td>86\textsuperscript{e}</td>
<td>96:4</td>
</tr>
<tr>
<td>4</td>
<td>(E)-3e Ph</td>
<td>12</td>
<td>91</td>
<td>96:4</td>
</tr>
<tr>
<td>5</td>
<td>(Z)-3a Et</td>
<td>12</td>
<td>86</td>
<td>96:4</td>
</tr>
<tr>
<td>6</td>
<td>(Z)-3b Me</td>
<td>24</td>
<td>91</td>
<td>98:2</td>
</tr>
<tr>
<td>7</td>
<td>(Z)-3c c-Pent</td>
<td>12</td>
<td>89\textsuperscript{d}</td>
<td>96:4</td>
</tr>
<tr>
<td>8</td>
<td>(Z)-3d i-Pr</td>
<td>12</td>
<td>91\textsuperscript{e}</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>9</td>
<td>(Z)-3e Ph</td>
<td>12</td>
<td>95</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>10</td>
<td>(Z)-3f (CH\textsubscript{2})\textsubscript{3}OTBS</td>
<td>12</td>
<td>91</td>
<td>97:3</td>
</tr>
<tr>
<td>11</td>
<td>(Z)-3g (CH\textsubscript{2})\textsubscript{3}OBz</td>
<td>12</td>
<td>97</td>
<td>99:1</td>
</tr>
<tr>
<td>12</td>
<td>(Z)-3h (CH\textsubscript{2})\textsubscript{3}N(Phth)</td>
<td>12</td>
<td>93</td>
<td>96:4</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conditions: 1a (0.4 mmol), 3 (0.6 mmol), [Rh(nbd)(CH\textsubscript{3}CN)\textsubscript{2}]SbF\textsubscript{6} (5 mol%), and dppm (5 mol%) in 1,2-dichloroethane (4 ml) for 12 h at 90 °C.

\textsuperscript{b} Isolated yields.

\textsuperscript{c} Determined by \textsuperscript{1}H NMR.

\textsuperscript{d} Using 3c (1.2 mmol) and 10 mol% of [Rh(nbd)(CH\textsubscript{3}CN)\textsubscript{2}]SbF\textsubscript{6}/dppm.

\textsuperscript{e} Using 3d (1.2 mmol) and 7.5 mol% of [Rh(nbd)(CH\textsubscript{3}CN)\textsubscript{2}]SbF\textsubscript{6}/dppm.
diastereoselectivities ($anti/syn = 88:12 \sim 89:11$) (entries 1 and 2). The reaction of $(E)$-3-isopropyl- and $(E)$-3-phenyl-1-propenylboronates 3d and 3e having a bulkier substituent at the 3-position showed a higher diastereoselectivity ($vide infra$) ($anti/syn = 96:4$, entries 3 and 4).

It was also examined the use of the corresponding $(Z)$-isomers of 3a–e, which were accessible by the rhodium(I)-catalyzed trans-hydroboration reaction of terminal alkynes developed by Miyaura et al. The $(Z)$-isomers underwent an allylation reaction with 1a to give the homoallylic alcohols 5aa–ae in comparable or better yields (entries 5–9). It was noteworthy that all $(Z)$-isomers of 3a–e showed much higher diastereoselectivities ($anti/syn = 94:6 \sim >99:1$) than the corresponding $(E)$-isomers. Thus, $(Z)$-1-alkenylboronates proved better surrogates for $(E)$-2-alkenylboronates in terms of reactivity as well as stereoselectivity. In addition, functionalized $(Z)$-1-alkenylboronates 3f–h having siloxy, benzyloxy, and 1,3-dioxoisooindolin-2-yl groups in the alkyl chain also afforded $anti$ homoallylic alcohols 5af–ah stereoselectively in high yields (entries 10–12). Furthermore, the reaction with 3-methyl-1-butenylboronate 3i and 2-methyl-1-propenylboronate 3j proceeded in an analogous manner to give the homoallylic alcohols 5ai and 5aj in high yields, respectively (Eqs 1 and 2).

Next, the scope of aldehydes was examined using $(Z)$-3a (Table 2). An electronically and sterically diverse array of aromatic aldehydes 1b–g were suitably reactive to give the homoallylic alcohols 5ba–ga in yields ranging from 82% to 96% with high diastereoselectivities ($anti/syn = 95:5 \sim 99:1$, entries 1–6). In addition, aliphatic aldehydes such as 3-phenylpropanal (1h) and cyclohexanecarbaldehyde (1i) also participated in the reaction. Slightly lower diastereoselectivities were observed with aliphatic aldehydes probably because they were less reactive than aromatic aldehydes and required a longer reaction time, during which the $E/Z$ ratio of the intermediate
2-pentenylboronate could decrease (*vide infra*) (entries 7 and 8). On the other hand, ketones such as acetophenone and methyl phenethyl ketone failed to undergo the allylation reaction with (Z)-3a.

The following experiments were carried out in order to obtain mechanistic insights into the isomerization/addition process. First, a 1:1 mixture of (E)-isomer (1.5 equiv) and (Z)-isomer (1.5 equiv) of crotylboronate 6b was reacted with 1a (1.0 equiv) to compare their reactivities. The *anti/syn* ratio of the resulting homoallylic alcohol 5ab (>95% yield) was 58:42, suggesting that (E)- and (Z)-isomers added to the aldehyde 1a at comparable rates (Eq 3).

![Chemical structure](attachment:image.png)
Secondly, (E)- and (Z)-1-butenylboronates 3b and (E)-crotylboronate 6b were separately treated with a catalytic amount of the rhodium(I) complex (90 °C, 1,2-dichloroethane) in the absence of the aldehyde 1a, and their isomerization reaction was monitored by 1H NMR after 20 min and 6 h (Scheme 1). They all underwent isomerization in terms of both the stereochemistry and the position of the carbon–carbon double bond to give a mixture of (E)- and (Z)-3b and (E)- and (Z)-6b. After 6 h, a mixture of an almost identical composition [(E)-3b:(Z)-3b:(E)-6b:(Z)-6b = 64:6:19:11] resulted from (E)- and (Z)-3b and (E)-6b. This ratio reached after 6 h would be an equilibrium ratio at 90 °C reflecting their thermodynamic stabilities. In the meantime, however, (Z)-3b isomerized faster and more selectively in favor for (E)-6b than (E)-3b; after 20 min starting from (E)-3b, the ratio of (E)-3b:(Z)-3b:(E)-6b:(Z)-6b was 85:6:6:3, which meant that only 15% of (E)-3b underwent isomerization and that the E:Z ratio of the resulting 6b was 67:33. In contrast, after 20 min starting from (Z)-3b, the ratio of (E)-3b:(Z)-3b:(E)-6b:(Z)-6b was 28:20:49:3, which meant that 80% of (Z)-3b isomerized and that the E:Z ratio of the resulting 6b was >95:5. Thus, the most likely scenario of the highly stereoselective production of anti homoallylic alcohol 5ab from (Z)-3b is as follows; the double bond isomerization of (Z)-3b occur on a cationic rhodium center in a stereoselective manner to produce (E)-6b, which immediately reacts.
with 1a via a six-membered transition state to afford anti-configured 5ab.

It is assumed that the isomerization of 3b proceeds through \( \pi \)-allyl rhodium intermediates A–D\(^{16} \) and is reversible (Figure 2). When starting from (Z)-3b, the intermediate A would be significantly more stable than the intermediate B due to steric and the formation of (E)-6b is kinetically favored. The resultant (E)-6b immediately reacts with the aldehyde 1a in a stereospecific way giving anti-5ab. Although (E)-6b is also more stable than (Z)-6b, the energetic difference would be less than that between the intermediate A and B. Therefore, when the addition reaction to a carbonyl compound is slow, the initial kinetic preference for (E)-6b over (Z)-6b gradually decreases. This can account for the lower anti/syn selectivity observed with the products of the reaction with aliphatic aldehydes (Table 2, entries 7 and 8). When starting from (E)-3b, the intermediate C is more stable than the intermediate D, but the energetic difference is less than that between the intermediates A and B. Therefore, the E/Z selectivity of 6b under kinetic conditions is not as high as in the case starting from (Z)-3b. As shown in Table 1 (entries 3 and 4), (E)-3d and (E)-3e having isopropyl and phenyl groups at the 3-position exhibited higher anti-selectivity than (E)-3b having a methyl group at the 3-position. This can be also explained by an increase in the energetic difference between intermediates corresponding to C and D.

Figure 2. Proposed isomerization pathways through \( \pi \)-allyl rhodium intermediates.
Scheme 2. A one pot sequence via hydroboration/isomerization/allylation reaction.

Finally, a one-pot diastereoselective synthesis of homoallylic alcohols starting from terminal alkynes was carried out to demonstrate the practical convenience of the present method (Scheme 2). Treatment of terminal alkynes (7, 2.2–3.3 equiv) with pinacolborane (8a, 2.0–3.0 equiv) in the presence of dicyclohexylborane (20 mol%) generated (E)-1-alkenylboronates. Then, 4-chlorobenzaldehyde (1a, 1.0 equiv) and a cationic rhodium(I)/dppm catalyst (5–7.5 mol%) were added to the reaction mixture to cause an isomerization/allylation reaction. After the mixture was stirred at 90 °C for 12–24 h, the corresponding homoallylic alcohols were isolated in high yields with good to high diastereoselectivities. Interestingly, even the ketones successfully participated in the one-pot reaction when 9-borabicyclo[3.3.1]nonane (8b, 9-BBN-H) was used for the initial hydroboration.
reaction since the resulting allylborane intermediate was more reactive than allylboronic esters.\textsuperscript{17}

**Conclusion**

In summary, the author has been demonstrated that 1-alkenylboronates, which are readily synthesized by hydroboration of terminal alkynes,\textsuperscript{14,15} act as the synthetic equivalent to $\gamma$-substituted allylboronates in the presence of a cationic rhodium(I) catalyst. The present reaction provides a unique method for the diastereoselective synthesis of functionalized homoallylic alcohols.
Experimental Section

General. All reactions were carried out with standard Schlenk techniques under an argon atmosphere. IR measurements were performed on a Shimadzu FTIR-8100 spectrometer or a Horiba FT-720. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AVANCE 500 ($^1$H at 500 MHz and $^{13}$C at 125 MHz) spectrometer using tetramethylsilane ($^1$H, $\delta = 0.00$) and CDCl$_3$ ($^{13}$C, $\delta = 77.0$) as an internal standard. High-resolution mass spectra were recorded on a JEOL JMS-SX102A, a JEOL JMS-HX110A, or a Thermo Scientific Exactive™ spectrometer. Flash column chromatography was performed with silica gel 60 N (Kanto), diol-silica gel DIOL MB 100–40/75 (Fuji Silysia Chemical Ltd.), or NH-silica gel NH-DM1020 (Fuji Silysia Chemical Ltd.).

Materials. The dehydrated solvents were purchased and used without further purification. All of aldehydes and ketone were obtained from commercial suppliers and used without further purification. (E)-Pentenylboronic acid (2a), 1-alkenylboronic pinacolate [(E)-3a, (E)-3c, and 3j], and (E)-crotylboronic pinacolate (6b) were purchased and used without further purification. [Rh(OH)(cod)]$_2$ was prepared according to the literature procedure.$^{18}$ The other materials were prepared by the following methods:

1. [Rh(nbd)(CH$_3$CN)$_2$]SbF$_6$

   ![Diagram of Rh(nbd)(CH$_3$CN)$_2$]SbF$_6$

   To a solution of [RhCl(nbd)$_2$] (1.3 g, 2.82 mmol) in CH$_3$CN (8.5 mL) and CH$_2$Cl$_2$ (35 mL) was added AgSbF$_6$ (2.03 g, 5.92 mmol). The reaction mixture was stirred at room temperature for 30 min. Then, the precipitate was removed by filtration through Celite®. The filtrate was poured into Et$_2$O (180 mL), and the resultant precipitate was collected by filtration and dried under reduced pressure to give [Rh(nbd)(CH$_3$CN)$_2$]SbF$_6$ (2.10 g; 73% yield) as a yellow crystal.

   IR (KBr): 3004, 2952, 2897, 2256, 1303, 1171, 935, 667 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 1.30$ (t, $J = 1.6$ Hz, 2H), 2.32 (s, 6H), 3.91–3.94 (m, 2H), 4.31 (q, $J = 2.3$ Hz, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 2.6$, 51.3 (d, $J_{\text{Rh-C}} = 2.6$ Hz), 60.5 (d, $J_{\text{Rh-C}} = 10.1$ Hz), 62.5 (d, $J_{\text{Rh-C}} = 6.3$ Hz), 123.8; Anal. Calcd for C$_{11}$H$_{14}$F$_6$N$_2$RhSb: C, 25.76; H, 2.75; N, 5.46. Found: C, 25.65; H, 2.64; N, 5.36.
2. (E)-Alkenylboronic Pinacolate

The pinacolates (E)-3b and (E)-3e were synthesized by condensation of the corresponding commercially available boronic acids and pinachol. The pinacolates (E)-3d and 3j were synthesized by cis-hydroboration of terminal alkynes with pinacolborane developed by Hoshi et al.\textsuperscript{14}

\textbf{(E)-But-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((E)-3b)}

![Image](image1)

To an oven-dried flask was added (E)-1-butenylboronic acid (0.83 g, 8.31 mmol), pinacol (0.98g, 8.31 mmol), MgSO\textsubscript{4} (2.50 g, 20.8 mmol), CH\textsubscript{2}Cl\textsubscript{2} (8 mL). The reaction mixture was stirred at room temperature overnight. Then, MgSO\textsubscript{4} was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by flash silica gel column chromatography (hexane:ethyl acetate = 97:3) to give (E)-3b (1.38 g, 91% yield). 

\textbf{IR (neat): 2978, 1638, 1401, 1325, 1260, 1211, 1146, 1021 cm\textsuperscript{-1}}; \textbf{\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): }\delta = 1.02 (t, J = 7.5 Hz, 3H), 1.27 (s, 12H), 2.13–2.21 (m, 2H), 5.44 (dt, J = 18.0 Hz, 1.7 Hz, 1H), 6.70 (dt, J = 18.0 Hz, 5.9 Hz, 1H); \textbf{\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): }\delta = 12.3, 24.7, 28.5, 82.9, 117.3 (br), 156.0; \textbf{HRMS (EI\textsuperscript{+}): }Calcd for C\textsubscript{10}H\textsubscript{19}O\textsubscript{2}B (M\textsuperscript{+}) 182.1478. Found m/z 182.1474.

\textbf{(E)-3-Phenylprop-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((E)-3e)}

![Image](image2)

To an oven-dried flask was added (E)-3-phenylprop-1-enyl-boronic acid (1.17 g, 7.22 mmol), pinacol (0.90 g, 7.58 mmol), and benzene (30 mL). The reaction mixture was stirred at reflux temperature for 6 h, during which H\textsubscript{2}O was removed azeotropically. Then, the solvent was removed under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane:ethyl acetate = 95:5 ~ 90:10) to give (E)-3e (1.28 g, 73% yield).

\textbf{IR (neat): 2979, 2931, 1637, 1495, 1396, 1363, 1323, 1146 cm\textsuperscript{-1}}; \textbf{\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): }\delta = 1.25 (s, 12H), 3.48 (dd, J = 6.4 Hz, 1.4 Hz, 2H), 5.44 (dt, J = 17.9 Hz, 1.6 Hz, 1H), 6.76 (dt, J = 17.9 Hz, 6.3 Hz, 1H), 7.14–7.22 (m, 3H), 7.26–7.31 (m, 2H); \textbf{\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): }\delta = 24.7, 42.2, 83.0, 119.7 (br), 126.1, 128.4, 128.9, 139.0,
152.4; HRMS (APCI): Calcd for C\textsubscript{13}H\textsubscript{25}O\textsubscript{2}B ([M+H]\textsuperscript{+}) 245.1707. Found m/z 245.1704.

**\((E)-4\text{-Methylnpent-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (} \((E)-3d\)**

\[ \text{\begin{center}
\includegraphics[width=0.2\textwidth]{diagram}
\end{center}} \]

To an oven-dried flask was added Cy\textsubscript{2}BH (0.1 M in THF, 2.5 mL, 0.25 mmol). The solvent was removed under reduced pressure, and the flask was filled with argon. Then, 4-methyl-1-pentyne (403 mg, 4.91 mmol) and pinacolborane (0.71 mL, 4.91 mmol) were added. The reaction mixture was stirred at room temperature for 16 h under neat conditions. The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 99:1) to give \((E)-3d\) (573 mg, 56% yield).

IR (neat): 2956, 2871, 1639, 1464, 1360, 1317, 1271, 1242, 1144 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta = 0.90 \text{ (d, } J = 6.7 \text{ Hz, 6H), 1.27 (s, 12H), 1.65–1.76 (m, 1H), 2.04 (dt, } J=1.4 \text{ Hz, 6.8 Hz, 2H), 5.41 (dt, } J=17.9 \text{ Hz, 1.5 Hz, 1H), 6.60 (dt, } J=17.9 \text{ Hz, 6.9 Hz, 1H); 13C NMR (125 MHz, CDCl\textsubscript{3}): } \text{δ} = 22.4, 24.8, 27.7, 45.5, 82.9, 119.8 \text{ (br), 133.5;} \text{ HRMS (EI\textsuperscript{+}): Calcd for C}_{12}H_{23}O_{2}B (M\textsuperscript{+}) 210.1791. Found m/z 210.1790.

**\((E)-3\text{-Methyl-but-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (} 3i\)**

\[ \text{\begin{center}
\includegraphics[width=0.2\textwidth]{diagram}
\end{center}} \]

The compound 3i was prepared according to the same procedure as that of the synthesis of \((E)-3d\). The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 20:1) to give 3i (84% yield).

IR (neat): 2979, 2932, 2870, 1638, 1464, 1356, 1323, 1215, 1148 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta = 1.01 \text{ (d, } J = 6.8 \text{ Hz, 6H), 1.27 (s, 12H), 2.30–2.41 (m, 1H), 5.38 (dd, } J = 18.1 \text{ Hz, 1.5 Hz, 1H), 6.62 (dd, } J = 18.1 \text{ Hz, 6.1 Hz, 1H); 13C NMR (125 MHz, CDCl\textsubscript{3}): } \text{δ} = 21.4, 24.7, 33.5, 82.9, 115.3 \text{ (br), 160.9;} \text{ HRMS (EI\textsuperscript{+}): Calcd for C}_{11}H_{21}O_{2}B (M\textsuperscript{+}) 196.1635. Found m/z 196.1642.

3. **(Z)-Alkenylboronic Pinacolate**

The (Z)-alkenylboronic pinacolates except (Z)-3b were prepared by a rhodium(I)-catalyzed trans-hydroboration of terminal alkynes with pinacolborane developed by Miyaura et al.\textsuperscript{15} The pinacolate (Z)-3b was prepared by borylation of
(Z)-butenylbromide\textsuperscript{19} because 1-butyne is a low boiling substance.

**(Z)-Pent-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((Z)-3a)**

\[
\begin{array}{c}
\text{B} \\
\text{O} \\
\text{O}
\end{array}
\]

To a two-neck flask was charged \([\text{RhCl(cod)}]_2\) (0.148 g, 0.300 mmol) and Cy\textsubscript{3}PHBF\textsubscript{4} (0.442 g, 1.20 mmol). The flask was evacuated and refilled with argon. Then, cyclohexane (60 mL), Et\textsubscript{3}N (13.94 mL, 100 mmol), and pinacolborane (2.90 mL, 20.0 mmol) were added at room temperature. After 1 h, 1-pentyne (3.94 mL, 40 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 4 h. The solvent was evaporated, and the residue was purified by flash silica gel column chromatography (hexane:ethyl acetate = 100:0 ~ 97:3) to give (Z)-3a (1.95 g, 50\% yield).

IR (neat): 2978, 2931, 1628, 1425, 1373, 1321, 1147 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta = 0.91\) (t, \(J = 7.5\) Hz, 3H), 1.27 (s, 12H), 1.37–1.46 (m, 2H), 2.37 (dq, \(J = 1.3\) Hz, 7.4 Hz, 2H), 5.34 (dt, \(J = 13.5\) Hz, 1.3 Hz, 1H), 6.37–6.48 (m, 1H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}, the boron-bound carbon was not detected due to quadrupolar relaxation): \(\delta = 13.5, 22.6, 24.8, 34.2, 82.7, 154.9\); HRMS (APCI): Calcd for C\textsubscript{11}H\textsubscript{22}O\textsubscript{2}B ([M+H]\textsuperscript{+}) 197.1707. Found m/z 197.1705.

**(Z)-But-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((Z)-3b)**

\[
\begin{array}{c}
\text{B} \\
\text{O} \\
\text{O}
\end{array}
\]

To a solution of (Z)-butenylbromide\textsuperscript{19} (2.90 g, 21.48 mmol) in Et\textsubscript{2}O (100 mL) was added tert-BuLi (1.6 M in pentane, 26.9 mL, 43.0 mmol) at –75°C. After 1 h, triisopropylborate (5.95 mL, 25.8 mol) was added, and the reaction temperature was gradually raised to 5 °C. After 4 h, pinacol (3.05 g, 25.8 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with aqueous NH\textsubscript{4}Cl. The organic layer was separated and washed with water and brine, and dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed under reduced pressure and the residue was purified by flash silica gel column chromatography (hexane:ethyl acetate = 97:3 ~ 95:5) to give (Z)-3b (1.40 g, 36 % yield).

IR (neat): 2978, 2935, 2873, 1630, 1423, 1373, 1329, 1261, 1147 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta = 0.99\) (t, \(J = 7.6\) Hz, 3H), 1.27 (s, 12H), 2.35–2.43 (m, 2H), 5.29 (dt,
$J=13.5$ Hz, 1.3 Hz, 1H), 6.37–6.49 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$, the boron-bound carbon was not detected due to quadrupolar relaxation): $\delta = 14.2$, 24.8, 25.7, 82.8, 156.7; HRMS (APCI): Calcd for C$_{10}$H$_{20}$O$_2$B ([M+H]$^+$) 183.1551. Found m/z 183.1550.

(Z)-3-Cyclopentylprop-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((Z)-3c)

(Z)-3c was prepared according to the same procedure as that of the synthesis of (Z)-3a. The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 100:0 ~ 98:2) to give (Z)-3c (43 % yield).

IR (neat): 2978, 2949, 2868, 1628, 1425, 1373, 1323, 1259, 1146 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 1.13$–1.23 (m, 2H), 1.26 (s, 12H), 1.45–1.54 (m, 2H), 1.56–1.65 (m, 2H), 1.66–1.74 (m, 2H), 1.81–1.19 (m, 1H), 2.40 (dt, $J = 1.2$ Hz, 7.4 Hz, 2H), 5.33 (dt, $J = 13.5$ Hz, 1.3 Hz, 1H), 6.38–6.50 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 24.8$, 25.0, 32.0, 38.2, 39.8, 82.7, 117.9 (br), 154.4; HRMS (APCI): Calcd for C$_{14}$H$_{26}$O$_2$B ([M+H]$^+$) 237.2020. Found m/z 237.2016.

(Z)-4-Methylpent-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((Z)-3d)

(Z)-3d was prepared according to the same procedure as that of the synthesis of (Z)-3a. The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 100:0 ~ 98:2) to give (Z)-3d (58 % yield).

IR (neat): 2979, 2958, 2871, 1628, 1425, 1373, 1321, 1259, 1147 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 0.90$ (d, $J = 6.7$ Hz, 6H), 1.27 (s, 12H), 1.60–1.70 (m, 1H), 2.27–2.32 (m, 2H), 5.37 (dt, $J = 13.6$ Hz, 1.3 Hz, 1H), 6.40–6.49 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$, the boron-bound carbon was not detected due to quadrupolar relaxation): $\delta = 22.2$, 24.8, 28.5, 41.1, 82.7, 153.8; HRMS (EI$^+$): Calcd for C$_{12}$H$_{23}$O$_2$B (M$^+$) 210.1791. Found m/z 210.1794.
(Z)-3-Phenylprop-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((Z)-3e)

(Z)-3e was prepared according to the same procedure as that of the synthesis of (Z)-3a. The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 100:0 ~ 99:1) to give (Z)-3e (30 % yield).

IR (neat): 2979, 2931, 1628, 1419, 1373, 1325, 1261, 1144 cm^{-1}; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 1.30\) (s, 12H), 3.76 (d, \(J = 7.7\) Hz, 2H), 5.43 (dt, \(J = 13.3\) Hz, 1.3 Hz, 1H), 6.50–6.59 (m, 1H), 7.17–7.25 (m, 3H), 7.26–7.32 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), the boron-bound carbon was not detected due to quadrupolar relaxation): \(\delta = 24.9, 38.7, 83.0, 125.9, 128.4, 128.6, 140.7, 152.7\); HRMS (EI\(^+\)): Calcd for C\(_{15}\)H\(_{21}\)O\(_2\)B (M\(^+\)) 244.1635. Found m/z 244.1633.

(Z)-6-tert-Butyldimethylsilyloxyhex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((Z)-3f)

(Z)-3f was prepared according to the same procedure as that of the synthesis of (Z)-3a. The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 100:0 ~ 98:2) to give (Z)-3f (40 % yield).

IR (neat): 2931, 2858, 1630, 1423, 1373, 1319, 1257, 1146, 1103 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 0.05\) (s, 6H), 0.89 (s, 9H), 1.26 (s, 12H), 1.38–1.47 (m, 2H), 1.50–1.58 (m, 2H), 2.41 (dq, \(J = 1.2\) Hz, 7.5 Hz, 2H), 3.61 (t, \(J = 6.6\) Hz, 2H), 5.34 (dt, \(J = 13.5\) Hz, 1.2 Hz, 1H), 6.38–6.47 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), the boron-bound carbon was not detected due to quadrupolar relaxation): \(\delta = -5.3, 18.4, 24.8, 25.6, 26.0, 31.9, 32.3, 63.1, 82.8, 155.0\); HRMS (APCI): Calcd for C\(_{18}\)H\(_{38}\)O\(_3\)BSi ([M+H]\(^+\)) 341.2678. Found m/z 341.2668.

(Z)-6-Benzoyloxyhex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((Z)-3g)
(Z)-3g was prepared according to the same procedure as that of the synthesis of (Z)-3a. The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 100:0 ~ 97:3) to give (Z)-3g (32 % yield).

IR (neat): 2979, 2935, 2862, 1720, 1628, 1423, 1373, 1317, 1275, 1115 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 1.26\) (s, 12H), 1.52–1.60 (m, 2H), 1.76–1.83 (m, 2H), 2.48 (dq, \(J = 1.2\) Hz, 7.5 Hz, 2H), 4.34 (t, \(J = 6.7\) Hz, 2H), 5.38 (dt, \(J = 13.4\) Hz, 1.2 Hz, 1H), 6.39–6.49 (m, 1H), 7.41–7.46 (m, 2H), 7.53–7.58 (m, 1H), 8.02–8.06 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), the boron-bound carbon was not detected due to quadrupolar relaxation): \(\delta = 24.8, 25.8, 28.0, 31.6, 64.9, 82.9, 128.3, 129.5, 130.5, 132.8, 154.2, 166.7\); HRMS (APCI): Calcd for C\(_{19}\)H\(_{28}\)O\(_4\)B ([M+H]+) 331.2075. Found m/z 331.2068.

(Z)-6-Phthalimidylhex-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((Z)-3h)

![Z-3h](image)

To a two-neck flask was charged [RhCl(cod)]\(_2\) (0.065 g, 0.132 mmol) and Cy\(_3\)PHBF\(_4\) (0.194 g, 0.528 mmol). The flask was evacuated and refilled with argon. Then, cyclohexane (20 mL), Et\(_3\)N (6.13 mL, 44.0 mmol), and pinacolborane (1.28 mL, 8.80 mmol) were added at room temperature. After 1 h, a solution 6-phthalimido-1-hexyne (4.00 g, 17.6 mmol) in toluene (10 mL) was added in one portion. The reaction mixture was stirred at room temperature for 6 h. The solvent was evaporated, and the residue was purified by flash silica gel column chromatography (toluene:ethyl acetate = 100:0 ~ 90:10) to give (Z)-3h (1.22 g, 39% yield).

IR (KBr): 2981, 2937, 2866, 1707, 1628, 1404, 1373, 1333, 1259, 1144, 1045 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 1.25\) (s, 12H), 1.41–1.48 (m, 2H), 1.66–1.73 (m, 2H), 2.44 (dq, \(J = 1.2\) Hz, 7.5 Hz, 2H), 3.70 (t, \(J = 7.3\) Hz, 2H), 5.34 (dt, \(J = 13.5\) Hz, 1.1 Hz, 1H), 6.35–6.44 (m, 1H), 7.68–7.73 (m, 2H), 7.82–7.86 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\), the boron-bound carbon was not detected due to quadrupolar relaxation): \(\delta = 24.7, 26.6, 27.9, 31.5, 37.8, 82.7, 123.0, 132.1, 133.7, 154.1, 168.3\); HRMS (ESI\(^+\)): Calcd for C\(_{20}\)H\(_{27}\)O\(_4\)BN ([M+H]+) 356.2028. Found m/z 356.2021.
A Rhodium(I)-Catalyzed Reaction of 1-Alkenylboronate with Aldehydes or Ketone.

Compounds 4aa\textsuperscript{20}, 5ab\textsuperscript{21}, 5ae\textsuperscript{21}, 5ai\textsuperscript{22}, 5aj\textsuperscript{23}, 5ba\textsuperscript{24}, 5ia\textsuperscript{24}, 9ab\textsuperscript{25} had been already reported. Relative configurations of 5ab, 5ae, 5ba, 5ia and 9ab were identified as anti-form by comparison with the known literature. On the other hand, the relative configuration of 5aa, 5ac, 5ad, 5af, 5ag, 5ah, 5ca, 5da, 5ea, 5fa, 5ga, and 5ha were estimated by analogy.

1. A [Rh(OH)(cod)]\textsubscript{2}-Catalyzed Reaction of 4-Chlorobenzaldehyde (1a) with (E)-1-Butenyl-boronic Acid (Figure 1. Conditions A).

To an oven-dried side-arm tube was charged [Rh(OH)(cod)]\textsubscript{2} (2.3 mg, 0.005 mmol), dppf (5.5 mg, 0.01 mmol), 4-chlorobenzaldehyde (1a) (28.1 mg, 0.200 mmol), (E)-1-butylboronic acid (2a, 34.2 mg, 0.300 mmol). The tube was evacuated and refilled with argon three times. Then, 1,4-dioxane/H\textsubscript{2}O (2 mL) was added via syringe. After heating at 90 °C for 12 h, the reaction mixture was cooled at room temperature. The solution was passed through a pad of florisil\textsuperscript{®} (1.5 x 5 cm) and eluted with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash silica gel column chromatography (hexane:ethyl acetate = 95:5 ~ 90:10) to give 4aa (33.7 mg, 80% yield).

\begin{align*}
\text{1-(4-Chlorophenyl)hexan-1-one (4aa)}^{20}
\end{align*}

\begin{center}
\begin{tikzpicture}
\end{tikzpicture}
\end{center}

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta = 0.86–0.97\) (m, 3H), 1.32–1.40 (m, 4H), 1.68–1.78 (m, 2H), 2.93 (t, \(J = 7.5\) Hz, 2H), 7.41–7.46 (m, 2H), 7.88–7.92 (m, 2H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta = 13.9, 22.5, 24.0, 31.5, 38.5, 128.8, 129.5, 135.4, 139.3, 199.3\).

2. Typical Procedure for the Allylation Reaction of Aldehydes with 1-Alkenylboronates (Table 1, Entry 5, Conditions B).

To an oven-dried side-arm tube was charged [Rh(nbd)(CH\textsubscript{3}CN)\textsubscript{2}]SbF\textsubscript{6} (10.3 mg, 0.02 mmol) and dppm (7.7 mg, 0.02 mmol). The tube was evacuated and refilled with argon. Then, 1,2-dichloroethane (1 mL) was added via syringe. To the resulting orange solution was added a solution of 1a (56.2 mg, 0.40 mmol) and (Z)-3a (117.7 mg, 0.60 mmol) in 1,2-dichloroethane (3 mL). After heating at 90 °C for 12 h, the reaction mixture was cooled to room temperature. The mixture was passed through a pad of florisil\textsuperscript{®} (1.5 x 5 cm) and eluted with ethyl acetate (50 mL). The filtrate was concentrated under reduced
pressure and the residue was purified by flash diol-SiO$_2$ column chromatography (hexane:ethyl acetate = 97:3 ~ 90:10) to give 5aa (72.7 mg, 86% yield, anti/syn = 96:4). (1S*,2S*)-1-(4-Chlorophenyl)-2-ethylbut-3-en-1-ol (5aa)

\[
\text{IR (neat): } 3416, 2968, 1639, 1597, 1491, 1412, 1383, 1089 \text{ cm}^{-1}; \text{ } ^1\text{H NMR (500 MHz, CDCl}_3\text{): } \text{anti-form } \delta = 0.79 (t, J = 7.5 \text{ Hz, 3H}), 1.11–1.29 (m, 2H), 2.10–2.17 (m, 1H), 2.18 (d, J = 2.4 \text{ Hz, 1H}), 4.39 (dd, J = 7.9 \text{ Hz, 2.3 Hz, 1H}), 5.20 (ddd, J = 17.1 \text{ Hz, 1.9 Hz, 1H}), 5.29 (dd, J = 10.3 \text{ Hz, 1.9 Hz, 1H}), 5.62 (ddd, J = 17.1 \text{ Hz, 10.3 Hz, 9.3 Hz, 1H}), 7.25–7.29 (m, 2H), 7.39–7.33 (m, 2H); \text{ } ^13\text{C NMR (125 MHz, CDCl}_3\text{): } \text{anti-form } \delta = 11.7, 23.3, 54.6, 75.8, 119.3, 128.26, 128.32, 133.2, 138.6, 141.0; \text{HRMS (FAB\textsuperscript{+}): Calcd for C}_{12}\text{H}_{14}\text{OCl ([M–H]}\textsuperscript{+}) 209.0739. Found m/z 209.0741.
\]

(1S*, 2S*)-1-(4-Chlorophenyl)-2-methylbut-3-en-1-ol (5ab)

The crude mixture was purified by flash diol-SiO$_2$ column chromatography (hexane:ethyl acetate = 95:5 ~ 90:10) to give 5ab (71.2 mg, 91% yield, anti/syn = 98:2, Table 1, entry 6).

\[
\text{IR (neat): } 3423, 2949, 2866, 1489, 1412, 1308, 1192, 1088, 1053, 1009 \text{ cm}^{-1}; \text{ } ^1\text{H NMR (500 MHz, CDCl}_3\text{): } \text{anti-form } \delta = 0.87 (d, J = 6.8 \text{ Hz, 3H}), 2.15 (d, J = 2.6 \text{ Hz, 1H}), 2.39–2.47 (m, 1H), 4.35 (dd, J = 7.8 \text{ Hz, 2.6 Hz, 1H}), 5.17–5.23 (m, 2H), 5.72–5.82 (m, 1H), 7.25–7.29 (m, 2H), 7.30–7.34 (m, 2H); \text{ } ^13\text{C NMR (125 MHz, CDCl}_3\text{): } \text{anti-form } \delta = 16.4, 46.4, 77.1, 117.3, 128.2, 128.4, 133.3, 140.2, 140.8.
\]

(1S*, 2R*)-1-(4-Chlorophenyl)-2-cyclopentylbut-3-en-1-ol (5ac)

The crude mixture was purified by flash diol-SiO$_2$ column chromatography (hexane:ethyl acetate = 97:3 ~ 95:5) to give 5ab (89.5 mg, 89% yield, anti/syn = 94:6, Table 1, entry 7).

\[
\text{IR (neat): } 3423, 2949, 2866, 1489, 1412, 1308, 1192, 1088, 1053, 1009 \text{ cm}^{-1}; \text{ } ^1\text{H NMR (500 MHz, CDCl}_3\text{): } \text{anti-form } \delta = 1.13–1.27 (m, 2H), 1.39–1.51 (m, 2H), 1.51–1.59 (m, 2H), 1.59–1.68 (m, 2H), 1.71–1.81 (m, 1H), 2.07–2.11 (m, 1H), 2.21 (dt, J = 9.4 \text{ Hz, 6.7 Hz, 1H}).
\]
Hz, 1H), 4.61 (dd, J = 6.6 Hz, 3.0 Hz, 1H), 5.04 (dd, J = 17.3 Hz, 1.7 Hz, 1H), 5.22 (dd, J = 10.3 Hz, 2.0 Hz, 1H), 5.75 (dt, J = 17.3 Hz, 10.0 Hz, 1H), 7.24–7.27 (m, 2H), 7.28–7.32 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): anti-form $\delta$ = 25.0, 25.3, 28.9, 31.1, 39.8, 57.1, 74.9, 119.6, 128.0, 128.3, 133.0, 136.1, 141.6; HRMS (EI$^+$): Caled for C$_{15}$H$_{19}$OCl ([M–H]$^+$) 250.1124. Found m/z 250.1128.

(1S*, 2S*)-1-(4-Chlorophenyl)-2-isopropylbut-3-en-1-ol (5ad)

The crude mixture was purified by flash diol-SiO$_2$ column chromatography (hexane:ethyl acetate = 95:5) to give 5ad (81.5 mg, 91% yield, anti/syn = >99:1, Table 1, entry 8).

IR (neat): 3436, 2961, 1638, 1597, 1491, 1385, 1090, 1015 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): anti-form $\delta$ = 0.84 (t, J = 6.5 Hz, 6H), 1.41–1.50 (m, 1H), 2.06–2.12 (m, 2H), 4.60 (dd, J = 8.3 Hz, 2.2 Hz, 1H), 5.14 (dd, J = 17.1 Hz, 1.8 Hz, 1H), 5.31 (dd, J = 10.3 Hz, 2.1 Hz, 1H), 5.78 (dt, J = 17.1 Hz, 10.1 Hz, 1H), 7.25–7.29 (m, 2H), 7.30–7.34 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): anti-form $\delta$ = 17.5, 21.8, 27.5, 58.9, 73.9, 120.5, 128.2, 128.4, 133.2, 135.3, 141.3; HRMS (EI$^+$): Caled for C$_{13}$H$_{16}$OCl ([M–H]$^+$) 223.0895. Found m/z 223.0880.

(1S*, 2R*)-1-(4-Chlorophenyl)-2-phenylbut-3-en-1-ol (5ae)

The crude mixture was purified by flash diol-SiO$_2$ column chromatography (hexane:ethyl acetate = 95:5) to give 5ae (98.5 mg, 95% yield, anti/syn = >99:1, Table 1, entry 9).

$^1$H NMR (500 MHz, CDCl$_3$): anti-form $\delta$ = 2.37 (brs, 1H), 3.47 (t, J = 8.5 Hz, 1H), 4.80 (d, J = 7.9 Hz, 1H), 5.24 (dd, J = 17.1 Hz, 0.8 Hz, 1H), 5.28 (dd, J = 10.1 Hz, 1.3 Hz, 1H), 6.22 (dd, J = 17.1 Hz, 10.1 Hz, 9.1 Hz, 1H), 7.01–7.07 (m, 4H), 7.14–7.18 (m, 3H), 7.19–7.24 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): anti-form $\delta$ = 59.3, 76.5, 118.7, 126.7, 128.0 (two signals overlapping), 128.2, 128.4, 133.0, 137.5, 140.1, 140.3.
(1S*,2S*)-5-(tert-Butyldimethylsilyloxy)-1-(4-chlorophenyl)-2-vinylpentan-1-ol (5af)

The crude mixture was purified by flash diol-SiO\textsubscript{2} column chromatography (hexane:ethyl acetate = 97:3 ~ 95:5) to give 5af (129.6 mg, 91% yield, \textit{anti/syn} = 97:3, Table 1, entry 10).

IR (neat): 3431, 2929, 2856, 1491, 1468, 1387, 1254, 1092, 1009 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \textit{anti}-form \(\delta = -0.03\) (s, 6H), 0.83 (s, 9H), 1.13–1.38 (m, 3H), 1.47–1.55 (m, 1H), 2.19–2.28 (m, 2H), 3.49 (t, \(J = 6.4\) Hz, 2H), 4.38 (dd, \(J = 7.9\) Hz, 2.2 Hz, 1H), 5.19 (dd, \(J = 17.0\) Hz, 1.7 Hz, 1H), 5.28 (dd, \(J = 10.2\) Hz, 1.8 Hz, 1H), 5.63 (dt, \(J = 17.0\) Hz, 10.2 Hz, 1H), 7.24–7.28 (m, 2H), 7.29–7.33 (m, 2H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \textit{anti}-form \(\delta = -5.39, -5.38, 18.2, 25.8, 26.6, 30.4, 52.7, 62.7, 76.0, 119.2, 128.26, 128.35, 133.2, 138.8, 140.9\); HRMS (EI\textsuperscript{+}): Calcd for C\textsubscript{19}H\textsubscript{31}O\textsubscript{2}ClSi (M\textsuperscript{+}) 354.1782. Found m/z 354.1799.

(S*)-4-((S*)-(4-Chlorophenyl)(hydroxy)methyl)hex-5-enyl benzoate (5ag)

The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 90:10 ~ 85:15) to give 5ag (133.2 mg, 97% yield, \textit{anti/syn} = 99:1, Table 1, entry 11).

IR (neat): 3484, 1719, 1601, 1491, 1453, 1277, 1117, 1092 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \textit{anti}-form \(\delta = 1.23–1.42\) (m, 2H), 1.54–1.64 (m, 1H), 1.74–1.85 (m, 1H), 2.18–2.23 (m, 1H), 2.26–2.35 (m, 1H), 4.22 (t, \(J = 6.7\) Hz, 2H), 4.41 (dd, \(J = 7.8\) Hz, 2.3 Hz, 1H), 5.23 (dd, \(J = 17.2\) Hz, 1.1 Hz, 1H), 5.31 (dd, \(J = 10.3\) Hz, 1.7 Hz, 1H), 5.66 (ddd, \(J = 17.2\) Hz, 10.3 Hz, 9.6 Hz, 1H), 7.24–7.27 (m, 2H), 7.27–7.31 (m, 2H), 7.40–7.46 (m, 2H), 7.53–7.58 (m, 1H), 7.89–7.93 (m, 2H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \textit{anti}-form \(\delta = 26.3, 26.6, 52.3, 64.3, 76.0, 119.7, 128.2, 128.3, 128.9, 129.4, 130.2, 132.9, 133.3, 138.3, 140.7, 166.5\); HRMS (EI\textsuperscript{+}): Calcd for C\textsubscript{20}H\textsubscript{21}O\textsubscript{3}Cl (M\textsuperscript{+}) 344.1179. Found m/z 344.1186.
Chapter 5

2-((S*)-4-((S*)-(4-Chlorophenyl)(hydroxy)methyl)hex-5-enyl)isoindoline-1,3-dione (5ah)

The crude mixture was purified by flash diol-SiO₂ column chromatography (hexane then hexane:ethyl acetate = 80:20) to give 5ah (138.0 mg, 93% yield, anti/syn = 96:4, Table 1, entry 12).

IR (neat): 3496, 2937, 1770, 1712, 1398, 1369, 1088, 1051, 1012 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): anti-form δ = 1.19–1.27 (m, 2H), 1.45–1.56 (m, 1H), 1.65–1.77 (m, 1H), 2.23–2.33 (m, 2H), 3.57 (t, J = 7.5 Hz, 2H), 4.39 (d, J = 7.4 Hz, 1H), 5.18 (d, J = 17.1 Hz, 1H), 5.25 (d, J = 10.2 Hz, 1H), 5.60 (dt, J = 17.1 Hz, 9.8 Hz, 1H), 7.20–7.26 (m, 4H), 7.68–7.74 (m, 2H), 7.78–7.84 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): anti-form δ = 25.9, 27.3, 37.4, 51.9, 75.8, 119.3, 123.0, 128.1, 128.2, 131.8, 133.0, 133.8, 138.0, 140.7, 168.3; HRMS (ESI⁺): Calcd for C₂₁H₂₀O₃ClN ([M+Cl]⁺) 404.0815. Found m/z 404.0816.

1-(4-Chlorophenyl)-2,2-dimethylbut-3-en-1-ol (5ai)

The crude mixture was purified by flash diol-SiO₂ column chromatography (hexane:ethyl acetate = 95:5 ~ 90:10) to give 5ai (78.3 mg, 93% yield, eq. 1).

¹H NMR (500 MHz, CDCl₃): δ = 0.94 (s, 3H), 1.00 (s, 3H), 2.01 (d, J = 3.0 Hz, 1H), 4.41 (d, J = 2.9 Hz, 1H), 5.08 (dd, J = 17.5 Hz, 1.2 Hz, 1H), 5.16 (dd, J = 10.8 Hz, 1.2 Hz, 1H), 5.88 (dd, J = 17.6 Hz, 10.8 Hz, 1H), 7.22–7.25 (m, 2H), 7.27–7.30 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ = 20.8, 24.3, 42.2, 79.9, 114.2, 127.6, 129.1, 133.1, 139.1, 144.7.

1-(4-Chlorophenyl)-3-methylbut-3-en-1-ol (5aj)
Chapter 5

The crude mixture was purified by flash diol-SiO₂ column chromatography (hexane:ethyl acetate = 95:5 ~ 90:10) to give 5aj (65.0 mg, 83% yield, eq. 2).

\(^1\)H NMR (500 MHz, CDCl₃): \(\delta = 1.80\) (s, 3H), 2.13 (d, \(J = 2.3\) Hz, 1H), 2.33–2.43 (m, 2H), 4.79 (ddd, \(J = 8.1\) Hz, 5.3 Hz, 2.4 Hz, 1H), 4.84–4.86 (m, 1H), 4.93–4.95 (m, 1H), 7.32 (s, 4H); \(^{13}\)C NMR (125 MHz, CDCl₃): \(\delta = 22.3, 48.3, 70.7, 114.4, 127.1, 128.5, 133.0, 141.9, 142.5\).

\((1S^*, 2S^*)\)-2-Ethyl-1-phenylbut-3-en-1-ol (5ba)\(^2^4\)

\[
\begin{align*}
\text{OH} & \\
\text{CH₂CH₂CHCH₃} & \\
\text{C₆H₅} & \\
\end{align*}
\]

The crude mixture was purified by flash diol-SiO₂ column chromatography (hexane:ethyl acetate = 97:3 ~ 95:5) to give 5ba (63.2 mg, 90% yield, \(anti/syn = 96:4\), Table 2, entry 1).

\(^1\)H NMR (500 MHz, CDCl₃): \(anti\)-form \(\delta = 0.79\) (t, \(J = 7.5\) Hz, 3H), 1.11–1.20 (m, 1H), 1.20–1.30 (m, 1H), 2.16 (d, \(J = 2.4\) Hz, 1H), 2.16–2.24 (m, 1H), 4.40 (dd, \(J = 8.0\) Hz, 2.4 Hz, 1H), 5.21 (dd, \(J = 17.2\) Hz, 1.9 Hz, 1H), 5.28 (dd, \(J = 10.2\) Hz, 1.9 Hz, 1H), 5.66 (ddd, \(J = 17.2\) Hz, 10.2 Hz, 9.3 Hz, 1H), 7.26–7.31 (m, 1H), 7.31–7.37 (m, 4H); \(^{13}\)C NMR (125 MHz, CDCl₃): \(anti\)-form \(\delta = 11.7, 23.4, 54.6, 76.5, 118.9, 126.9, 127.6, 128.2, 131.9, 142.5\).

\((1S^*, 2S^*)\)-2-Ethyl-1-(4-nitrophenyl) but-3-en-1-ol (5ca)

\[
\begin{align*}
\text{OH} & \\
\text{CH₂CH₂CHCH₃} & \\
\text{NO₂} & \\
\text{C₆H₅} & \\
\end{align*}
\]

The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 90:10 ~ 85:15) to give 5ca (83.5 mg, 94% yield, \(anti/syn = 99:1\), Table 2, entry 2).

IR (KBr): 3518, 3078, 2966, 2873, 1603, 1520, 1344, 1219, 1105, 1051 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl₃): \(anti\)-form \(\delta = 0.84\) (t, \(J = 7.4\) Hz, 3H), 1.21–1.34 (m, 2H), 2.13–2.21 (m, 1H), 2.29 (d, \(J = 2.6\) Hz, 1H), 4.57 (ddd, \(J = 17.1\) Hz, 1.8 Hz, 0.6 Hz, 1H), 5.29 (dd, \(J = 10.2\) Hz, 1.8 Hz, 1H), 5.62 (ddd, \(J = 17.1\) Hz, 10.2 Hz, 9.3 Hz, 1H), 7.48–7.53 (m, 2H), 8.18–8.23 (m, 2H); \(^{13}\)C NMR (125 MHz, CDCl₃): \(anti\)-form \(\delta = 11.8, 23.4, 54.6, 75.6, 119.9, 123.4, 127.7, 137.7, 147.4, 150.1\); HRMS (APCI): Calcd for C\(_{12}\)H\(_{16}\)O\(_3\)N ([M+H]\(^+\)) 222.1125. Found m/z 222.1122.
(1S*, 2S*)-2-Ethyl-1-(4-methoxycarbonylphenyl)but-3-en-1-ol (5da)

The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 90:10 ~ 85:15) to give 5da (90.4 mg, 96% yield, anti/syn = 98:2, Table 2, entry 3).

IR (neat): 3457, 2961, 1722, 1611, 1437, 1281, 1113, 1042 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): anti-form δ = 0.81 (t, J = 7.5 Hz, 3H), 1.15–1.32 (m, 2H), 2.14–2.23 (m, 1H), 2.26 (d, J = 2.6 Hz, 1H), 3.91 (s, 3H), 4.49 (ddd, J = 7.5 Hz, 2.5 Hz, 1H), 5.18 (dd, J = 17.2 Hz, 1.7 Hz, 1H), 5.27 (dd, J = 10.2 Hz, 1.8 Hz, 1H), 5.63 (ddd, J = 17.2 Hz, 10.2 Hz, 9.4 Hz, 1H), 7.40 (d, J = 8.3 Hz, 2H), 8.01 (d, J = 8.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): anti-form δ = 11.7, 23.3, 52.0, 54.4, 76.1, 119.2, 126.8, 129.3, 129.4, 138.3, 147.9, 166.9; HRMS (EI⁺): Calcd for C₁₄H₁₈O₃ (M⁺) 234.1256. Found m/z 234.1258.

(1S*, 2S*)-2-Ethyl-1-(4-acetylphenyl)but-3-en-1-ol (5ea)

The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 90:10 ~ 85:15) to give 5ea (71.6 mg, 82% yield, anti/syn = 97:3, Table 2, entry 4).

IR (neat): 3437, 2964, 2931, 2875, 1680, 1606, 1414, 1360, 1271, 1041 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): anti-form δ = 0.81 (t, J = 7.5 Hz, 3H), 1.16–1.32 (m, 2H), 2.15–2.23 (m, 1H), 2.22 (d, J = 2.6 Hz, 1H), 2.61 (s, 3H), 4.50 (dd, J = 7.5 Hz, 2.5 Hz, 1H), 5.19 (ddd, J = 17.2 Hz, 1.8 Hz, 0.5 Hz, 1H), 5.29 (dd, J = 10.2 Hz, 1.8 Hz, 1H), 5.63 (ddd, J = 17.2 Hz, 10.2 Hz, 9.3 Hz, 1H), 7.41–7.45 (m, 2H), 7.93–7.96 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): anti-form δ = 11.7, 23.3, 26.6, 54.5, 75.9, 119.3, 127.0, 128.2, 136.4, 138.3, 148.1, 197.9; HRMS (APCI): Calcd for C₁₄H₁₉O₂ ([M+H]⁺) 219.1380. Found m/z 219.1373.
(1S*, 2S*)-2-Ethyl-1-(3-methoxyphenyl)but-3-en-1-ol (5fa)

The crude mixture was purified by flash diol-SiO₂ column chromatography (hexane:ethyl acetate = 97:3 ~ 95:5) to give 5fa (77.5 mg, 94% yield, anti/syn = 98:2, Table 2, entry 5).

IR (KBr): 3431, 3394, 2964, 2881, 1599, 1487, 1257, 1163, 1043 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): anti-form δ = 0.80 (t, J = 7.5 Hz, 3H), 1.11–1.22 (m, 1H), 1.22–1.32 (m, 1H), 2.14–2.23 (m, 2H), 3.82 (s, 3H), 4.38 (dd, J = 8.0 Hz, 2.4 Hz, 1H), 5.20 (dd, J = 17.2 Hz, 1.7 Hz, 1H), 5.27 (dd, J = 10.3 Hz, 1.9 Hz, 1H), 5.65 (ddd, J = 17.2 Hz, 10.3 Hz, 9.2 Hz, 1H), 6.81–6.84 (m, 1H), 6.89–6.92 (m, 2H), 7.23–7.28 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): anti-form δ = 11.7, 23.4, 54.5, 55.2, 76.5, 112.4, 113.0, 118.9, 119.4, 129.1, 139.0, 144.3, 159.6; HRMS (APCI): Calcd for C₁₃H₁₉O₂ ([M+H]+) 207.1380. Found m/z 207.1374.

(1S*, 2S*)-2-Ethyl-1-o-tolylbut-3-en-1-ol (5ga)

The crude mixture was purified by flash diol-SiO₂ column chromatography (hexane:ethyl acetate = 97:3 ~ 95:5) to give 5ga (68.4 mg, 90% yield, anti/syn = 95:5, Table 2, entry 6).

IR (neat): 3422, 2963, 1638, 1460, 1383, 1123, 1036 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): anti-form δ = 0.81 (t, J = 7.4 Hz, 3H), 1.19–1.29 (m, 2H), 2.07 (d, J = 2.6 Hz, 1H), 2.20–2.28 (m, 1H), 2.36 (s, 3H), 4.73 (dd, J = 7.9 Hz, 2.6 Hz, 1H), 5.19 (ddd, J = 17.3 Hz, 1.9 Hz, 0.7 Hz, 1H), 5.28 (dd, J = 10.2 Hz, 1.9 Hz, 1H), 5.69 (ddd, J = 17.2 Hz, 10.3 Hz, 9.2 Hz, 1H), 7.11–7.15 (m, 1H), 7.17 (dt, J = 1.5 Hz, 7.5 Hz, 1H), 7.22 (dt, J = 1.4 Hz, 7.5 Hz, 1H), 7.40 (dd, J = 7.8 Hz, 1.2 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): anti-form δ = 12.0, 19.5, 23.3, 54.2, 72.1, 118.9, 126.1, 126.5, 127.2, 130.2, 135.4, 139.2, 140.8; HRMS (EI⁺): Calcd for C₁₃H₁₈O ([M⁺]⁺) 190.1358. Found m/z 190.1356.

(3R*, 4S*)-4-Ethyl-1-phenylhex-5-en-3-ol (5ha)
The crude mixture was purified by flash diol-SiO₂ column chromatography (hexane:ethyl acetate = 97:3 ~ 95:5) to give **5ha** (64.5 mg, 79% yield, anti/syn = 90:10, Table 2, entry 7). IR (neat): 3398, 2961, 2932, 2874, 1638, 1603, 1497, 1455, 1038 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): anti-form δ = 0.86 (t, J = 7.4 Hz, 3H), 1.27–1.38 (m, 1H), 1.48–1.63 (m, 2H), 1.68–1.77 (m, 1H), 1.78–1.87 (m, 1H), 1.90–1.98 (m, 1H), 2.67 (ddd, J = 13.8 Hz, 10.0 Hz, 6.6 Hz, 1H), 2.83 (ddd, J = 13.9 Hz, 10.3 Hz, 5.4 Hz, 1H), 3.47–3.54 (m, 1H), 5.11 (dd, J = 17.2 Hz, 1.9 Hz, 1H), 5.20 (dd, J = 10.3 Hz, 2.0 Hz, 1H), 5.63 (dt J = 17.3 Hz, 10.0 Hz, 1H), 7.16–7.23 (m, 3H), 7.28 (t, J = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): anti-form δ = 11.9, 23.6, 32.2, 36.6, 52.3, 72.8, 118.2, 125.7, 128.3, 128.4, 138.5, 142.3; HRMS (EI⁺): Calcd for C₁₄H₂₀O (M⁺) 204.1514. Found m/z 204.1509.

(1R*, 2S*)-1-Cyclohexyl-2-ethylbut-3-en-1-ol (5ia)

The crude mixture was purified by flash diol-SiO₂ column chromatography (hexane:ethyl acetate = 98:2 ~ 96:4) to give **5ia** (45.5 mg, 62% yield, anti/syn = 91:9, Table 2, entry 8). IR (neat): ¹H NMR (500 MHz, CDCl₃): anti-form δ = 0.88 (t, J = 7.4 Hz, 3H), 0.99–1.28 (m, 5H), 1.30–1.44 (m, 3H), 1.44–1.54 (m, 1H), 1.61–1.68 (m, 2H), 1.71–1.80 (m, 2H), 1.80–1.87 (m, 1H), 2.05–2.13 (m, 1H), 3.19 (q, J = 5.2 Hz, 1H), 5.08 (dd, J = 17.3 Hz, 2.0 Hz, 1H), 5.18 (dd, J = 10.3 Hz, 2.1 Hz, 1H), 5.66 (ddd, J = 17.3 Hz, 10.3 Hz, 9.3 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): anti-form δ = 11.9, 23.9, 26.1, 26.4, 26.5, 27.6, 29.7, 40.5, 48.5, 77.4, 117.6, 138.6.

3. A One-Pot Sequence via Hydroboration/Isomerization/Allylation Reaction.

(1) An Upper Equation in Scheme 2 (Representative Procedure of 1a and terminal alkyne 7e).
3-phenyl-1-propyne (102 mg, 0.88 mmol) and pinacolborane (102 mg, 0.80 mmol) were added. The reaction mixture was stirred at room temperature for 6 h under neat condition, and 1,2-dichloroethane (1 mL) was added. The solvent was removed under reduced pressure. After the flask was refilled with argon, a solution of 1a (56.2 mg, 0.4 mmol) in 1,2-dichloroethane (3 mL) and a solution of [Rh(nbd)(CH₃CN)₂]SbF₆ (10.3 mg, 0.02 mmol) and dppm (7.7 mg, 0.02 mmol) in 1,2-dichloroethane (1 mL) was added via syringe. After heating at 90 °C for 12 h, the reaction mixture was cooled to room temperature. The mixture was passed through a pad of florisil® (1.5 x 5 cm) and eluted with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash diol-SiO₂ column chromatography (hexane:ethyl acetate = 95:5) to give 5ae (95.0 mg, 92% yield, anti/syn = 98:2, scheme 2).

(2) A Lower Equation in Scheme 2 (Representative Procedure of ketone 9b and 1-butyne).

To a suspension of 9-BBN dimer (244 mg, 1.0 mmol) in THF (1 mL) at 0 °C was added 1-butyne (ca 0.5 mL, large excess) via syringe. After being stirred at 0 °C for 5 min, the reaction mixture was additionally stirred at room temperature for 1 h. The solvent was removed under reduced pressure. After the flask was refilled with argon, 1,2-dichloroethane (1 mL), a solution of 1a (56.2 mg, 0.4 mmol) in 1,2-dichloroethane (2 mL), and a solution of [Rh(nbd)(CH₃CN)₂]SbF₆ (10.3 mg, 0.02 mmol) and dppm (7.7 mg, 0.02 mmol) in 1,2-dichloroethane (1 mL) was added via syringe. After heating at 80 °C for 6 h, the reaction mixture was cooled to room temperature. The mixture was passed through a pad of NH-silica gel (1.5 x 5 cm) and eluted with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash silica gel column chromatography (hexane:ethyl acetate = 95:5 ~ 90:10) to give 10bb (67.5 mg, 83% yield, anti/syn = 89:11).
(3R*,4S*)-3,4-Dimethyl-1-phenylhex-5-en-3-ol (10bb)²⁵

\[
\begin{align*}
&\text{1H NMR (500 MHz, CDCl} _3): \text{anti-form } \delta = 1.05 (d, J = 6.9 \text{ Hz, 3H}), 1.18 (s, 3H), 1.54 (\text{brs, 1H}), 1.76–1.81 (m, 2H), 2.29–2.38 (m, 1H), 2.62–2.80 (m, 2H), 5.12–5.17 (m, 2H), 5.86 (dd, J = 17.9 \text{ Hz, 9.7 Hz, 8.6 Hz, 1H}), 7.16–7.23 (m, 3H), 7.28 (t, J = 7.5 \text{ Hz, 2H}); \\
&\text{13C NMR (125 MHz, CDCl}_3): \text{anti-form } \delta = 14.9, 23.5, 29.8, 42.0, 47.4, 73.5, 116.6, 125.7, 128.3 (\text{two signals overlapping}), 140.1, 142.7.
\end{align*}
\]

(2S*, 3S*)-3-Methyl-2-phenylpent-4-en-2-ol (10ab)²⁵

\[
\begin{align*}
&\text{The crude mixture was purified by flash NH-silica gel column chromatography (hexane:ethyl acetate = 95:5 ~ 90:10) to give 10ab (49.5 mg, 70\% yield, anti/syn = 85:15).} \\
&\text{1H NMR (500 MHz, CDCl} _3): \text{anti-form } \delta = 0.97 (d, J = 6.9 \text{ Hz, 3H}), 1.53 (s, 3H), 1.94 (s, 1H), 2.56–2.65 (m, 1H), 5.08–5.14 (m, 2H), 5.71 (dd, J = 17.1 \text{ Hz, 10.7 Hz, 7.6 Hz, 1H}), 7.22–7.26 (m, 1H), 7.31–7.36 (m, 2H), 7.42–7.45 (m, 2H); \text{13C NMR (125 MHz, CDCl}_3): \text{anti-form } \delta = 14.1, 25.9, 48.8, 75.7, 116.6, 125.5, 126.6, 127.9, 139.9, 147.0.
\end{align*}
\]

The Experiments to Obtain the Mechanistic Insight.

1. Reaction of (E)- and (Z)-Crotylboronic Pinacolate (6b) with 4-Chlorobenzaldehyde (1a) (Eq 3).

To a solution of 1a (0.40 mmol) in 1,2-dichloroethane (2.5 mL) at 90 °C was added a solution of (E)-6b (0.60 mmol) and (Z)-6b (0.60 mmol) in 1,2-dichloroethane (1.5 mL). After being stirred for 30 min, the reaction mixture was cooled to room temperature. The mixture was passed through a pad of florisil® (1.5 x 5 cm) and eluted with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure. To the residue was added tetrachloroethane (34.7 mg, 0.206 mmol) as an internal standard, and it was analyzed by 1H NMR. The anti/syn ratio of the resulting homoallylic alcohol 5ab (>95% yield) was 58:42.

2. A Control Experiment in the Absence of Aldehydes (Scheme 1).

(E)-3b, (Z)-3b and (E)-6b were separately treated with a catalytic amount of the
rhodium(I) complex by the similar manner in the absence of the aldehyde 1a. At three positions of 0 min, 20 min, and 6 h after heating at 90 °C, a part (0.1 mL) of the reaction mixture was taken out via syringe. The samples were passed through a pad of florisil® (5 mm x 3 cm) and eluted with CDCl₃ (3 mL). The filtrates were concentrated under reduced pressure and the residues were monitored by ¹H NMR. The resulting NMR spectra are shown in Figure 1S and 2S. The product ratio estimated from the integral value of the ¹H NMR spectrum is shown in Scheme 1.
Figure 18. The time course of $^1$H NMR spectrum (0.3-7.1 ppm) for a control experiment in the absence of aldehyde.
Figure 28: The time course of 1H NMR (1.4-2.6 ppm) spectrum for a control experiment in the absence of aldehyde.
References and notes


11. The following phosphine ligands gave inferior results (1H NMR yield of 5aa, anti/syn): PPh3 (12%, 50:50), P(2-furyl)3 (76%, 78:22), dppe (91%, 82:18), and dppf (21%, 81:19).


13. When isolated (E)-crotylboronate (6b, 1.5 equiv) was reacted with 1a (1.0 equiv) in 1,2-dichloroethane at 90 °C at 30 min, homoallylic alcohol 5ab was formed in >95% yield with high anti selectivity (anti/syn = >95:5).


Chapter 5
List of Publications

Chapter 1 Synthesis of α-keto esters by the rhodium-catalysed reaction of cyanoformate with arylboronic acids
Hiroshi Shimizu and Masahiro Murakami

Chapter 2 Synthesis of Functionalized Isoindoles by the Rhodium-Catalyzed Reaction of Cyanoformates with ortho-Borylbenzalacetone Derivatives
Hiroshi Shimizu, Tomohiro Igarashi and Masahiro Murakami

Chapter 3 Reaction of 2-Alkynylbenzoyl Cyanides with Carboxylic Acids Producing Functionalized Indenones
Hiroshi Shimizu and Masahiro Murakami
Synlett 2008, 1817-1820.

Chapter 4 Stereoselective synthesis of vinyl-substituted (Z)-stilbenes by rhodium-catalysed addition of arylboronic acids to allenic alcohols
Tomoya Miura, Hiroshi Shimizu, Tomohiro Igarashi and Masahiro Murakami

Chapter 5 Rhodium-Catalyzed Reaction of 1-Alkenylboronates with Aldehydes Leading to Allylation Products
Hiroshi Shimizu, Tomohiro Igarashi, Tomoya Miura, and Masahiro Murakami