Development of New Synthetic Reactions

Using

Rhodium Catalysts and Organoboronic Acid Derivatives

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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.

 The author wishes to express his thanks to Professor Michinori Suginome, Lecture Toshimichi Ohmura, Lecturer Takanori Matsuda and Assistant Professor Naoki Ishida for their helpful discussions and advises.

 The author had the great assistance of Mr. Tomohiro Igarashi. The author acknowledges to him for his patience, earnest, and collaboration.

 The author wishes to express his gratitude to Dr. Sho Kadowaki, Dr. Munehiro Hasegawa, Dr. Masahiro Shimada, Dr. Shinji Ashida, Dr. Masanori Shigeno, Dr. Motoshi Yamauchi, Dr. Takeharu Toyoshima, Mr. Tatsuro Harumashi, Mr. Tsuyoshi Goya, Mr. Yusuke Takahashi, Mr.Tomoya Tsuboi, Mr. Yoshiyuki Yamaguchi, Mr. Yoshiteru Ito, Ms. Mizuna Narumi, Mr.Tatsuo Shinmoto, Mr. Tomohiro Tamai, Mr. Keita Ueda, Mr. Taisaku Moriya, Mr. Yohei Maruyama, Mr. Yasuhiro Shimamoto, Mr. Masao Morimoto, Mr. Osamu Kato, Dr. Markus Mosimann, Dr. Karl Deutsche, Dr. Peter Bruchner, Dr. Akiko Okamoto.

 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.

Contents

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.[1] 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[2] 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[2, 3]. For example, addition reactions to non-polar functional groups such as simple alkynes[4] and alkenes[5] 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[6] and imines[7], 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 (OR = 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 H_2O or ROH, and the other is β-oxygen elimination from β-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.
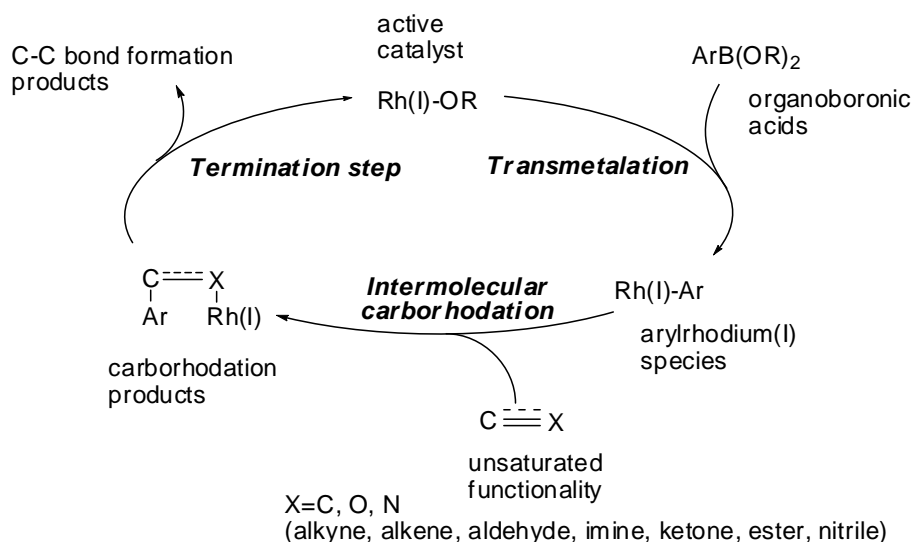
Figure 1. General reaction pathway of Rh(I)-catalyzed addition reaction of organoboronic acids
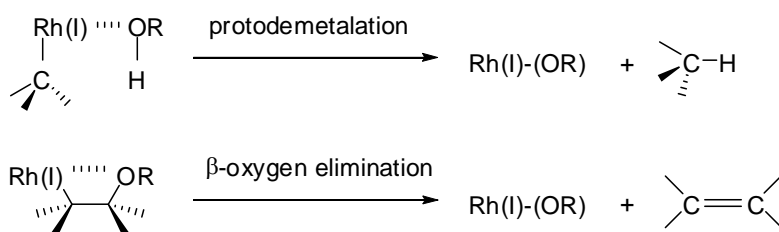
Figure 2. Two types of termination step for Rh(I)-catalyzed addition reaction
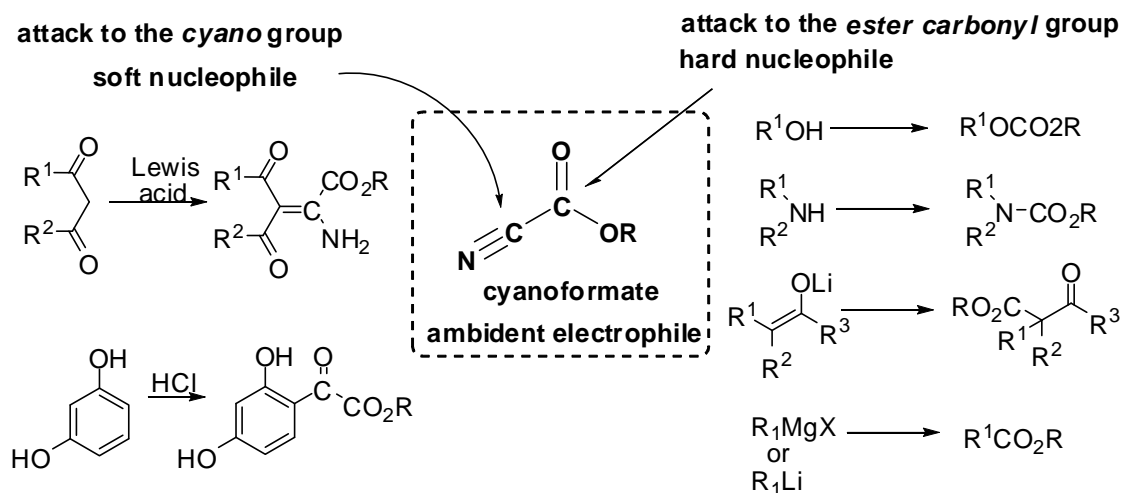
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The author examined the rhodium-catalyzed addition reaction of organoboronic acid derivatives using two kinds of substrates in order to find reactivities of organorhodium species which were different from those of main group organometallics or other 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.[8] 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.[9] 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[7h, 10] and ester groups.[11]
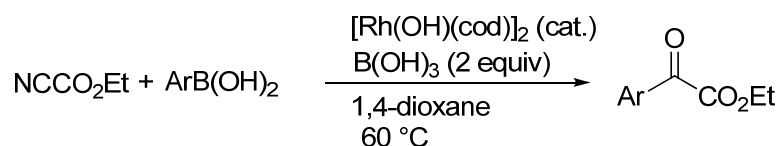
Cyanoformate[12] is an interesting electrophilic substrate in order to compare the reactivities of the cyano group and the ester group toward nucleophiles. Since the two functionalities are both electron-withdrawing, their electrophilic reactivities are enhanced relative to isolated ester or nitrile groups. Generally, hard nucleophiles such as organomagnesium[13] and organolithium[14] compounds, alcohols[15], and amines[16] selectively add to the ester's carbonyl group of cyanoformate with elimination of the cyano group to afford the corresponding alkoxycarbonylated products. In particular, the reaction with the lithium enolates is widely used as synthetic method for β-ketoesters[12, 17]. On the other hand, nucleophilic addition to the cyano group preferentially occurs by soft nucleophiles such as electron-rich aromatic compounds[18] and active methylene compounds[19] under acidic reaction conditions.

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attack to the *cyano* group
soft nucleophile

attack to the *ester carbonyl* group
hard nucleophile

cyanoformate
ambident electrophile

$R^1OH \longrightarrow R^1OCO2R$

$\overset{R^1}{\underset{R^2}{}}NH \longrightarrow \overset{R^1}{\underset{R^2}{}}N{-}CO_2R$

R_1MgX or $R_1Li \longrightarrow R^1CO_2R$

Figure 3. The reactivity of various nucleophiles to cyanoformate

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 [Rh(OH)(cod)]$_2$ and boric acid to give α-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.

$$NCCO_2Et + ArB(OH)_2 \xrightarrow[\substack{1,4\text{-dioxane} \\ 60\,°C}]{\substack{[Rh(OH)(cod)]_2 \text{ (cat.)} \\ B(OH)_3 \text{ (2 equiv)}}} Ar\overset{O}{\underset{}{C}}CO_2Et$$

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 *ortho*-borylbenzalacetone derivatives onto the cyano group of cyanoformate, and the following intramolecular cyclization of an

imine intermediate. Isoindoles[20] have attracted much attention in materials science due to their interesting photophysical properties in fluorescence and electroluminescence.[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.
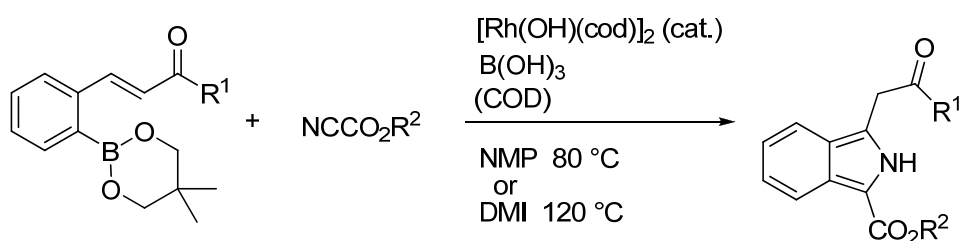
In chapter 3, a reaction of 2-alkynylbenzoyl cyanides with carboxylic acids was explained. It was found during the study on the reaction using 2-alkynylbenzoyl cyanides in place of cyanoformate that a 2-alkynylbenzoyl cyanide cyclized on heating together with a carboxylic acid to produce a 2-acylamino-3-acylindenone. 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.

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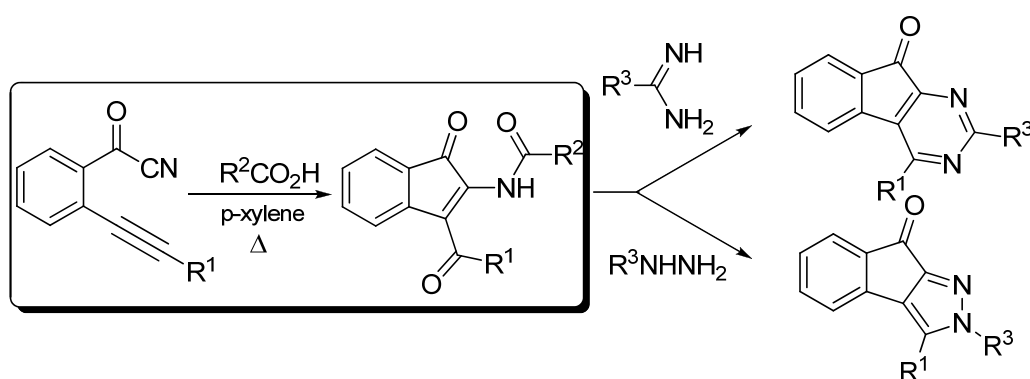
(2) Addition reaction to allenic alcohols

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 S_N2' reaction of palladium(0) species, which occurs from the less hindered side (d-side) as shown in Figure 5 to produce an *E*-product.
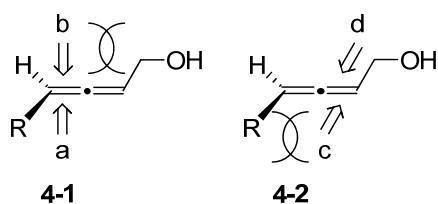
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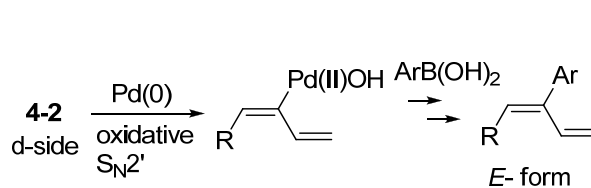Figure 4. attack to allenic alcohol   Figure 5. Pd(0)-catalyzed reaction

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.
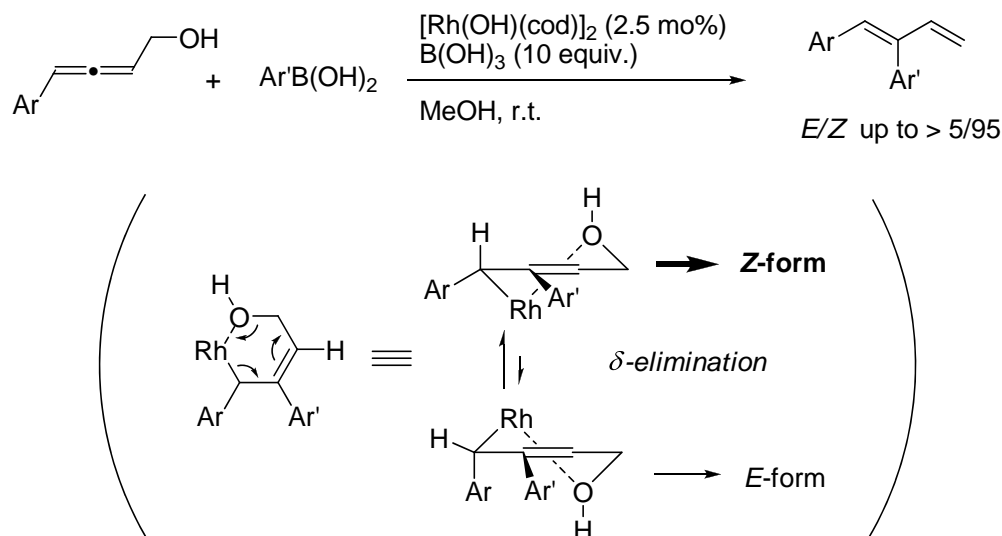
II. Reaction utilizing the capability of the rhodium complexes which induce alkene isomerization

Cationic rhodium complexes are possible to induce isomerization of alkenes[25] by the following mechanism; (i) allylic C-H activation, (ii) π-allyl complex generation and (iii) reductive elimination (Figure 6). This isomerization of alkenes is often used for isomelization of allyl ethers, allyl alcohols and allyl amines to enol ethers, carbonyl compounds and enamines, and these asymmetric reactions have been studied extensively[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.
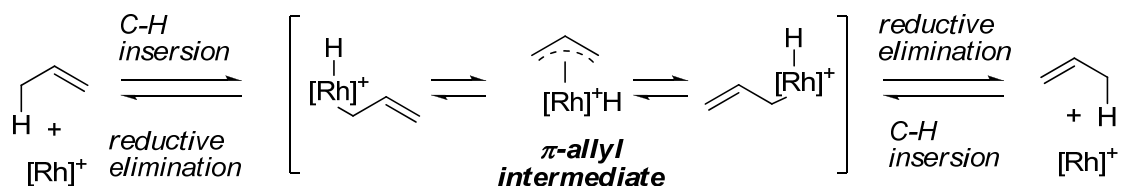

Figure 6. Capability of transition metals to induce alkene isomerization

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 (allylboronic acid) derivatives react with aldehydes at the γ-position to boron selectively to give the homoallylic alcohols without any catalysts.[27] 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 allylboronic compounds. However, stereoselective preparation of geometrically-defined allylboronic compounds 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*)-allylboron reagents was described. 1-Alkenylboronic pinacolates reacted with aldehydes in the presence of [Rh]$^+$/dppm complex to give *anti*-configured homoallylic alcohols with high diastereoselectivity. This reaction proceeds through the generation of kinetically preferred (*E*)-allylboronates from 1-alkenylboronates by the catalysis of a cationic rhodium complex. 1-Alkenylboronates are readily prepared in one step by hydroboration of terminal alkynes.[28, 29] Hence, this allylation reaction provides a convenient and straightforward synthetic method of stereo-defined homoallyl alcohols from terminal alkynes and aldehydes.

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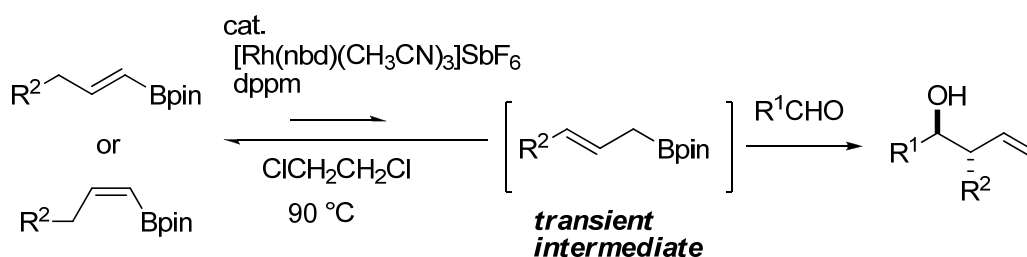
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Chapter 1

Synthesis of α-Keto Esters by the Rhodium-Catalysed

Reaction of Cyanoformate with Arylboronic Acids

Abstruct: An arylrhodium(I) species selectively reacts with the cyano group of ethyl cyanoformate to afford the corresponding α-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.[1] The reaction generally proceeds by transmetallation to generate an intermediate organorhodium species, which then undergoes 1,2-addition to alkynes, [2] alkenes, [3] aldehydes, [4] imines, [5] esters, [6] acid anhydrides, [7] 1,2-dicarbonyl compounds[6,8] and nitriles[5h,9] in an intermolecular fashion. Murakami et al have developed cascade reactions in which an organorhodium intermediate adds intramolecularly to a cyano group,[10] 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[11] and –lithium[12] compounds, lithium enolates,[13] lithiated amides,[14] alcohols,[15] and amines[16] 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,[17] electron-rich benzenes,[18] and organocadmium compounds.[19] The previous studies in Murakami laboratory on rhodium-catalysed cascade reactions[10] 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.
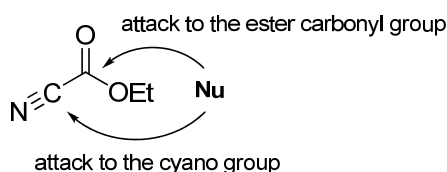
Figure 1. Ambident electrophilicity of cyanoformate.

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 ^{1}H NMR spectrum of the crude reaction mixture. The selective formation of **3a** suggests that the phenylrhodium intermediate generated by transmetallation 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).

$$\text{NCCO}_2\text{Et} + \text{PhB(OH)}_2 \xrightarrow[\substack{\text{1,4-dioxane (0.5 M)} \\ \text{3 h}}]{\substack{\text{[Rh(OH)(cod)]}_2\text{ (2.5 mol \%)} \\ \text{additive}}} \text{Ph}\overset{\overset{\displaystyle O}{\|}}{\underset{}{C}}\text{CO}_2\text{Et}$$

1 **2a** **3a**
(1.0 equiv)
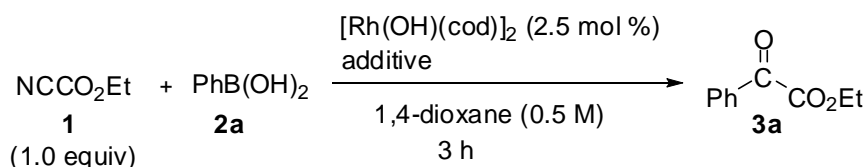
Table 1. The effect of additives$^{a)b)}$

entry	additive (1.0eq)	Yield (%)
1	none	40
2	B(OH)$_3$	62
3	H$_2$O	24
4	PhOH	44
5	NH$_4$Cl	23
6	AcOH	trace

a)1.5 eq of PhB(OH)$_2$ was used.
b)the reaction was performed at 80°C.

Table 2. The effect of B(OH)$_3$ as an additive$^{a)}$

entry	B(OH)$_3$	Temp (°C)	Yield (%)
1	none	80	37
2	1.0eq	80	62
3	2.0eq	80	78
4	2.0eq	60	83
5	2.0eq	40	53

a)1.2 eq of PhB(OH)$_2$ was used.

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).

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**

entry	**2**	Ar	**3** product	yield (%)^a
1	**2a**	Ph	**3a**	83
2	**2b**	4-MeO-C$_6$H$_4$	**3b**	80
3	**2c**	3-MeO-C$_6$H$_4$	**3c**	74
4	**2d**	2-MeO-C$_6$H$_4$	**3d**	87
5	**2e**	4-Br-C$_6$H$_4$	**3e**	82
6	**2f**	4-F-C$_6$H$_4$	**3f**	73
7	**2g**	3-Cl-C$_6$H$_4$	**3g**	81
8	**2h**	2-Cl-C$_6$H$_4$	**3h**	46
9	**2i**	2-Me-C$_6$H$_4$	**3i**	83
10	**2j**	2-Ph-C$_6$H$_4$	**3j**	50
11	**2k**	4-MeO$_2$C-C$_6$H$_4$	**3k**	58
12	**2l**	3-CHO-C$_6$H$_4$	**3l**	50

^{a} Isolated yields
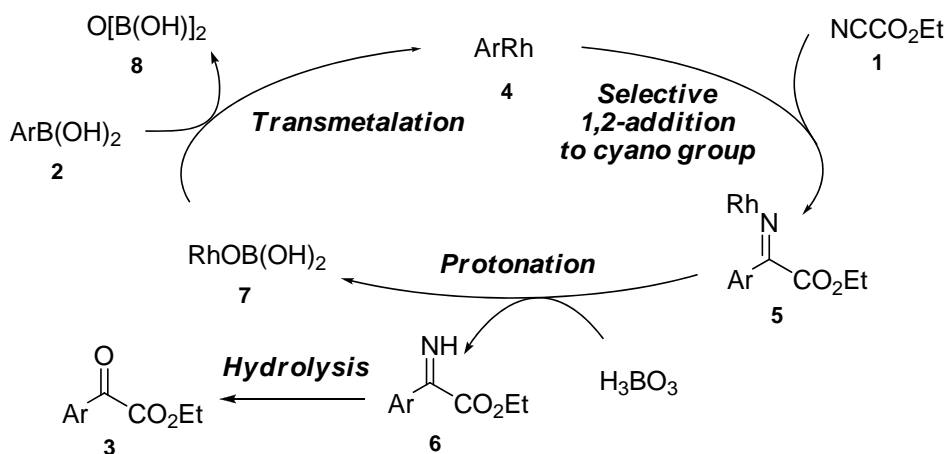
Scheme 1. Proposed mechanism for the formation of **3** from **1** and **2**.

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).

$$
\text{NCCO}_2\text{Et} + (\text{PhBO})_3 \xrightarrow[\substack{\text{1,4-dioxane (0.5 M)}\\ 60\,°\text{C, 3 h}\\ \text{additive}}]{[\text{Rh(OH)(cod)}]_2\ (2.5\ \text{mol \%})} \underset{\substack{\textbf{3a}}}{\overset{O}{\text{Ph}\overset{\|}{\text{C}}\text{CO}_2\text{Et}}} \qquad (1)
$$

1	**9**
(1.0 equiv)	(1.2 equiv)

additive   **3a**
none   trace
B(OH)$_3$ (2.0 equiv)   83%
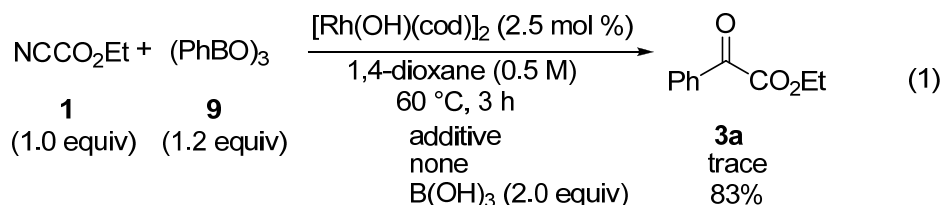
The selective reaction of the cyano group of **1** with organometallic reagents is rare. The reaction of **1** with phenylcadmium bromide in the presence of zinc dichloride has been reported to give **3** in 31% yield.[19] For comparison, we carried out reactions of **1** with phenylmagnesium bromide 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.

$$
\underset{\substack{\textbf{1}\\ (1.0\ \text{equiv.})}}{\text{NCCO}_2\text{Et}} + \underset{\substack{(1.05\ \text{equiv.})}}{\text{PhM}} \xrightarrow{\hspace{5cm}} \text{PhCO}_2\text{Et} \qquad (2)
$$

M= MgBr : -20 °C to r.t. / THF   89%

M= Li   : -78 °C to 5°C / Et$_2$O   36%
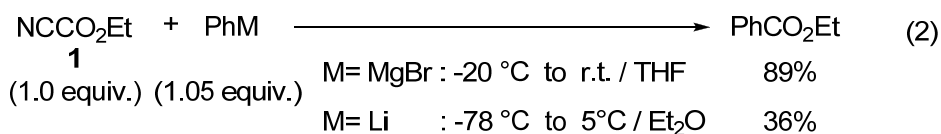
Conclusion

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, δ = 7.26) and CDCl$_3$ (^{13}C, δ =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.[20] 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.[21]

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.
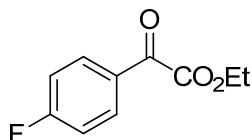
Ethyl benzoylformate (3a)[22]
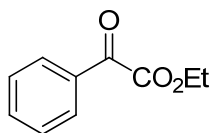
According to general procedure, **3a** (73.7 mg, 83%) was prepared from **1** (49.5mg, 0.5 mmol) and **2a** (73.2 mg, 0.6 mmol). : ^{1}H NMR: δ = 1.43 (t, *J* = 7.2 Hz, 3H), 4.46 (q, *J* = 7.2 Hz, 2H), 7.49-7.55 (m, 2H), 7.63-7.69 (m, 1H), 8.00-8.03 (m, 2H); ^{13}C NMR: δ = 14.2, 62.4, 128.9, 130.0, 132.4, 135.0, 163.8, 186.4
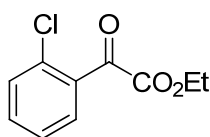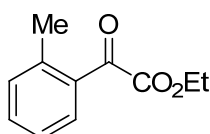
Ethyl 4-methoxybenzoylformate (3b)[23]
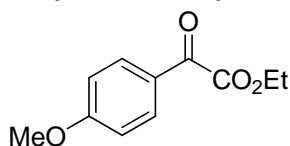
According to general procedure, **3b** (83.6 mg, 80%) was prepared from **1** (49.5mg, 0.5 mmol) and **2b** (91.2 mg, 0.6 mmol).: ^{1}H NMR: δ = 1.42 (t, J = 7.2 Hz, 3H), 3.90 (s, 3H), 4.43 (q, J = 7.2 Hz, 2H), 6.96-6.99 (m, 2H), 7.99-8.02 (m, 2H); ^{13}C NMR: δ = 14.2, 55.7, 62.3, 114.3, 125.5, 132.6, 164.2, 165.0, 184.9

Ethyl 3-methoxybenzoylformate (3c)[24]
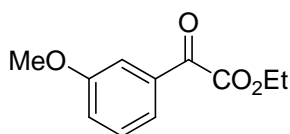
According to general procedure, **3c** (77.5 mg, 74%) was prepared from **1** (49.5mg, 0.5 mmol) and **2c** (91.2 mg, 0.6 mmol).: ^{1}H NMR: δ = 1.43 (t, J = 7.2 Hz, 3H), 3.87 (s, 3H), 4.45 (q, J = 7.2 Hz, 2H), 7.20 (ddd, J = 0.9Hz, 2.7Hz, 8.1Hz, 1H), 7.42 (t, J = 8.1Hz, 1H), 7.51-7.59 (m, 2H); ^{13}C NMR: δ = 14.2, 55.6, 62.5, 113.3, 121.9, 123.2, 130.0, 133.7, 160.0, 163.9, 186.4
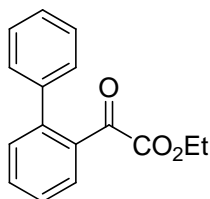
Ethyl 2-methoxybenzoylformate (3d)[25]
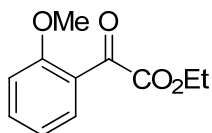
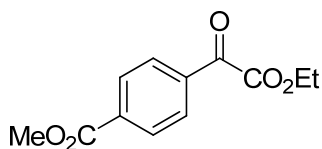According to general procedure, **3d** (90.1 mg, 87%) was prepared from **1** (49.5mg, 0.5 mmol) and **2d** (91.2 mg, 0.6 mmol). : ^{1}H NMR: δ = 1.40 (t, J = 7.2 Hz, 3H), 3.87 (s, 3H), 4.49 (q, J = 7.2 Hz, 2H), 6.99 (d, J = 6.6Hz, 1H), 7.04-7.11 (m, 1H), 7.55-7.63 (m, 1H), 7.88 (dd, J = 1.8Hz, 7.8Hz, 1H); ^{13}C NMR: δ = 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)[23]
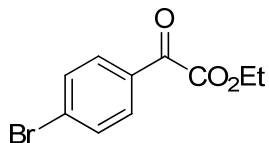
According to general procedure, **3e** (105.2 mg, 82%) was prepared from **1** (49.5mg, 0.5 mmol) and **2e** (120.5 mg, 0.6 mmol). : ^{1}H NMR: δ = 1.43 (t, J = 6.9 Hz, 3H), 4.45 (q, J = 6.9 Hz, 2H), 7.64-7.68 (m, 2H), 7.88-7.92 (m, 2H); ^{13}C NMR: δ = 14.2, 62.7, 130.6,

131.3, 131.5, 132.3, 163.2, 185.1

Ethyl 4-fluorobenzoylformate (3f)[23]

According to general procedure, **3f** (71.3 mg, 73%) was prepared from **1** (49.5mg, 0.5 mmol) and **2f** (84.0 mg, 0.6 mmol). : ^{1}H NMR: δ = 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: δ = 14.2, 62.6, 116.3 (d, J_{C-F} = 22.1Hz), 129.0 (d, J_{C-F} = 3.5Hz), 133.0 (d, J_{C-F} = 9.3Hz), 163.4, 166.8 (d, J_{C-F} = 257.5Hz), 184.6

Ethyl 3-chlorobenzoylformate (3g)[26]
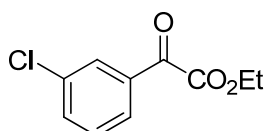
According to general procedure, **3g** (85.8 mg, 81%) was prepared from **1** (49.5mg, 0.5 mmol) and **2g** (93.8 mg, 0.6 mmol). : ^{1}H NMR: δ = 1.43 (t, J = 7.2 Hz, 3H), 4.46 (q, J = 7.2 Hz, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.60-7.65 (m, 1H), 7.89-7.94 (m, 1H), 8.00-8.03 (m, 1H); ^{13}C NMR: δ = 14.2, 62.8, 128.3, 129.9, 130.3, 134.1, 134.9, 135.3, 163.0, 184.9

Ethyl 2-chlorobenzoylformate (3h)[27]

According to general procedure, **3h** (48.6 mg, 46%) was prepared from **1** (49.5mg, 0.5 mmol) and **2h** (93.8 mg, 0.6 mmol). : ^{1}H NMR: δ = 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 = 1.8Hz, 7.8Hz, 1H); ^{13}C NMR: δ = 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]

According to general procedure, **3i** (79.7 mg, 83%) was prepared from **1** (49.5mg, 0.5

mmol) and **2i** (81.2 mg, 0.6 mmol). : ^{1}H NMR: δ = 1.42 (t, *J* = 7.2 Hz, 3H), 2.61 (s, 3H), 4.43 (q, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.5Hz, 2H), 7.45-7.53 (m, 1H), 7.69 (d, *J* = 7.5Hz, 1H); ^{13}C NMR: δ = 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)

According to general procedure, **3j** (63.5 mg, 50%) was prepared from **1** (49.5mg, 0.5 mmol) and **2j** (118.8 mg, 0.6 mmol). : ^{1}H NMR: δ = 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* = 1.5Hz, 7.5Hz, 1H), 7.82 (dd, *J* = 1.2Hz, 7.8Hz, 1H); ^{13}C NMR: δ = 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$^+$ 254.0943.　Found m/z 254.0945.

Ethyl 4-methoxycarbonylbenzoylformate (3k)

According to general procedure, **3k** (68.6 mg, 58%) was prepared from **1** (49.5mg, 0.5 mmol) and **2k** (108.0 mg, 0.6 mmol). : ^{1}H NMR: δ = 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: δ = 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)
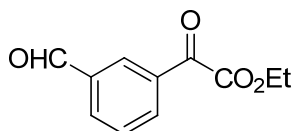
According to general procedure, **3l** (51.7 mg, 50%) was prepared from **1** (49.5mg, 0.5 mmol) and **2l** (90.0 mg, 0.6 mmol). : ^{1}H NMR: δ = 1.45 (t, *J* = 6.9 Hz, 3H), 4.49 (q, *J* = 6.9 Hz, 2H), 7.72 (t, *J* = 7.8 Hz, 1H), 8.19 (dt, *J* = 1.5Hz, 7.8Hz, 1H), 8.32 (dt, *J* =

1.5Hz, 7.8Hz, 1H), 8.53 (t, *J* = 1.5Hz, 1H), 10.10 (s, 1H); ^{13}C 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.

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Chapter 2

Synthesis of Functionalized Isoindoles

by the Rhodium-Catalyzed Reaction of Cyanoformates

with *ortho*-Borylbenzalacetone Derivatives

Abstruct: 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.[1] 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.[2] 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.[3] 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).[2] 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).
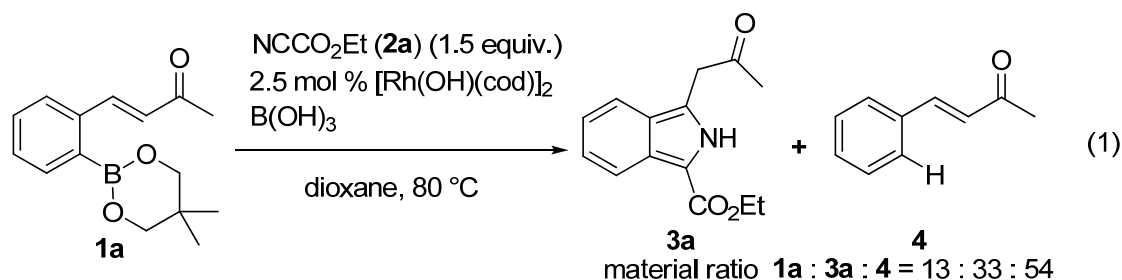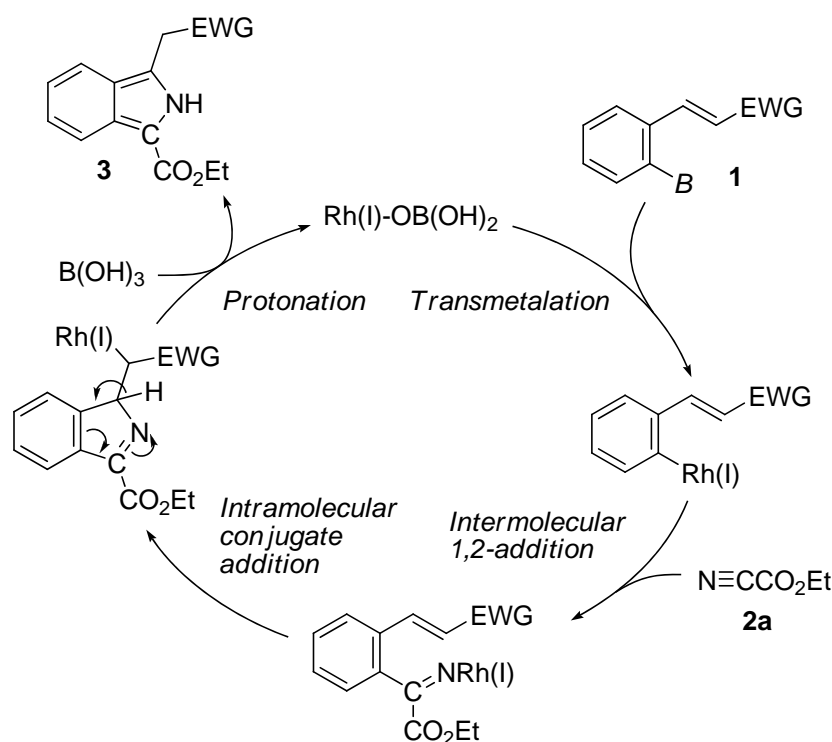
Figure 1. A plausible mechanism for formation of isoindole

A plausible mechanism for the formation of isoindole **3a** is shown in Figure 1. An arylrhodium species is initialy 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**

Entry	Solvent	2a (equiv.)	B(OH)$_3$ (equiv.)	Time (h)	Ratio^a		
					1a :	**3a** :	**4**
1	Dioxane	1.5	1.0	15	13 :	33 :	54
2	Toluene	1.5	1.0	15	0 :	0 :	100
3	NMP	1.5	1.0	15	56 :	27 :	17
4	NMP	1.5	3.0	3	0 :	71 :	29
5	NMP	3.0	3.0	3	0 :	87 :	13
						(75%)^b	

^{a} Determined by ^{1}H NMR integral value of crude reaction mixture.
^{b} Isolated yield of **3a**.

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 2. Synthesis of various 3-acylmethyl-2*H*-isoindoles (**3**) from **1** and **2**

2.5 mol % [Rh(OH)(cod)]$_2$, B(OH)$_3$ 3.0 equiv., NMP, 80 °C, 3 h
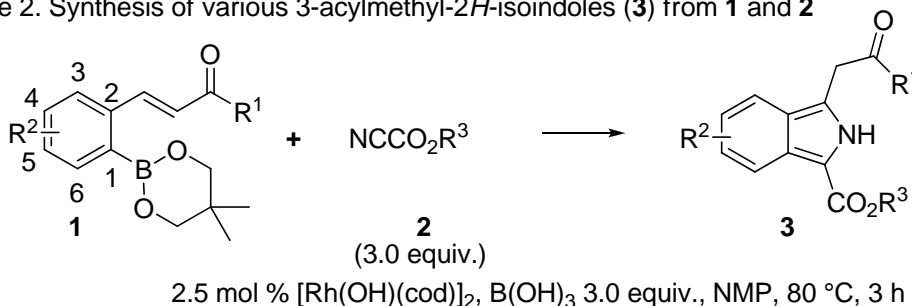
Entry	1	R^1	R^2	2	R^3	3	Yield(%)^a
1	**1a**	Me	H	**2a**	Et	**3a**	75
2	**1a**	Me	H	**2b**	Me	**3b**	57
3	**1a**	Me	H	**2c**	^{i}Pr	**3c**	72
4	**1a**	Me	H	**2d**	^{i}Bu	**3d**	76
5	**1b**	Me	4-MeO	**2b**	Et	**3e**	72
6	**1c**	Me	5-MeO	**2b**	Et	**3f**	69
7	**1d**	Me	4-Cl	**2b**	Et	**3g**	26
8	**1e**	Me	5-Cl	**2b**	Et	**3h**	46
9	**1f**	Ph	H	**2b**	Et	**3i**	59

^{a} Isolated yield of **3**.

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).[4] 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**.
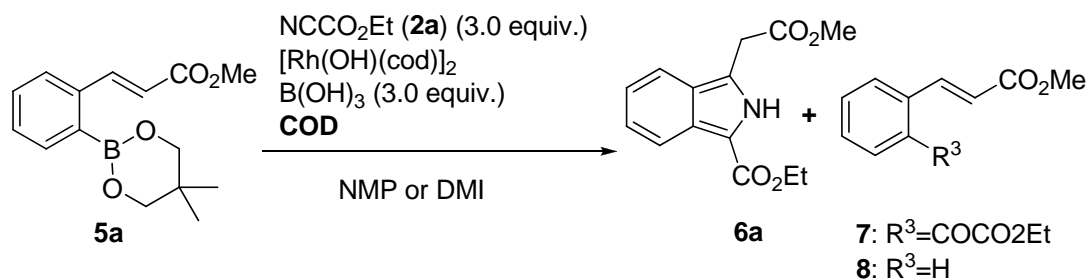
Entry	[Rh(OH)(cod)]$_2$	COD (equiv.)	Temp (°C)	Time (h)	Ratio[a] 5a : 6a : 7 : 8
1	2.5 mol %	none	80	12	83 : 10 : 7 : 0
2	2.5 mol %	1	80	12	60 : 24 : 9 : 7
3	2.5 mol %	10	80	12	23 : 49 : 16 : 12
4	2.5 mol %	10	120	12	23 : 63 : 5 : 9
5[b]	3.5 mol %	10	120	3	0 : 79 : 10 : 11 (59 %)[c]

[a] Determined by ^{1}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-2*H*-isoindoles (**6**) from **5** and **2a**

3.5 mol % [Rh(OH)(cod)]$_2$, B(OH)$_3$ 3.0 equiv., COD 10 equiv.

Entry	5	R^1	R^2	6	Yield(%)^a
1	**5a**	Me	H	**6a**	59
2	**5b**	Me	4-MeO	**6b**	62
3	**5c**	Me	5-MeO	**6c**	56
4	**5d**	tBu	H	**6d**	50

^{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, δ = 7.26) or tetramethylsilane (^{1}H, δ = 0.00) and CDCl$_3$ (^{13}C, δ = 77.0) or DMSO-d$_6$ (^{13}C, δ = 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^{TM} 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)$_2$]$_2$ was prepared according to the reported procedure.[9] 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 Ph3P=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%).

(*E*)-4-(2-(5, 5-Dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)but-3-en-2-one (1a)
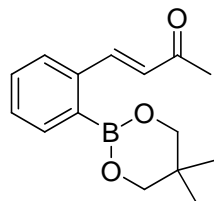
IR (KBr): 2964, 2894, 1662, 1622, 1591, 1478, 1412, 1327, 1207, 1132, 1090, 1032 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.06 (s, 6H), 2.39 (s, 3H), 3.83 (s, 4H), 6.57 (d, *J* = 16.2 Hz, 1H), 7.33-7.45 (m, 2H), 7.63-7.66 (m, 1H), 7.86 (dd, *J* = 6.9 Hz, 1.8 Hz, 1H), 8.47 (d, *J* = 16.2 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, the boron-bound carbon was not detected due to quadrupolar relaxation): δ = 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)
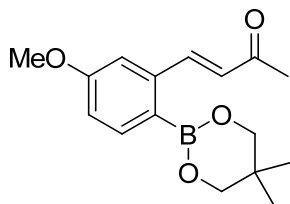
IR (KBr): 3094, 3077, 3006, 1671, 1624, 1593, 1553, 1478, 1443, 1426, 1402, 1377, 1179, 1132 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.05 (s, 6H), 2.39 (s, 3H), 3.81 (s, 4H), 3.84 (s, 3H), 6.54 (d, *J* = 16.2 Hz, 1H), 6.92 (dd, *J* = 8.7 Hz, 2.7Hz, 1H), 7.14(d, *J* = 2.7 Hz, 1H), 7.82 (d, *J* = 8.7 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): δ = 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)
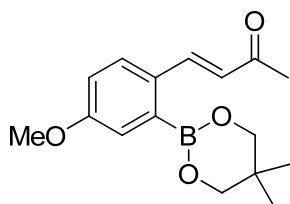
IR (KBr): 2961, 1663, 1651, 1619, 1593, 1489, 1428, 1377, 1304, 1240, 1146, 1092 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.07 (s, 6H), 2.36 (s, 3H), 3.83 (s, 4H), 3.85 (s, 3H), 6.51 (d, *J* = 16.2 Hz, 1H), 6.96 (dd, *J* = 8.7 Hz, 2.7Hz, 1H), 7.36(d, *J* = 2.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 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): δ = 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

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(*E*)-4-(5-Chloro-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)but-3-en-2-one (1d)
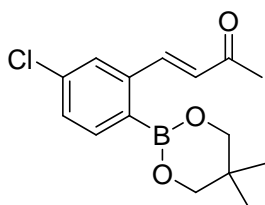
IR (ATR): 2962, 1668, 1624, 1577, 1541, 1471, 1419, 1290, 1257, 1230, 1126, 1105 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.05 (s, 6H), 2.38 (s, 3H), 3.82 (s, 4H), 6.55 (d, *J* = 16.0 Hz, 1H), 7.33 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 8.41 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$, the boron-bound carbon was not detected due to quadrupolar relaxation): δ = 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.

(*E*)-4-(4-Chloro-2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)but-3-en-2-one (1e)
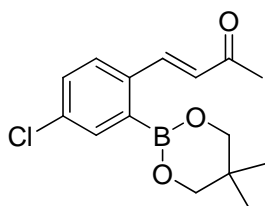
IR (ATR): 2962, 1654, 1579, 1477, 1423, 1361, 1286, 1252, 1200, 1140, 1088 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.04 (s, 6H), 2.37 (s, 3H), 3.81 (s, 4H), 6.53 (d, *J* = 16.5 Hz, 1H), 7.31 (dd, *J* = 8.1 Hz, 2.1 Hz, 1H), 7.58 (d, *J* = 2.1 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 8.40 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, the boron-bound carbon was not detected due to quadrupolar relaxation): δ = 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$^+$)

292.1038. Found m/z 292.1040.

(*E*)-3-(2-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)phenyl)-1-phenylprop-2-en-1-one (1f)
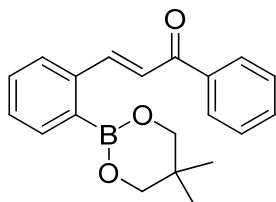
IR (KBr): 2959, 1657, 1606, 1589, 1578, 1564, 1475, 1412, 1375, 1336, 1304, 1279, 1244, 1213, 1132, 1091, 1036 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.03 (s, 6H), 3.80 (s, 4H), 7.33 (d, *J* = 15.9 Hz, 1H), 7.38-7.59 (m, 6 H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.85 (dd, *J* = 6.9 Hz, 1.5 Hz, 1H), 7.90-8.02 (m, 2 H), 8.59 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, the boron-bound carbon was not detected due to quadrupolar relaxation): δ = 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$^+$): 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)
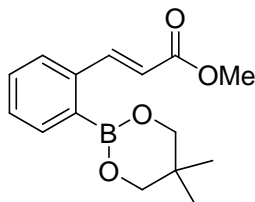
IR (KBr): 2943, 1707, 1630, 1593, 1563, 1480, 1433, 1412, 1372, 1325, 1302, 1267, 1244, 1196, 1179, 1165, 1134 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.05 (s, 6H), 3.80 (s, 3H), 3.82 (s, 4H), 6.34 (d, *J* = 15.9 Hz, 1H), 7.31-7.44 (m, 2 H), 7.61-7.66 (m, 1H), 7.80-7.84 (m, 1H), 8.54 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$, the boron-bound carbon was not detected due to quadrupolar relaxation): δ = 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$^+$): 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)
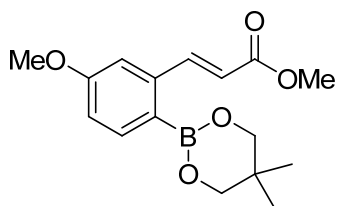
IR (KBr): 2957, 1700, 1632, 1597, 1557, 1480, 1335, 1302, 1250, 1229, 1177, 1132, 1024 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.03 (s, 6H), 3.80 (s, 7H), 3.84 (s, 3H), 6.32 (d, *J* = 15.9 Hz, 1H), 6.90 (dd, *J* = 8.4 Hz, 2.7 Hz, 1H), 7.13 (d, *J* = 2.7 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 8.58 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 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 C$_{16}$H$_{21}$BO$_5$ (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)
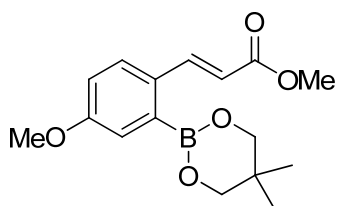
IR (KBr): 2963, 1701, 1622, 1593, 1491, 1445, 1426, 1331, 1242, 1211, 1144, 1092, 1042 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.05 (s, 6H), 3.78 (s, 3H), 3.82 (s, 4H), 3.84 (s, 3H), 6.26 (d, *J* = 15.9 Hz, 1H), 6.94 (dd, *J* = 8.7 Hz, 2.7 Hz, 1H), 7.32 (d, *J* = 2.7 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 8.50 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$, 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 C$_{16}$H$_{21}$BO$_5$ (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)
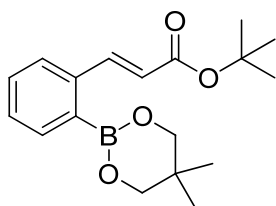
IR (KBr): 2969, 1703, 1630, 1593, 1561, 1478, 1416, 1368, 1327, 1300, 1267, 1246, 1208, 1152, 1001 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.05 (s, 6H), 1.54 (s, 9H), 3.82 (s, 4H), 6.28 (d, J = 15.9 Hz, 1H), 7.28-7.42 (m, 2H),7.61-7.66 (m, 1H), 7.78-7.83 (m, 1H), 8.45 (d, J = 15.9 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$, the boron-bound carbon was not detected due to quadrupolar relaxation): δ = 21.8, 28.2, 31.6, 72.4, 80.0, 120.6, 125.8, 128.6, 130.3, 135.2, 139.9, 145.1, 166.6; HRMS (FAB$^+$): Calcd for C$_{18}$H$_{26}$BO$_4$ [M+H]$^+$ 317.1919. Found m/z 317.1920.

The rhodium-catalyzed reaction of cyanoformates with ortho-borylbenzalacetone Derivatives.

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

To a mixture of **1a** (78.3 mg, 0.30 mmol), B(OH)$_3$ (55.6 mg, 0.90mmol), 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$_2$O (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$_2$SO$_4$. 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)
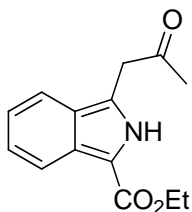
IR (KBr): 3214, 1717, 1651, 1471, 1291; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.47 (t, J = 7.2 Hz, 3H), 2.26 (s, 3H), 4.18 (s, 2H), 4.46 (q, J = 7.2 Hz, 2H), 7.11 (dd, J = 9.0 Hz, 6.9 Hz, 1H), 7.28 (dd, J = 8.7 Hz, 6.9 Hz, 1H), 7.57 (dd, J = 8.7 Hz, 0.6 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H), 11.05 (brs, 1H); ^{13}C 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$_{14}$H$_{15}$NO$_3$, M$^+$ 245.1052. Found m/z 245.1052.

Methyl 3-(2-oxopropyl)-2*H*-isoindole-1-carboxylate (3b)
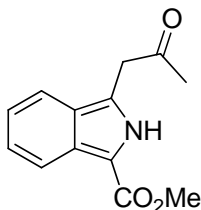
IR (ATR): 3219, 1720, 1653, 1473, 1315, 1292, 1209, 1159, 1088, 1014; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 2.30 (s, 3H), 3.98 (s, 3H), 4.17 (s, 2H), 7.08-7.14 (m, 1H), 7.25-7.30 (m, 1H), 7.53-7.58 (m, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 11.07 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d$_6$): δ = 29.5, 40.1, 50.7, 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)-2*H*-isoindole-1-carboxylate (3c)
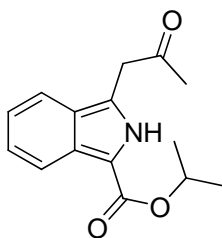
IR (KBr): 3227, 1717, 1647, 1474, 1370, 1289, 1190, 1163, 1090, 1013; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.48 (d, *J* = 6.0Hz, 6H), 2.21 (s, 3H), 4.19 (s, 2H), 5.36 (quint, *J* = 6.0Hz, 1H), 7.09-7.15 (m, 1H), 7.26-7.33 (m, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 12.12 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 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)-2*H*-isoindole-1-carboxylate (3d)
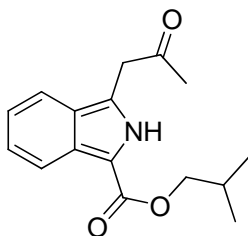
IR (KBr): 3231, 1717, 1647, 1475, 1468, 1321, 1281, 1204, 1184, 1163, 1088; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.01 (d, *J* = 6.6Hz, 6H), 1.95-2.08 (m, 1H), 2.17 (s, 3H), 4.08 (d, *J* = 6.9 Hz, 2H), 4.20 (s, 2H), 6.96-7.03 (m, 1H), 7.17-7.24 (m, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 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)-2*H*-isoindole-1-carboxylate (3e)
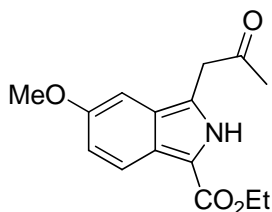
IR (ATR): 3234, 1720, 1653, 1454, 1286, 1186, 1163, 1078, 1028; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.45 (t, J = 7.2Hz, 3H), 2.28 (s, 3H), 3.86 (s, 3H), 4.10 (s, 2H), 4.42 (q, J = 7.2 Hz, 2H), 6.74 (d, J = 2.2 Hz, 1H), 6.97 (dd, J = 9.2 Hz, 2.2 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 10.85 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 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; HRMS (ESI$^+$): calcd. for $C_{15}H_{18}NO_4$, [M+H]$^+$ 276.1230. Found m/z 276.1232.

Ethyl 6-methoxy-3-(2-oxopropyl)-2*H*-isoindole-1-carboxylate (3f)
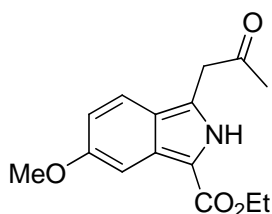
IR (KBr): 3214, 1717, 1649, 1634, 1480, 1451, 1431, 1312, 1293, 1246, 1227, 1177, 1136, 1088, 1028; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.44 (t, J = 7.1 Hz, 3H), 2.29 (s, 3H), 3.90 (s, 3H), 4.11 (s, 2H), 4.42 (q, J = 7.1 Hz, 2H), 6.79 (dd, J = 9.1 Hz, 2.3 Hz, 1H), 7.35 (brs, 1H), 7.43 (d, J = 9.1 Hz, 1H), 10.67 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d$_6$): δ = 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; HRMS (EI$^+$): calcd. for $C_{15}H_{17}NO_4$, [M]$^+$ 275.1158. Found m/z 275.1158.

Ethyl 5-chloro-3-(2-oxopropyl)-2*H*-isoindole-1-carboxylate (3g)
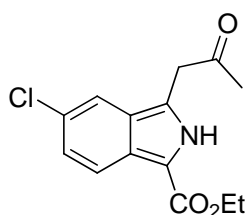
IR (ATR): 3224, 1718, 1651, 1498, 1458, 1290, 1203, 1161, 1103, 1049; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.45 (t, *J* = 7.2 Hz, 3H), 2.32 (s, 3H), 4.13 (s, 2H), 4.43 (q, *J* = 7.2 Hz, 2H), 7.18 (dd, *J* = 9.0 Hz, 1.8 Hz, 1H), 7.53 (dd, *J* = 1.8 Hz, 0.6 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 11.15 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d$_6$): 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 C$_{14}$H$_{15}$ClNO$_3$, [M+H]$^+$ 280.0735. Found m/z 280.0736.

Ethyl 6-chloro-3-(2-oxopropyl)-2*H*-isoindole-1-carboxylate (3h)
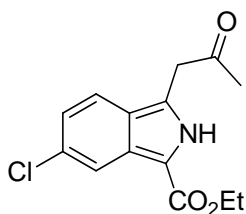
IR (ATR): 3213, 1714, 1649, 1498, 1464, 1425, 1288, 1186, 1161, 1092, 1057, 1030; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.46 (t, *J* = 7.1 Hz, 3H), 2.31 (s, 3H), 4.15 (s, 2H), 4.44 (q, *J* = 7.1 Hz, 2H), 7.03 (dd, *J* = 9.0 Hz, 1.9 Hz, 1H), 7.48 (d, *J* = 9.0 Hz, 1H), 8.04 (brs, 1H), 11.10 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d$_6$): 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 C$_{14}$H$_{15}$ClNO$_3$, [M+H]$^+$ 280.0735. Found m/z 280.0737.

Ethyl 3-(2-oxo-2-phenylethyl)-2*H*-isoindole-1-carboxylate (3i)
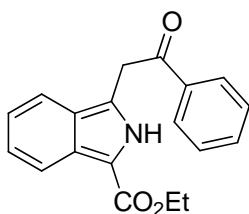
IR (KBr): 3227, 1686, 1646, 1482, 1468, 1287, 1204, 1184, 1084,1036; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.41 (t, *J* = 6.9 Hz, 3H), 4.39 (q, *J* = 6.9 Hz, 2H), 4.92 (s, 2H), 6.99-7.11 (m, 1H),7.21-7.32 (m, 1H), 7.56-7.68 (m, 2H), 7.68-7.80 (m, 2H), 8.01 (d, *J* = 8.4 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 2H), 13.17 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d$_6$): 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 C$_{14}$H$_{15}$ClNO$_3$, [M]$^+$ 307.1208. Found m/z 307.1210.

A typical procedure for the synthesis of 3-alkoxycarbonylmethyl-2*H*-isoindole derivatives 6.

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)-2*H*-isoindole-1-carboxylate (6a)
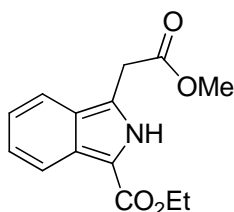
IR (KBr): 3206, 1742, 1663, 1482, 1313; ^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 1.36 (t, *J* = 7.2 Hz, 3H), 3.63 (s, 3H), 4.15 (s, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 7.02 (dd, *J* = 6.9 Hz, 0.6 Hz, 1H), 7.22 (dd, *J* = 6.9 Hz, 0.6 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 13.1 (brs, 1H); ^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 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)-2*H*-isoindole-1-carboxylate (6b)
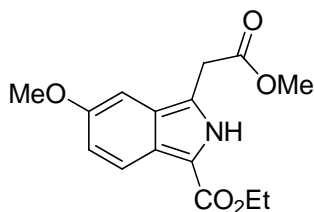
IR (ATR): 3232, 1734, 1653, 1541, 1471, 1433, 1288, 1217, 1167, 1078, 1018; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.44 (t, *J* = 7.2Hz, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 4.02 (s, 2H), 4.42 (q, *J* = 7.2 Hz, 2H), 6.77 (d, *J* = 2.2 Hz, 1H), 6.96 (dd, *J* = 9.2 Hz, 2.2 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 10.55 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d$_6$): δ = 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.

Ethyl 6-methoxy-3-(2-methoxy-2-oxoethyl)-2*H*-isoindole-1-carboxylate (6c)
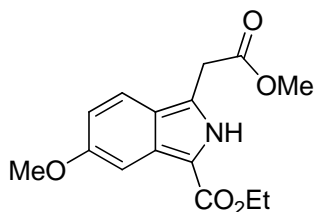
IR (KBr): 3206, 1732, 1653, 1634, 1483, 1451, 1314, 1250, 1227, 1196, 1179, 1136, 1088, 1022, 1005; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.44 (t, *J* = 7.1 Hz, 3H), 3.78 (s, 3H), 3.89 (s, 3H), 4.03 (s, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 6.79 (dd, *J* = 9.1 Hz, 2.3 Hz, 1H), 7.34 (brs, 1H), 7.46 (d, *J* = 9.1 Hz, 1H), 10.55 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d$_6$): δ = 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 (EI$^+$): 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)
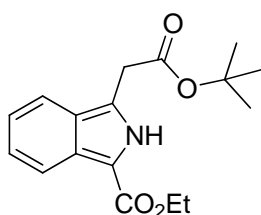
IR (KBr): 3193, 1736, 1665, 1468, 1368, 1304, 1288, 1208, 1163, 1140, 1125, 1084, 1026; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.46 (t, *J* = 7.2 Hz, 3H), 1.48 (s, 9H), 4.01 (s, 2H), 4.46 (q, *J* = 7.2 Hz, 2H), 7.05-7.13 (m, 1H), 7.23-7.30 (m, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 11.28 (brs, 1H); ^{13}C NMR (125 MHz, DMSO-d$_6$): δ = 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 (EI$^+$): calcd. for C$_{17}$H$_{21}$NO$_4$, M$^+$ 303.1471, Found m/z 303.1463.

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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 CH_2Cl_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 CH_3CN at 70 °C.[4] Isolation by column chromatography on silica gel afforded the desired benzoyl cyanide **2a** in 79% yield (Equation 1).

$$\text{(1)}$$
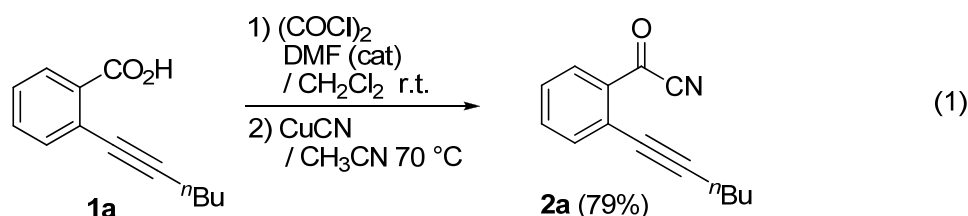
When 2-(1-hexyn-1-yl)benzoyl cyanide **2a** thus obtained was treated with 3-phenylpropylamine, the amino group attacked the carbonyl group of **2a**, with the cyano group acting as a leaving group to afford the corresponding amide (**3a**) in 97% yield. The related reaction between 3-phenylpropanol and **2a** in the presence of Et_3N 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-benzoylamino-3-pentanoylindenone **5aa** as shown in Equation 3.[5]

PhCH_2CH_2CH_2NH_2
(1.0 equiv)
or
PhCH_2CH_2CH_2OH
(1.0 equiv)
$\underrightarrow{\text{Et}_3\text{N (1.2 equiv)}}$
dioxane r.t.
1h

X=NH **3a** (97%)
X=O **3b** (88%)

(2)

PhCO_2H
4a
(2.0 equiv)

(3)

2a → **5aa**

in p-xylene, 140 °C, 24h   84%
in toluene,   100 °C, 48h   84%
in dioxane,   100 °C, 48h   87%
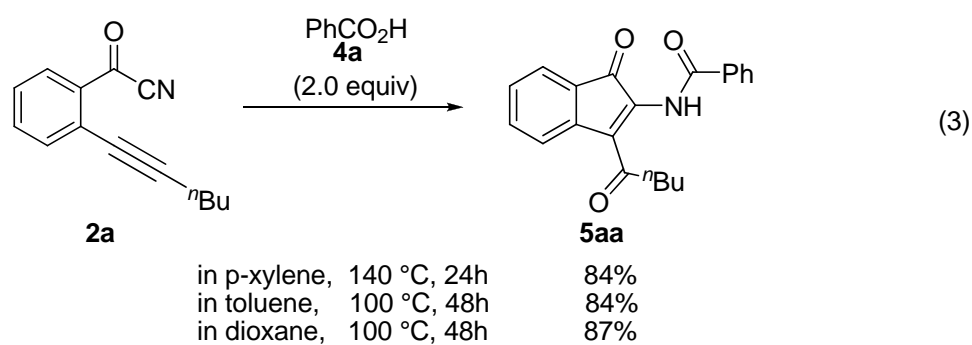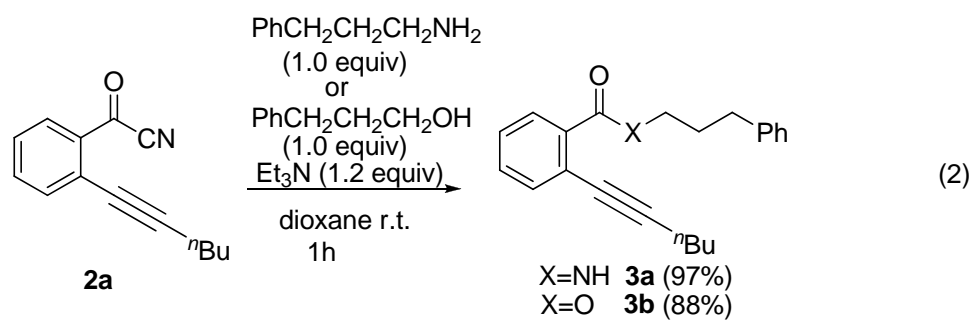
Table 1. Reaction of **2a** with various carboxylic acids (**4**).

R^2CO_2H
4a~k
(2.0 equiv)

p-xylene
140 °C
24h

2a → **5aa~5ak**

entry	4	R^2	product 5	yield(%)[a]
1	**4a**	Ph	**5aa**	84
2	**4b**	4-MeO-C_6H_4	**5ab**	64
3	**4c**	4-Cl-C_6H_4	**5ac**	89
4	**4d**	4-Br-C_6H_4	**5ad**	88
5	**4e**	4-MeO_2C-C_6H_4	**5ae**	60
6	**4f**	2-Pyridyl	**5af**	62
7	**4g**	2-Thienyl	**5ag**	83
8	**4h**	(E)-PhCH=CH-	**5ah**	87
9	**4i**	Me	**5ai**	92[b]
10	**4j**	^iPr	**5aj**	83
11	**4k**	^tBu	**5ak**	87

[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-acylaminoindenone **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**[6] bearing a terminal alkyne resulted in the formation of a mixture of intractable compounds.

$$\text{(4)}$$

5ba R=Ph (73%)
5bi R=Me (91%)
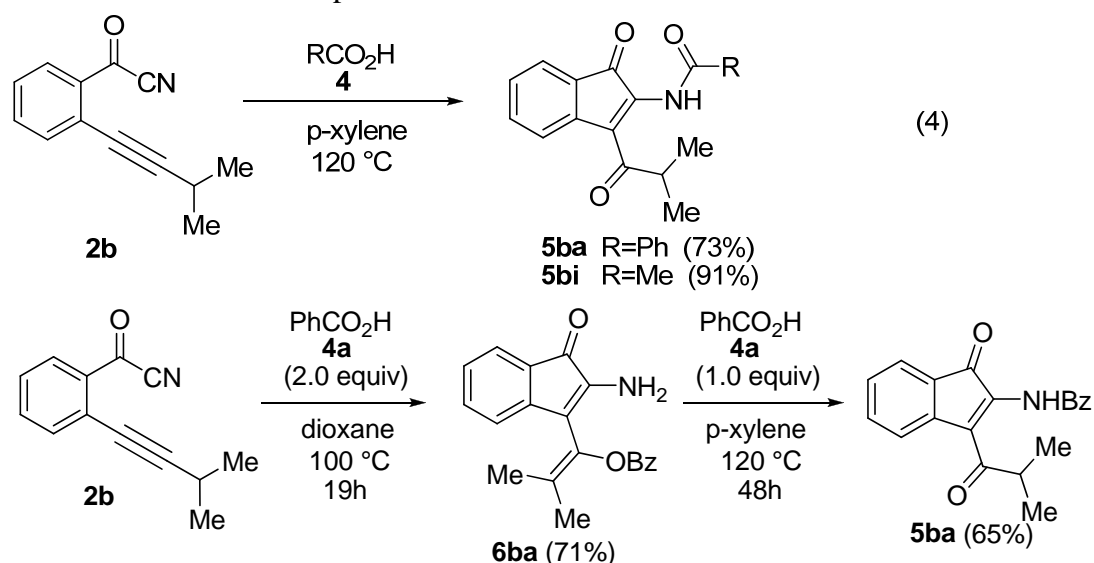
Scheme 1. Formation of **5ba** from **2b** and **4a** *via* enole ester **6ba**.

2c R=*t*Bu
2d R=Ph
2e R=TMS
2f R=H
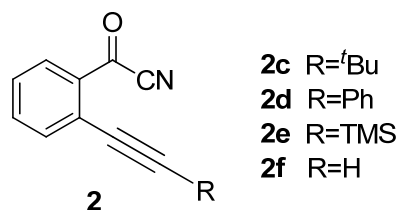
Figure 1. The substrate which failed to react with carboxylic acids.

$$(5)$$
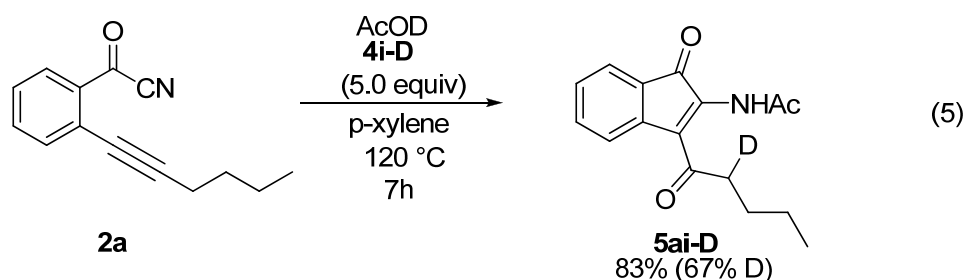
In order to gain a further insight into the mechanism, it was treated **2a** with acetic acid-d$_1$ **4i-D** (5 equiv) in p-xylene at 120 °C for 7 h. Under these conditions, **5ai-D** which incorporated a deuterium at the α-position of the carbonyl group (67% D), was isolated in 83% yield (Equation 5).[7] 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**).
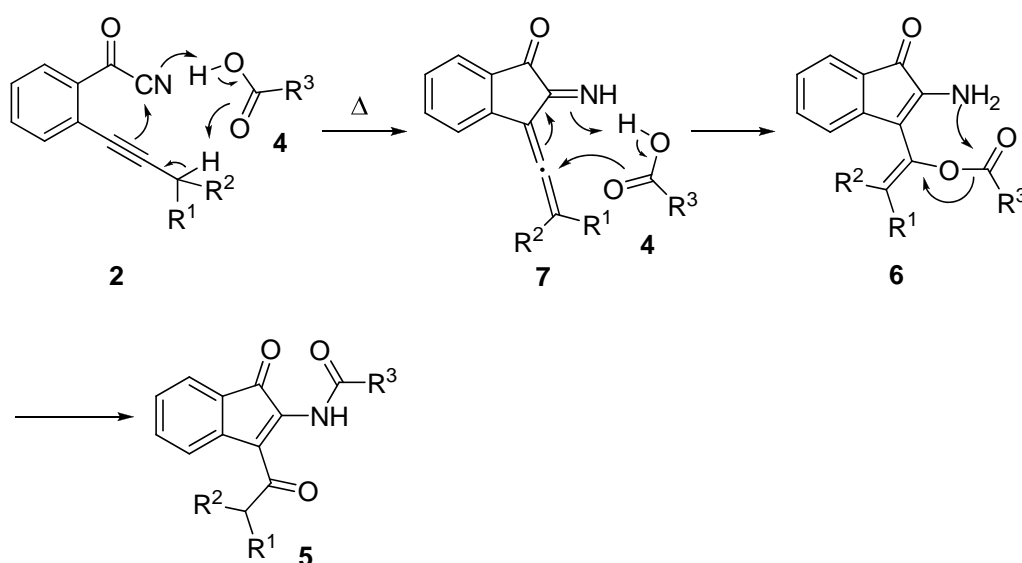
Scheme 2. Proposed mechanism for the formation of **5** from **2** and **4**.

Next, the reactivities of the product were examined. Treatment of **5aa** with a primary amine resulted in a facile substitution reaction of the acetylamino 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]

R= -CH₂CH₂CH₂Ph **11aaa** (95%)
R= -CHMePh   **11aab** (97%)

(6)

R¹=ⁿBu, R²=Ph   **9aia** (89%)
R¹=ⁿBu, R²=Me   **9aib** (68%)
R¹=ⁱPr, R²=Ph   **9bia** (96%)

(7)

R1= ⁿBu **12ai** (52%)
     ⁱPr **12bi** (46%)

(8)
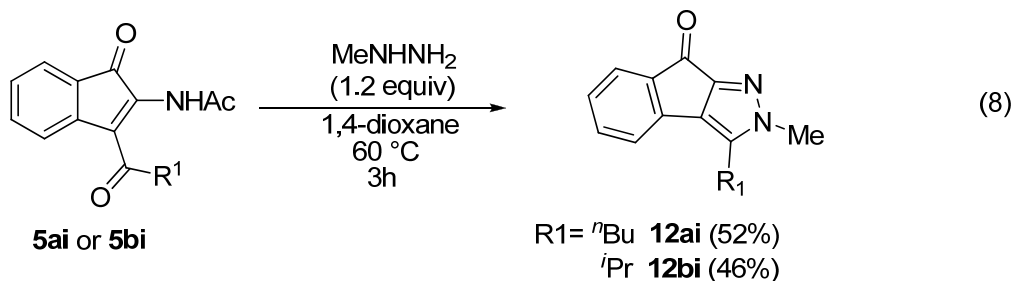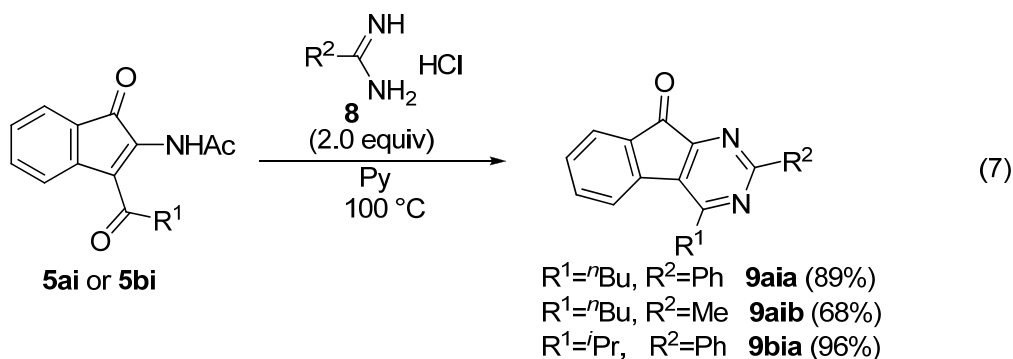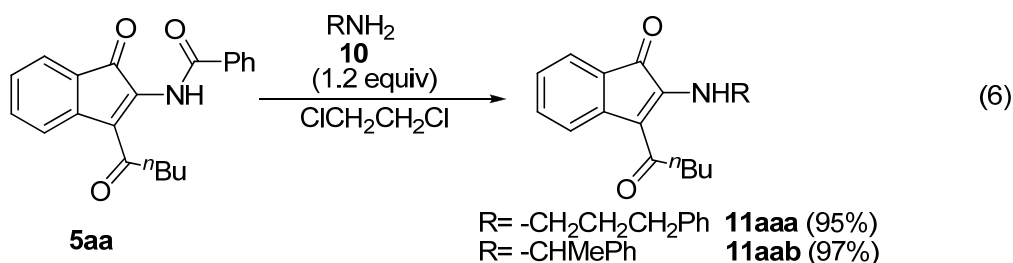
Conclusion

The indenone skeleton represents an important class of carbocyclic molecule, and many of these derivatives are found in important natural products.[11] Some of indenone derivatives are also known to be pharmacologically active compounds.[12] 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.[13] The author has found that 2-alkynylbenzoyl cyanides possessing a propargylic hydrogen react readily with carboxylic acids to provide 2-acylamino-3-acylindenones. 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-acylindenones 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, δ = 7.26) or tetramethylsilane (^{1}H, δ = 0.00) and CDCl$_3$ (^{13}C, δ = 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^{TM} 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-alkynylbenzoyl cyanides **2** were prepared from the corresponding 2-alkynylbenzoic acids by the following procedure.

Representative procedure for the preparation of 2-alkynylbenzoyl cyanides 2.

Oxalyl chloride (1.60 ml; 18.7 mmol) was added dropwise to a mixture of 2-(1-hexyn-1-yl) benzoic acid **1a** (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 **2a** (2.83g, 79%).

2-(Hexyn-1-yl)benzoyl cyanide (2a)
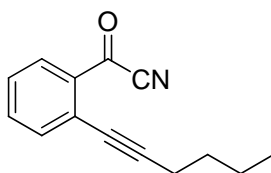
IR (neat): 2959, 2220, 1682, 1663, 1482, 1231 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.96 (t, J = 7.2 Hz, 3H), 1.42-1.58 (m, 2H), 1.58-1.72 (m, 2H), 2.51 (t, J = 7.2Hz, 2H), 7.42-7.52 (m, 1H), 7.54-7.67 (m, 2H), 8.05-8.12 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.8, 19.8, 22.2, 30.4, 77.9, 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 C$_{14}$H$_{13}$NO [M]$^+$: 211.0997; Found: 211.0997.

2-(3-Methylbutyn-1-yl)benzoyl cyanide (2b)
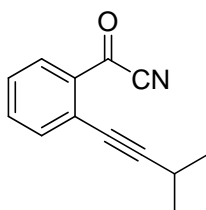
IR (ATR): 3066, 2933, 2873, 2222, 1680, 1591, 1558, 1479, 1279, 1226, 968 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.31 (d, J = 6.9 Hz, 6H), 2.87 (sept, J = 6.9 Hz, 1H), 7.44-7.51 (m, 1H), 7.55-7.66 (m, 2H), 8.05-8.09 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.8, 22.5, 77.1, 105.9, 113.5, 125.8, 127.9, 132.5, 133.7, 135.0, 135.1, 166.9; HRMS (EI$^+$): *m/z* Calcd for C$_{13}$H$_{11}$NO[M]$^+$: 197.0841; Found: 197.0843.

2-(3,3-Dimethylbutyn-1-yl)benzoyl cyanide (2c)
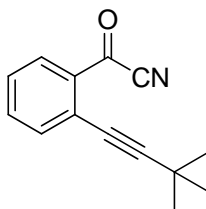
IR (ATR): 2968, 2359, 2218, 1668, 1589, 1552, 1471, 1360, 1290, 1227, 1203 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.37 (s, 9H), 7.42-7.50 (m, 1H), 7.54-7.66 (m, 2H), 8.04-8.09 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 28.5, 30.4, 76.4, 108.2, 113.5, 125.7, 127.8, 132.4, 133.6, 134.9, 135.0, 166.8; HRMS (EI$^+$): *m/z* Calcd for C$_{14}$H$_{13}$NO [M]$^+$: 211.0997; Found: 211.1001.

2-(Phenylethynyl)benzoyl cyanide (2d)
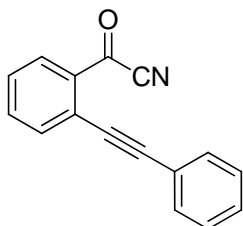
IR (ATR): 2362, 2210, 1672, 1552, 1491, 1273, 1230, 1020, 966 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.34-7.44 (m, 3H), 7.52-7.59 (m, 1H), 7.61-7.69 (m, 2H), 7.69-7.77 (m, 2H), 8.14-8.21 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 86.5, 98.0, 113.3, 122.3, 124.8, 128.5 (2 signals overlapping), 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)
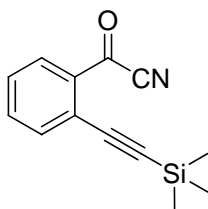
IR (ATR): 2958, 2360, 2218, 2156, 1676, 1591, 1560, 1477, 1234, 970, 843 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.29 (s, 9H), 7.50-7.59 (m, 1H), 7.62-7.70 (m, 2H), 8.08-8.14 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = -0.5, 100.9, 105.0, 113.2, 124.3, 128.7, 132.6, 133.8, 135.0, 135.5, 166.5; HRMS (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 (0.81g, 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) ware 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 CH_2Cl_2. 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)
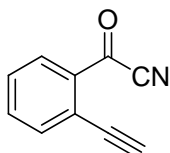
IR (ATR): 3276, 2360, 2218, 2102, 1672, 1589, 1556, 1475, 1302, 1236, 968 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.56 (s, 1H), 7.58-7.65 (m, 1H), 7.67-7.76 (m, 2H), 8.17-8.22 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 80.2, 85.7, 112.9, 123.2, 129.2, 133.3, 133.9, 135.2, 136.1, 166.3; HRMS (EI$^+$): *m/z* Calcd for C$_{10}$H$_5$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 Na$_2$SO$_4$. 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)
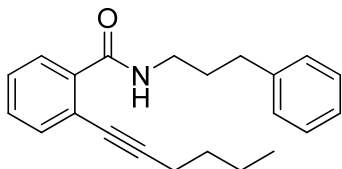
IR (ATR): 3269, 2949, 2870, 2227, 1635, 1545, 1429, 1358, 1309, 1236, 1173 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.92 (t, *J* = 7.5 Hz, 3H), 1.37-1.52 (m, 2H), 1.52-1.65 (m, 2H), 1.90-2.05 (m, 2H), 2.45 (t, *J* = 7.2Hz, 2H), 2.74 (t, *J* = 7.5Hz, 2H), 3.47-3.57 (m,

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$_3$): δ = 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)
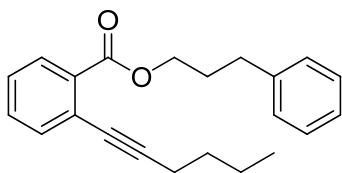
IR (ATR): 2956, 2931, 2866, 2229, 1726, 1711, 1483, 1450, 1288, 1244, 1130, 1078 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.95 (t, *J* = 7.4 Hz, 3H), 1.42-1.56 (m, 2H), 1.52-1.70 (m, 2H), 2.06-2.19 (m, 2H), 2.47 (t, *J* = 7.1Hz, 2H), 2.81 (t, *J* = 7.7Hz, 2H), 4.37 (t, *J* = 6.7 Hz, 2H), 7.16-7.26 (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$_3$): δ = 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)
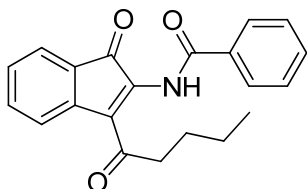
IR (KBr): 3312, 2959, 1726, 1678, 1662, 1512, 1277 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3H), 1.38 (pseudo sextet, *J* = 7.5 Hz, 2H), 1.74 (pseudo quintet, *J* = 7.5 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 7.14 (t, *J* = 7.5 Hz, 2H), 7.35 (dt, *J* =

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$_3$): δ = 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)
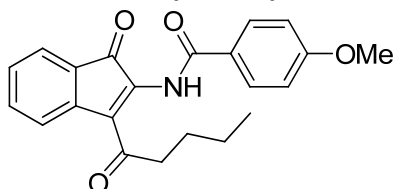
IR (ATR): 3280, 2956, 1720, 1672, 1604, 1533, 1502, 1458, 1309, 1248, 1173, 1124, 1080, 1020 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.91 (t, *J* = 7.5 Hz, 3H), 1.37 (pseudo sext, *J* = 7.5 Hz, 2H), 1.73 (pseudo quint, *J* = 7.5 Hz, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 3.88 (s, 3H), 6.95-7.02 (m, 2H), 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$_3$): δ = 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)
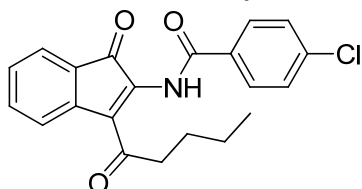
IR (ATR): 3290, 2958, 1722, 1657, 1516, 1456, 1271, 1088, 1009 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3H), 1.38 (pseudo sext, *J* = 7.2 Hz, 2H), 1.66-1.80 (m, 2H), 2.75 (t, *J* = 7.7 Hz, 2H), 7.10-7.19 (m, 2H), 7.32-7.40 (m, 1H), 7.44-7.52 (m, 3H), 7.81-7.88 (m, 2H), 8.40 (brs, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 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)
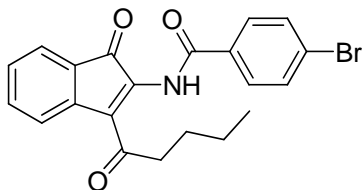
IR (ATR): 3282, 2956, 2870, 1724, 1660, 1522, 1458, 1298, 1178, 1070, 1007 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.94 (t, J = 7.5 Hz, 3H), 1.39 (pseudo sext, J = 7.5 Hz, 2H), 1.65-1.80 (m, 2H), 2.75 (t, J = 7.5 Hz, 2H), 7.09-7.19 (m, 2H), 7.36 (dt, J = 1.2 Hz, 7.5 Hz, 1H), 7.46 (d, J = 7.5Hz, 1H), 7.61-7.68 (m, 2H), 7.74-7.80 (m, 2H), 8.40 (brs, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 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)
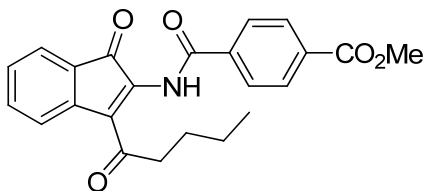
IR (ATR): 3303, 2956, 1720, 1678, 1520, 1458, 1433, 1279, 1111 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.92 (t, J = 7.2 Hz, 3H), 1.39 (pseudo sext, J = 7.2 Hz, 2H), 1.68-1.80 (m, 2H), 2.76 (t, J = 7.7 Hz, 2H), 3.96 (s, 3H), 7.10-7.19 (m, 2H), 7.36 (dt, J = 1.2 Hz, 7.5 Hz, 1H), 7.47 (d, J = 6.9 Hz, 1H), 7.92-7.99 (m, 2H), 8.13-8.19 (m, 2H), 8.46 (brs, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 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)
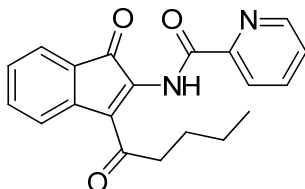
IR (ATR): 3315, 2954, 1718, 1691, 1597, 1508, 1456, 1173, 1117, 1068 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.91 (t, J = 7.2 Hz, 3H), 1.38 (pseudo sext, J = 7.2 Hz, 2H), 1.68-1.82 (m, 2H), 2.76 (t, J = 7.5 Hz, 2H), 7.09-7.18 (m, 2H), 7.35 (dt, J = 1.2 Hz, 7.7 Hz, 1H), 7.48 (d, J = 6.9 Hz, 1H), 7.53 (ddd, J = 7.8 Hz, 4.8 Hz, 1.2 Hz, 1H), 7.90 (dt, J

= 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$_3$): δ = 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; HRMS (EI$^+$): *m/z* Calcd for C$_{20}$H$_{18}$N$_2$O$_3$ [M]$^+$: 334.1317; Found: 334.1312.

2-(2-Thiophenecarbonyl)amino-3-pentanoylindenone (5ag)
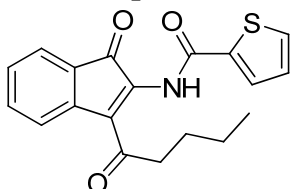
IR (ATR): 3294, 3087, 2960, 2868, 1724, 1651, 1510, 1454, 1415, 1358, 1282, 1176, 1082, 1047 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.92 (t, *J* = 7.2 Hz, 3H), 1.38 (pseudo sext, *J* = 7.2 Hz, 2H), 1.66-1.79 (m, 2H), 2.75 (t, *J* = 7.7 Hz, 2H), 7.09-7.19 (m, 3H), 7.35 (dt, *J* = 1.2 Hz, 7.5 Hz, 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$_3$): δ = 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; HRMS (EI$^+$): *m/z* Calcd for C$_{19}$H$_{17}$NO$_3$S [M]$^+$: 339.0929; Found: 339.0931.

2-Cinnamoylamino-3-pentanoylindenone (5ah)
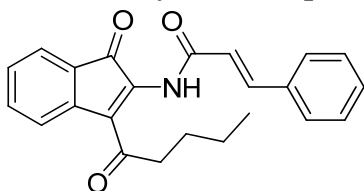
IR (ATR): 3334, 2954, 2866, 1722, 1684, 1628, 1520, 1452, 1342, 1198, 1157, 1124, 1070 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.93 (t, *J* = 7.2 Hz, 3H), 1.39 (pseudo sext, *J* = 7.2 Hz, 2H), 1.67-1.80 (m, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 6.59 (dd, *J* = 15.6 Hz, 1.2 Hz, 1H), 7.06-7.16 (m, 2H), 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$_3$): δ = 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; HRMS (EI$^+$): *m/z* Calcd for C$_{23}$H$_{21}$NO$_3$ [M]$^+$: 359.1521; Found: 359.1520.

2-Acetylamino-3-pentanoylindenone (5ai)
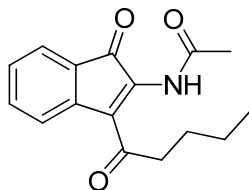
IR (ATR): 3332, 2931, 2868, 1720, 1699, 1604, 1516, 1454, 1369, 1244, 1082, 1043 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.92 (t, *J* = 7.5 Hz, 3H), 1.37 (pseudo sext, *J* = 7.5 Hz, 2H), 1.70 (pseudo quint, *J* = 7.5 Hz, 2H), 2.20 (s, 3H), 2.68 (t, *J* = 7.5 Hz, 2H), 7.04 (d, *J* = 7.5 Hz, 1H), 7.08-7.15 (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$_3$): δ = 14.1, 22.6, 23.8, 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)
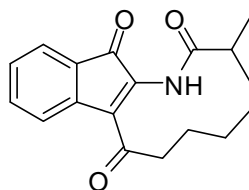
IR (ATR): 3288, 2960, 2927, 2871, 1726, 1678, 1512, 1458, 1379, 1200, 1124, 1086 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.91 (t, *J* = 7.5 Hz, 3H), 1.23 (d, *J* = 7.2 Hz, 6H), 1.36 (pseudo sext, *J* = 7.5 Hz, 2H), 1.60-1.75 (m, 2H), 2.52-2.68 (m, 3H), 7.07-7.14 (m, 2H), 7.28-7.35 (m, 1H), 7.39-7.44 (m, 1H), 7.61 (brs, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 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)
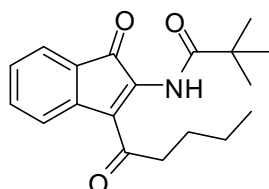
IR (ATR): 3354, 2958, 2931, 2870, 1724, 1678, 1500, 1454, 1369, 1184, 1140, 1080 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.91 (t, *J* = 7.5 Hz, 3H), 1.30 (s, 9H), 1.36 (pseudo sext, *J* = 7.5 Hz, 2H), 1.69 (pseudo quint, *J* = 7.5 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 2H), 7.07-7.14 (m, 2H), 7.28-7.36 (m, 1H), 7.40-7.45 (m, 1H), 7.84 (brs, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 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 (EI$^+$): *m/z* Calcd for C$_{19}$H$_{23}$NO$_3$ [M]$^+$: 313.1678; Found: 313.1676.

## 2-Benzoylamino-3-(propan-2-ylcarbonyl)indenone (5ba)
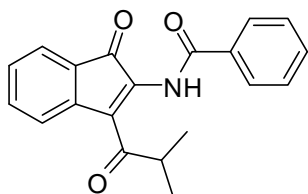
IR (ATR): 3323, 1722, 1666, 1510, 1454, 1271, 1178, 1065 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.21 (d, *J* = 7.2 Hz, 6H), 2.97 (sept, *J* = 7.2 Hz, 1H), 7.04-7.08 (m, 1H), 7.10-7.17 (m, 1H), 7.31-7.38 (m, 1H), 7.43-7.54 (m, 3H), 7.56-7.64 (m, 1H), 7.87-7.93 (m, 2H), 8.32 (brs, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): 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 (EI$^+$): *m/z* Calcd for C$_{20}$H$_{17}$NO$_3$ [M]$^+$: 319.1208; Found: 319.1208.

2-Acetylamino-3-(propan-2-ylcarbonyl)indenone (5bi)
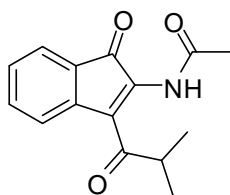
IR (ATR): 3327, 1724, 1691, 1606, 1520, 1456, 1371, 1242, 1063 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.17 (d, *J* = 7.2 Hz, 6H), 2.20 (s, 3H), 2.88 (sept, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 7.07-7.14 (m, 1H), 7.28-7.35 (m, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.63 (brs, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): 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 (EI$^+$): *m/z* Calcd for C$_{15}$H$_{15}$NO$_3$ [M]$^+$: 257.1052; Found: 257.1049.

2-Amino-3-(1-benzoyloxy-2-methyl-propen-1-yl)indenone (6ba)
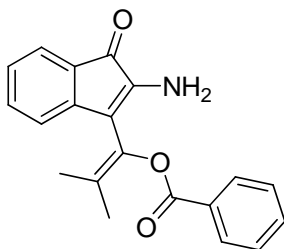
IR (ATR): 3464, 3361, 2920, 1720, 1639, 1606, 1454, 1277, 1244, 1176, 1107 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.81 (s, 3H), 1.82 (s, 3H), 4.27 (brs, 2H), 6.79-6.86 (m, 2H), 7.12-7.23 (m, 2H), 7.43-7.50 (m, 2H), 7.55-7.63 (m, 1H), 8.07-8.13 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 17.9, 19.8, 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)
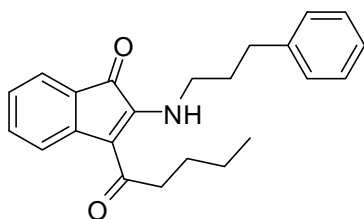
IR (ATR): 2922, 2858, 1714, 1599, 1558, 1464, 1261, 1049 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.98 (t, *J* = 7.5 Hz, 3H), 1.45 (pseudo sext, *J* = 7.5 Hz, 2H), 1.62-1.76 (m, 2H), 1.90-2.03 (m, 2H), 2.66 (t, *J* = 7.5Hz, 2H), 2.72 (t, *J* = 7.5Hz, 2H), 3.84 (q, *J* = 6.9 Hz, 2H), 6.86-6.94 (m, 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$_3$): δ = 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)
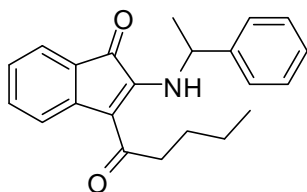
IR (ATR): 2956, 2868, 1716, 1606, 1558, 1458, 1371, 1263, 1078, 1022 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.98 (t, *J* = 7.5 Hz, 3H), 1.45 (pseudo sext, *J* = 7.5 Hz, 2H), 1.58 (d, *J* = 6.9 Hz, 3H), 1.64-1.76 (m, 2H), 2.67 (t, *J* = 7.5Hz, 2H), 5.83-5.96 (m, 1H), 6.84-6.92 (m, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.21-7.39 (m, 7H), 10.69 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 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 H_2O (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 $MgSO_4$. 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-9*H*-indeno[2,1-*d*]pyrimidin-9-one (9aia)
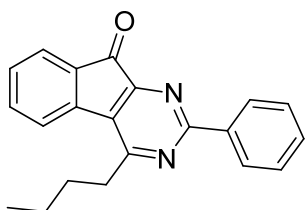
IR (KBr): 2959, 1730, 1572, 1458, 1390, 1186 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.04 (t, *J* = 7.5 Hz, 3H), 1.45-1.65 (m, 2H), 1.92 (quintet, *J* = 7.7 Hz, 2H), 3.13 (t, *J* = 7.5 Hz, 2H), 7.33-7.47 (m, 1H), 7.47-7.57 (m, 3H), 7.57-7.69 (m, 2H), 7.82 (d, *J* = 7.5 Hz, 1H), 8.47-8.62 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): 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)**
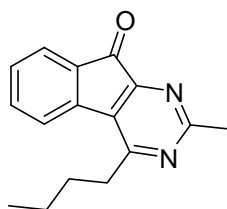
IR (ATR): 2951, 2866, 1730, 1601, 1574, 1400, 1373, 1182, 1101 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.01 (t, *J* = 7.2 Hz, 3H), 1.53 (pseudo sext, *J* = 7.2 Hz, 2H), 1.73-1.86 (m, 2H), 2.81 (s, 3H), 2.99-3.08 (m, 2H), 7.40 (ddd, *J* = 7.8 Hz, 6.6 Hz, 2.4 Hz, 1H), 7.57-7.65 (m, 2H), 7.78-7.82 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): 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.

4-(2-Propyl)-2-phenyl-*9H*-indeno[2,1-*d*]pyrimidin-9-one (9bia)
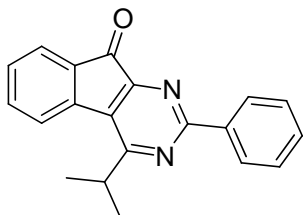
IR (ATR): 2970, 2929, 2868, 1726, 1599, 1564, 1458, 1383, 1298, 1180 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.51 (d, *J* = 6.9 Hz, 6H), 3.58 (sept, *J* = 6.9 Hz, 1H), 7.41 (dt, *J* = 0.9 Hz, 7.8 Hz, 1H), 7.47-7.54 (m, 3H), 7.63 (dt, *J* = 0.9 Hz, 7.5 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 8.56-8.65 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$): 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 C$_{20}$H$_{16}$N$_2$O [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; 0.12mmol) 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 H$_2$O (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 MgSO$_4$. The solvent was evaporated *in vacuo*. The residue was purified by preparative thin-layer chromatography (CHCl$_3$/AcOEt = 10/1) to afford **12ai** (12.4 mg, 52%).

3-Butyl-2-methyl-8*H*-indeno[2,1-*c*]pyrazol-8-one (12ai)
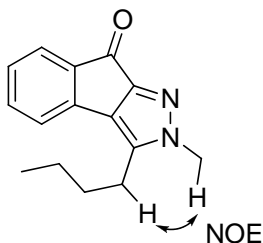
IR (KBr): 2939, 1714, 1603, 1491, 1317, 1169 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.97 (t, *J* = 7.3 Hz, 3H), 1.39-1.49 (m, 2H), 1.63-1.73 (m, 2H), 2.74 (t, *J* = 7.5 Hz, 2H), 3.83 (s, 3H), 7.09 -7.14 (m, 2H), 7.35 (dt, *J* = 1.1 Hz, 7.5 Hz, 1H), 7.52 (dd, *J* = 1.3 Hz, 7.7 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$): 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$^+$): *m/z* Calcd for C$_{15}$H$_{16}$N$_2$O [M]$^+$: 240.1263; Found: 240.1260.

3-(2-Propyl)-2-methyl-8*H*-indeno[2,1-*c*]pyrazol-8-one (12bi)
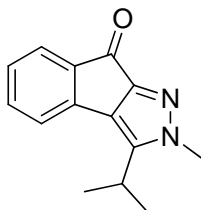
IR (ATR): 2970, 1712, 1603, 1481, 1371, 1317, 1167, 1090, 1007 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.42 (d, *J* = 7.0 Hz, 6H), 3.11 (sept, *J* = 7.0 Hz, 1H), 3.88 (s, 3H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.38 (dt, *J* = 1.2 Hz, 7.5 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 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$^+$): *m/z* Calcd for C$_{14}$H$_{14}$N$_2$O [M]$^+$: 226.1106; Found: 226.1108.

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1. For attack of carbon nucleophiles to the cyano group, see: (a) A. C. Veronese, R. Callegari, M. Basato, G. Valle, *J. Chem. Soc., Perkin Trans. 1* **1994**, *13*, 1779; (b) A. C. Veronese, V. Gandolfi, M. Basato, B. Corain, *J. Chem. Res. (S)* **1988**, *8*, 246; (c) M. Basato, B. Corain, M. Cofler, A. C. Veronese, G. Zanotti, *J. Chem. Soc., Chem. Commun.* **1984**, *23*, 1593.

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6. Compound **2f** was prepared by the SnCl$_4$ catalyzed reaction of acid chloride with TMSCN, see: G. A. Olah, M. Arvanaghi, G. K. S. Prakash, *Synthesis* **1983**, 636.

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.

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Chapter 3

Chapter 4

Stereoselective Synthesis of Vinyl-Substituted (*Z*)-Stilbenes

by Rhodium-Catalysed Addition of Arylboronic Acids

to Allenic Alcohols

Abstruct: 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.[1] 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 protodemetalation with H_2O or ROH,[2] and the other is β-elimination with an OR group located β to rhodium(I) of an organorhodium(I) intermediate.[3] Murakami et al have developed a variety of rhodium-catalysed reactions which proceed through a sequential addition/β-OR elimination pathway.[4] For example, the addition reaction of arylboroxines onto *cis*-allylic diols gave 2-arylalk-3-en-1-ols.[5] 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.[6,7]

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,[8] 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(PPh$_3$)$_4$.[9]
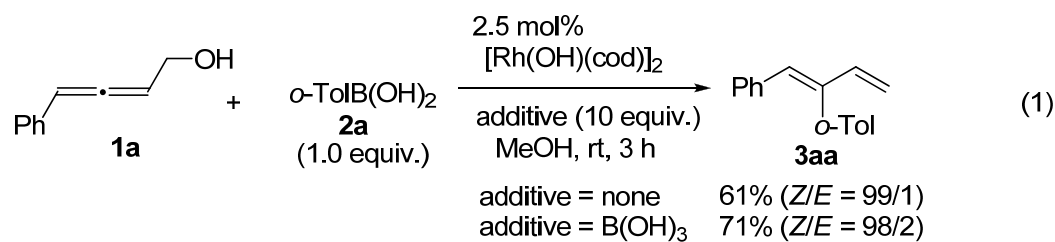
The stereoselective formation of (*Z*)-isomer **3aa** can be explained by assuming the reaction pathway involving δ-elimination of Rh(I)–OH, as depicted in Scheme 1.[10] Initially, *o*-tolylrhodium(I) species **A** is generated by transmetalation between Rh(I)–OH and **2a**. Regioselective *syn* addition 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**.[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.[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 δ-elimination of Rh(I)–OH with a double bond shift to afford (*Z*)-isomer **3aa** together with the catalytically active Rh(I)–OH species.
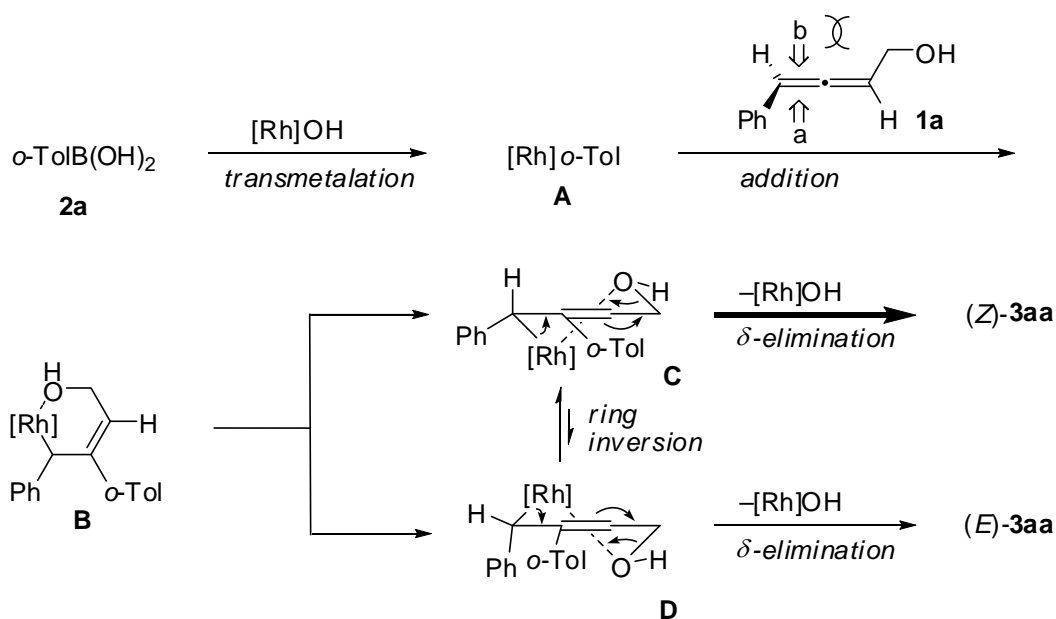
Scheme 1. Proposed reaction pathway.

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**[a].

Entry	2	R	3	Yield/%[b]	Z/E[c]
1	**2b**	*m*-Tol	**3ab**	68	>95:5
2	**2c**	*p*-Tol	**3ac**	77	>95:5
3	**2d**	Ph	**3ad**	68	95:5
4	**2e**	$o\text{-MeO–C}_6\text{H}_4$	**3ae**	76	>95:5
5	**2f**	$p\text{-MeO–C}_6\text{H}_4$	**3af**	68	92:8
6	**2g**	$p\text{-Br–C}_6\text{H}_4$	**3ag**	71	>95:5
7	**2h**	$p\text{-MeO}_2\text{C–C}_6\text{H}_4$	**3ah**	73	>95:5
8	**2i**	2-thienyl	**3ai**	61	93:7[d]
9	**2j**	3-thienyl	**3aj**	71	94:6[d]
10	**2k**	b-styryl	**3ak**	52	89:11
11	**2l**	(*E*)-hexenyl	**3al**	68	90:10

[a] Reaction conducted on a 0.2 mmol scale.
[b] Isolated yeild.
[c] Determined by ^{1}H 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*-tolylboronic acid (**2a**) to a-allenols **1**[a].

Entry	1	3	Yield/%[b]	Z/E[c]
1	Ph **1b** Me	Me / Ph / *o*-Tol **3ba**	46	>95:5[d]
2	Me Me OH Ph **1c**	Ph / Me / *o*-Tol Me **3ca**	62	91:9[d]
	OH Ar	Ar / *o*-Tol		
3	**1d** Ar = *p*-Cl–C₆H₄	**3da**	68	>95:5
4	**1e** Ar = *p*-MeO–C₆H₄	**3ea**	61	86:14

[a] The reaction conditions were the same as those in Table 1.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Using 2.5 equiv. of *o*-TolB(OH)$_2$ for 24 h.

For comparison, the reaction was carried out using alkyl-substituted allenic 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**.

(2)

4a R = Cy
4b R = *n*-Bu

5aa 65% (*E/Z* = >95/5)
5ba 56% (*E/Z* = 91/9)

71
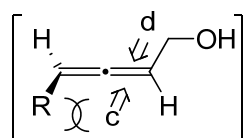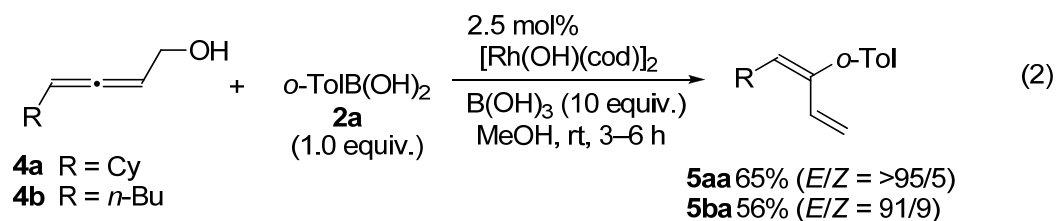
Conclusion

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, δ = 7.26) and CDCl$_3$ (^{13}C, δ = 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**,[2] **1b**,[6] **3ac**,[7] **3ad**,[8] **4a**,[3] and **4b**[3]) have been already reported.

2-Methyl-5-phenylpenta-3,4-dien-2-ol (1c)
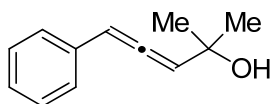
IR (neat): 3397, 3032, 2930, 1950, 1703, 1599, 1495, 1456, 1375, 1152 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.44 (6H, s), 5.79 (1H, d, *J* = 6.6 Hz), 6.33 (1H, d, *J* = 6.6 Hz), 7.13–7.25 (1H, m), 7.25–7.35 (4H, m); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 30.4, 70.5, 98.2, 105.3, 126.8, 127.3, 128.8, 134.2, 202.1; HRMS (EI$^+$): Calcd for C$_{12}$H$_{14}$O, M$^+$ 174.1045. Found m/z 174.1047.
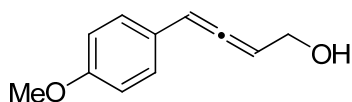
4-(4-Chlorophenyl)buta-2,3-dien-1-ol (1d)
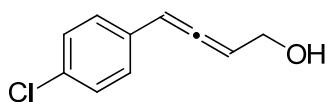
IR (neat): 3347, 2930, 2874, 1952, 1491, 1092, 1013 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$):

δ = 4.20–4.33 (2H, m), 5.73–5.85 (1H, m), 6.23–6.33 (1H, m), 7.17–7.35 (4H, m); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 60.4, 96.4, 96.5, 128.2, 129.0, 132.5, 133.0, 204.5; HRMS (EI$^+$): Calcd for C$_{10}$H$_9$ClO, M$^+$ 180.0342. Found m/z 180.0345.

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

IR (neat): 3386, 2838, 1948, 1607, 1512, 1464, 1441, 1300, 1248, 1173, 1032 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 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); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 55.5, 60.7, 96.0, 97.0, 114.4, 126.2, 128.1, 159.2, 203.7; HRMS (EI$^+$): Calcd for C$_{11}$H$_{12}$O$_2$, M$^+$ 176.0837. Found m/z 176.0836.

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 µmol) 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)
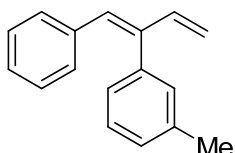### ((Z)-Vinyl-(2'-methyl)stilbene)
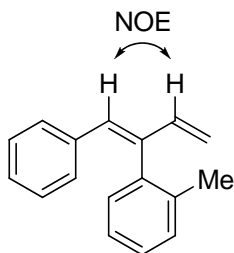
IR (neat): 3061, 3022, 2922, 1601, 1493, 1447 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.10 (3H, s), 4.67 (1H, d, J = 17.1Hz), 5.10 (1H, d, J = 10.5 Hz), 6.63 (1H, s), 6.73 (1H,

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$_3$): δ = 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$_3$): δ = 2.35 (3H, s), 4.85 (1H, d, J =17.1Hz), 5.15 (1H, d, J = 10.5Hz), 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$_3$): δ = 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)
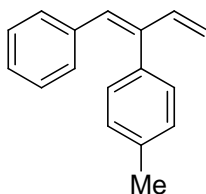
IR (KBr): 2919, 1599, 1512, 1445, 1109 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.40 (3H, s), 4.87 (1H, d, J = 17.1 Hz), 5.15 (1H, d, J = 10.5 Hz), 6.59 (1H, s), 6.73 (1H, dd, J = 17.1, 10.5 Hz), 6.88–6.98 (2H, m), 7.13–7.15 (5H, m), 7.16–7.24 (2H, m); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.5, 116.4, 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 220.1251.

### (Z)-2-(2-Methoxylphenyl)-1-phenylbuta-1,3-diene (3ae)
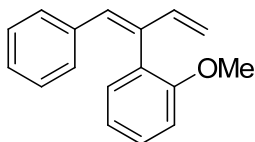
IR (neat): 3084, 2834, 1597, 1491, 1248, 1097 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.73 (3H, s), 4.83 (1H, d, J = 17.1 Hz), 5.16 (1H, d, J = 9.6 Hz), 6.75 (1H, s), 6.80 (1H,

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$_3$): δ = 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)
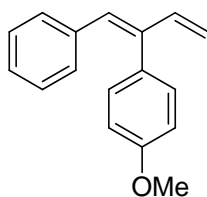
IR (KBr): 3017, 2934, 1603, 1509, 1441, 1287, 1244, 1183, 1173, 1030 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.85 (3H, s), 4.89 (1H, dd, J = 17.4 Hz), 5.15 (1H, dd, J = 11.1 Hz), 6.59 (1H, s), 6.73 (1H, dd, J = 17.1, 10.5Hz), 6.89–6.99 (4H, m), 7.05–7.15 (5H, m); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 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)
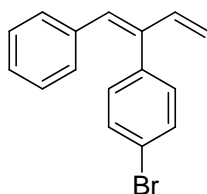
IR (KBr): 3092, 3046, 1597, 1485, 1445, 1406, 1389, 1069 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.83 (1H, d, J = 17.4 Hz), 5.17 (1H, d, J = 10.5 Hz), 6.63 (1H, s), 6.73 (1H, dd, J = 16.5, 10.5 Hz), 6.85–6.98 (2H, m), 7.03–7.20 (5H, m), 7.50–7.59 (2H, m); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 116.6, 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$_{13}$Br, M$^+$ 284.0201. Found m/z 284.0203.

(Z)-2-(4-Methoxycarbonylphenyl)-1-phenylbuta-1,3-diene (3ah)
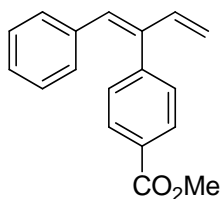
IR (neat): 2951, 1723, 1607, 1435, 1277, 1103 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.94 (3H, s), 4.79 (1H, d, *J* = 17.1 Hz), 5.17 (1H, dd, *J* = 10.5 Hz), 6.65 (1H, s), 6.74 (1H, dd, *J* = 17.1, 10.5 Hz), 6.85–6.95 (2H, m), 7.05–7.15 (3H, m), 7.24–7.32 (2H, m), 8.04–8.12 (2H, m); ^{13}C NMR (75 MHz, CDCl$_3$): 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 C$_{18}$H$_{16}$O$_2$, M$^+$ 264.1150. Found m/z 264.1151.

(Z)-1-Phenyl-2-(2-thienyl)buta-1,3-diene (3ai)
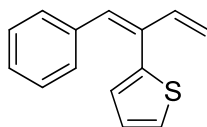
IR (neat): 3075, 2926, 1599, 1491, 1449, 1225 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.14 (1H, d, *J* = 16.5 Hz), 5.24 (1H, d, *J* = 10.2 Hz), 6.73 (1H, s), 6.76 (1H, dd, *J* = 16.8, 10.5 Hz), 6.86–6.92 (1H, m), 6.99–7.21 (6H, m), 7.34–7.42 (1H, m); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 116.5, 126.0, 127.28, 127.34, 127.35, 128.0, 129.4, 133.9, 134.1, 136.3, 137.9, 141.2; HRMS (EI$^+$): Calcd for C$_{14}$H$_{12}$S, M$^+$ 212.0660. Found m/z 212.0663.

(Z)-1-Phenyl-2-(3-thienyl)buta-1,3-diene (3aj)
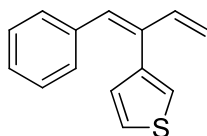
IR (KBr): 3102, 2924, 1597, 1489, 1444, 997 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.01 (1H, d, *J* = 17.1 Hz), 5.18 (1H, d, *J* = 9.6 Hz,), 6.64 (1H, s), 6.72 (1H, dd, *J* = 17.1, 11.4 Hz), 6.85–7.05 (3H, m), 7.05–7.23 (3H, m), 7.23–7.43 (1H, m); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 116.3, 123.7, 125.9, 127.2, 128.2, 129.1, 129.4, 132.5, 136.7, 136.9, 137.6, 141.4; HRMS (EI$^+$): Calcd for C$_{14}$H$_{12}$S, M$^+$ 212.0660. Found m/z 212.0664.

(Z)-1-Phenyl-2-[(*E*)-styryl]buta-1,3-diene (3ak)
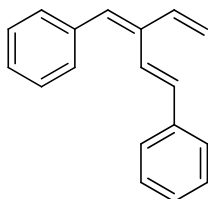
IR (neat): 3024, 2926, 1599, 1493, 1449 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 5.19 (1H, d, *J* = 10.8 Hz), 5.52 (1H, d, *J* = 17.1 Hz), 6.58 (1H, dd, *J* = 17.1, 10.8 Hz), 6.65 (1H, s), 6.72 (1H, d, *J* = 16.5 Hz), 7.06 (1H, d, *J* = 16.5 Hz), 7.10–7.43 (10H, m); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 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)
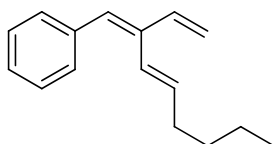
IR (neat): 3023, 2957, 2926, 2857, 1597, 1491, 1466, 1445, 1379, 1076, 1030 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.92 (3H, t, *J* = 7.2 Hz), 1.27–1.56 (4H, m), 2.05–2.24 (2H, m), 5.17 (1H, d, *J* = 11.1 Hz), 5.50 (1H, d, *J* = 17.1 Hz), 5.91 (1H, dt, *J* = 15.9, 7.2 Hz), 6.36 (1H, d, *J* = 15.6 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$_3$): δ = 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)
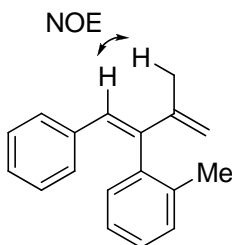
IR (neat): 3020, 2923, 1603, 1491, 1445, 1369 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$): δ = 2.08 (3H, s), 2.17 (3H, d, *J* = 0.7Hz), 4.55 (1H, d, *J* = 1.9 Hz), 5.05-5.07 (1H, m), 6.75 (1H, s), 6.82–6.84 (2H, m), 7.02 (1H, dd, *J* = 7.4, 1.4Hz), 7.05-7.11(3H, m), 7.18–7.27

(3H, m); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 19.4, 21.0, 116.9, 126.3, 126.9, 127.2, 127.4, 128.2, 129.2, 129.8, 130.3, 136.5, 137.3, 139.4, 142.5, 144.3; HRMS (EI$^+$): Calcd for C$_{18}$H$_{18}$, M$^+$ 234.1409. Found m/z 234.1405.

(Z)-4-Methyl-2-(2-methylphenyl)-1-phenylpenta-1,3-diene (3ca)
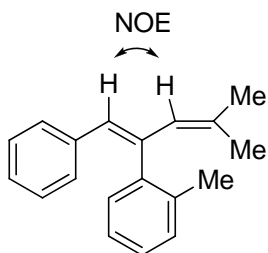
IR (neat): 3060, 2923, 1599, 1489, 1447, 1375 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.46 (3H, s), 1.83 (3H, s), 2.15 (3H, s), 5.96–6.00 (1H, m), 6.50 (1H, s), 6.82–6.86 (2H, m), 7.02–7.11 (4H, m), 7.15–7.26 (3H, m); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 18.8, 19.4, 27.9, 126.3, 126.4, 127.3, 128.0, 128.3, 128.5, 129.0, 129.8, 130.2, 135.3, 135.9, 137.5, 140.2, 140.4; HRMS (EI$^+$): Calcd for C$_{19}$H$_{20}$, M$^+$ 248.1565. Found m/z 248.1564.

(Z)-1-(4-Chlorophenyl)-2-(2-methylphenyl)buta-1,3-diene (3da)
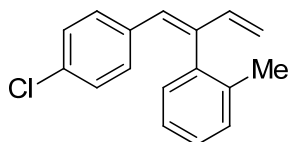
IR (KBr): 3002, 2921, 1584, 1487, 1455, 1090 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.09 (3H, s), 4.70 (1H, d, J = 17.1 Hz), 5.14 (1H, d, J = 11.1 Hz), 6.58 (1H, s), 6.71 (1H, dd, J = 17.1, 10.2 Hz), 6.73–6.82 (2H, m), 7.00–7.10 (3H, m), 7.19–7.35 (3H, m); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 19.3, 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 C$_{17}$H$_{15}$Cl, M$^+$ 254.0862. Found m/z 254.0860.

(Z)-1-(4-Methoxyphenyl)-2-(2-methylphenyl)buta-1,3-diene (3ea)
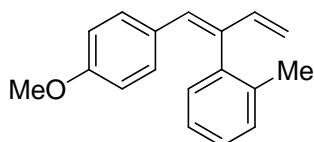
IR (KBr): 3007, 2965, 1595, 1509, 1460, 1254, 1179, 1028 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.11 (3H, s), 3.72 (3H, s), 4.62 (1H, d, J = 17.7 Hz), 5.05 (1H, d, J = 10.2

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$_3$): δ = 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)
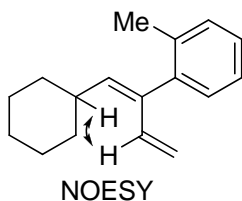
IR (neat): 2924, 2850, 1631, 1592, 1487, 1448, 986, 909 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.03–1.28 (3H, m), 1.28–1.42 (2H, m), 1.64–1.72 (1H, m), 1.72–1.80 (4H, m), 2.17 (3H, s), 2.55–2.65 (1H, m), 4.64 (1H, d, *J* = 17.5 Hz), 5.09 (1H, d, *J* = 10.6 Hz), 5.24 (1H, d, *J* = 9.4 Hz), 6.91 (1H, 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$_3$): δ = 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)
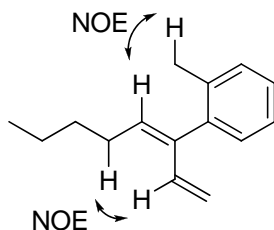
IR (neat): 3015, 2957, 1593, 1487, 1456, 1379, 1044 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.95 (3H, t, *J* = 7.1 Hz), 1.35–1.51 (4H, m), 2.19 (3H, s), 2.31–2.38 (2H, m), 4.66 (1H, d, *J* = 17.2, Hz), 5.10 (1H, d, *J* = 10.6 Hz), 5.41 (1H, t, *J* = 7.7 Hz), 6.91 (1H, d, *J* = 17.2, 10.6 Hz), 7.06 (1H, d, *J* = 7.1 Hz), 7.13–7.24 (3H, m); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 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.

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Chapter 5

Rhodium-Catalyzed Reaction of 1-Alkenylboronates

with Aldehydes Leading to Allylation Products

Abstruct: 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 γ-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 γ-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 allyboron 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*)-γ-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*)-γ-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*)-γ-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 γ-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/vinylic 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
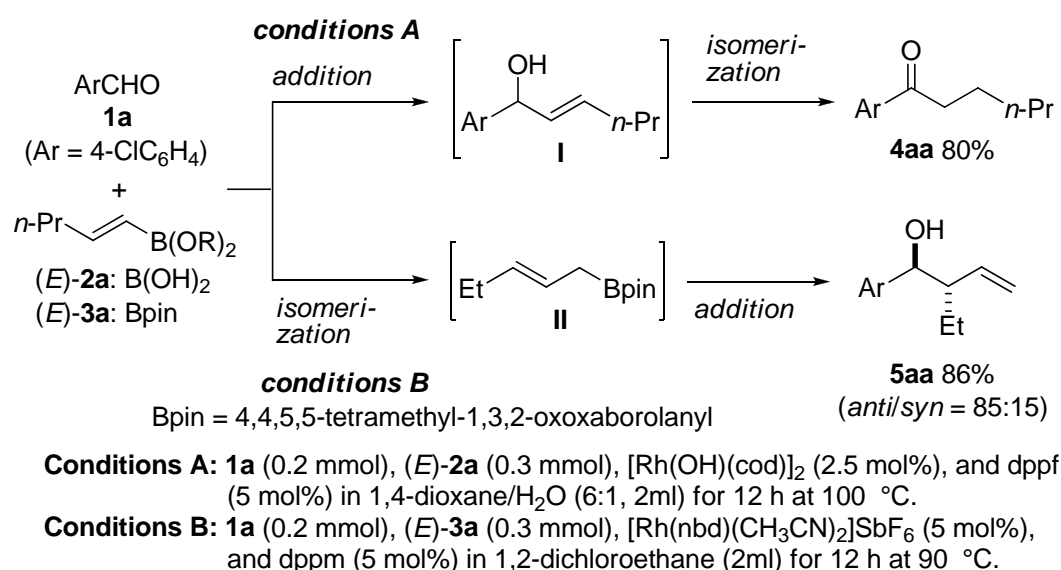
Figure 1. A rhodium-catalyzed reaction of 1a with (*E*)-**2a** and (*E*)-**3a**

A reaction of 4-chlorobenzaldehyde (**1a**) with (*E*)-1-pentenylboronic acid (**2a**) was initially examined in the presence of a rhodium(I) catalyst (Figure 1). As reported by Miyaura *et al.*,[10] 4-chlorophenyl pentyl 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/H$_2$O (6:1) at 100 °C for 12 h (conditions A). 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-pentenylboronic 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-pentenylboronic pinacolate (**3a**, 1.5 equiv) in the presence of [Rh(nbd)(CH$_3$CN)]SbF$_6$ (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).[12] 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-pentenylboronate **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 preferencial carbonyl addition of the (*E*)-isomer over the (*Z*)-isomer of **II** (*vide infra*).[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_2O in the media, transmetallation is retarded and isomerization is facilitated on a cationic rhodium center.

Table 1. Allylation reaction of **1a** with alkenylboronates **3b-h**.[a]

Entry	3	R^2	t (h)	5	Yield (%)[b]	*anti/syn*[c]
1	(*E*)-**3b**	Me	12	**5ab**	71	89:11
2	(*E*)-**3c**	*c*-Pent	24	**5ac**	89[d]	88:12
3	(*E*)-**3d**	*i*-Pr	24	**5ad**	86[e]	96:4
4	(*E*)-**3e**	Ph	12	**5ae**	91	96:4
5	(*Z*)-**3a**	Et	12	**5aa**	86	96:4
6	(*Z*)-**3b**	Me	24	**5ab**	91	98:2
7	(*Z*)-**3c**	*c*-Pent	12	**5ac**	89[d]	96:4
8	(*Z*)-**3d**	*i*-Pr	12	**5ad**	91[e]	>99:1
9	(*Z*)-**3e**	Ph	12	**5ae**	95	>99:1
10	(*Z*)-**3f**	$(CH_2)_3OTBS$	12	**5af**	91	97:3
11	(*Z*)-**3g**	$(CH_2)_3OBz$	12	**5ag**	97	99:1
12	(*Z*)-**3h**	$(CH_2)_3N(Phth)$	12	**5ah**	93	96:4

[a] Conditions: **1a** (0.4 mmol), **3** (0.6 mmol), $[Rh(nbd)(CH_3CN)_2]SbF_6$ (5 mol%), and dppm (5 mol%) in 1,2-dichloroethane (4 ml) for 12 h at 90 °C.
[b] Isolated yields.
[c] Determined by ^1H NMR.
[d] Using **3c** (1.2 mmol) and 10 mol% of $[Rh(nbd)(CH_3CN)_2]SbF_6$/dppm.
[e] Using **3d** (1.2 mmol) and 7.5 mol% of $[Rh(nbd)(CH_3CN)_2]SbF_6$/dppm.

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,[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

diastereoselectivities (*anti/syn* = 88:12 ~ 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.*[15] 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 ~ >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, benzoyloxy, and 1,3-dioxoisoindolin-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).
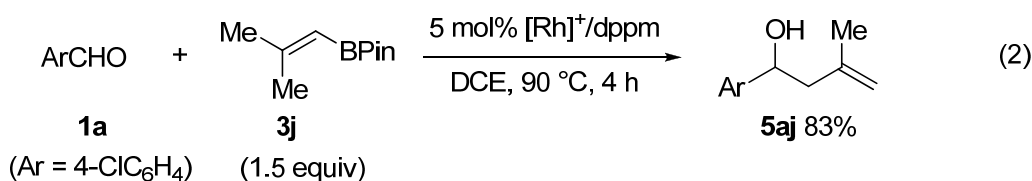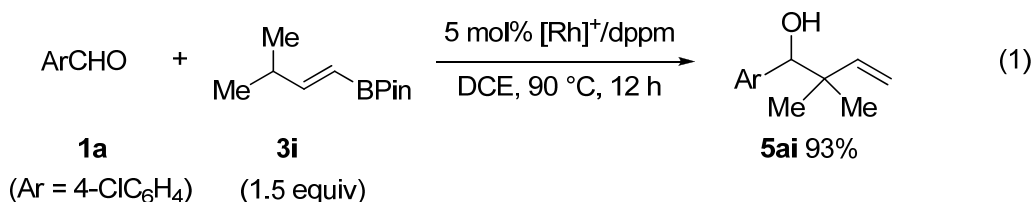
Next, the scope of aldehydes was examined using (*Z*)-**3a** (Table 2). An electronically and sterically diverse array of aromatic aldehydes **1b–g** were suitably reactive to give the homoallylic alcohols **5ba–ga** in yields ranging from 82% to 96% with high diastereoselectivities (*anti/syn* = 95:5 ~ 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.

Table 2. Allylation reaction of aldehydes **1b-i** with (*Z*)-**3a**.[a]

Entry	1	R¹	t (h)	5	Yield (%)[b]	*anti/syn*[c]
1	**1b**	Ph	12	**5ba**	90	96:4
2	**1c**	4-NO$_2$C$_6$H$_4$	3	**5ca**	94	99:1
3	**1d**	4-MeO$_2$CC$_6$H$_4$	6	**5da**	96	98:2
4	**1e**	4-MeC(O)C$_6$H$_4$	6	**5ea**	82	97:3
5	**1f**	3-MeOC$_6$H$_4$	12	**5fa**	94	98:2
6	**1g**	2-MeC$_6$H$_4$	12	**5ga**	90	95:5
7	**1h**	PhCH$_2$CH$_2$	12	**5ha**	79[d]	90:10
8	**1i**	Cy	24	**5ia**	62[e]	91:9

[a] Conditions: **1** (0.4 mmol), (*Z*)-**3a** (0.6 mmol), [Rh(nbd)(CH$_3$CN)$_2$]SbF$_6$ (5 mol%), and dppm (5 mol%) in 1,2-dichloroetane (4 ml) for 12 h at 90 °C.
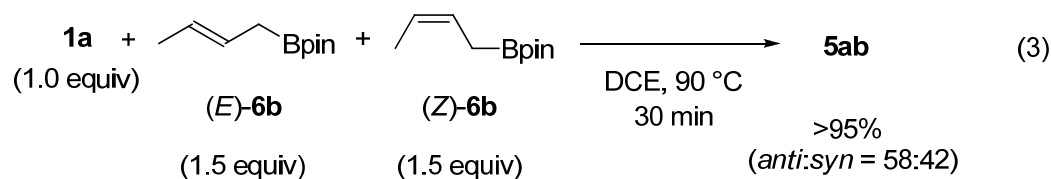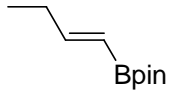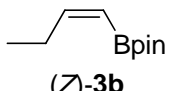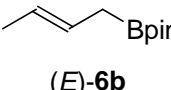[b] Isolated yields.
[c] Determined by ¹H NMR.
[d] Using (*Z*)-**3a** (1.2 mmol).
[e] Using (*Z*)-**3a** (1.2 mmol) and 10 mol% of [Rh(nbd)(CH$_3$CN)$_2$]SbF$_6$/dppm.

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).

(E)-3b → 5 mol % [Rh]+/dppm, DCE, 90 °C →	**3b**	+	**6b**
	E/Z	**3b:6b**	*E/Z*
0 min	100/0	100:0	–
20 min	93/7	91:9	67/33
6 h	91/9	70:30	64/36

(Z)-3b → 5 mol % [Rh]+/dppm, DCE, 90 °C →	**3b**	+	**6b**
	E/Z	**3b:6b**	*E/Z*
0 min	0/100	100:0	–
20 min	58/42	48:52	>95/5
6 h	92/8	69:31	63/37

(E)-6b → 5 mol % [Rh]+/dppm, DCE, 90 °C →	**3b**	+	**6b**
	E/Z	**3b:6b**	*E/Z*
0 min	–	0:100	100/0
20 min	43/57	29:71	91/9
6 h	92/8	70:30	66/34

Sheme 1. A control experiment in the absence of aldehydes.

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 ^{1}H 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 π-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 sterics 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**.
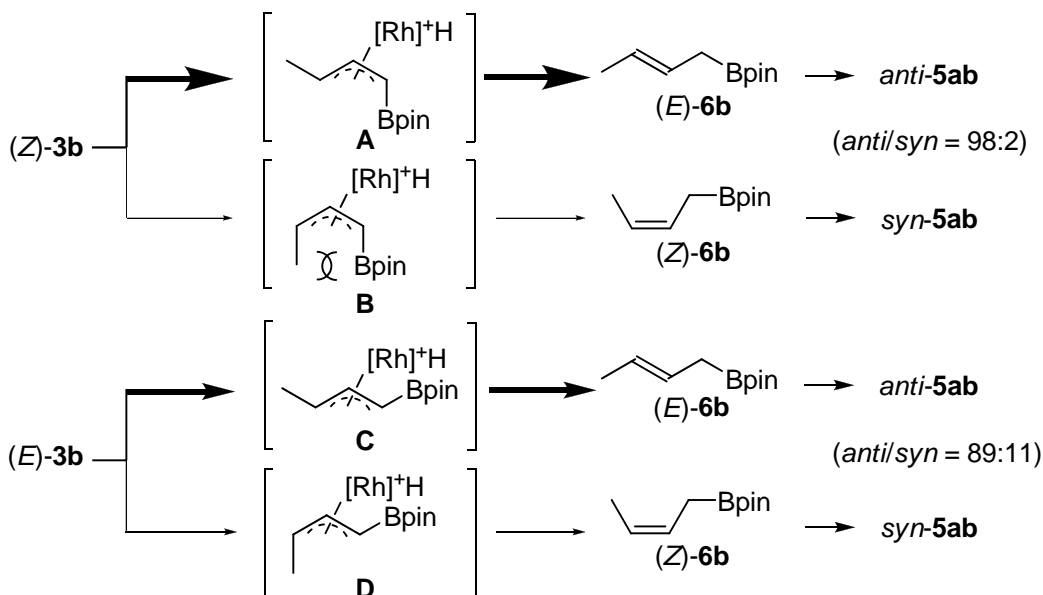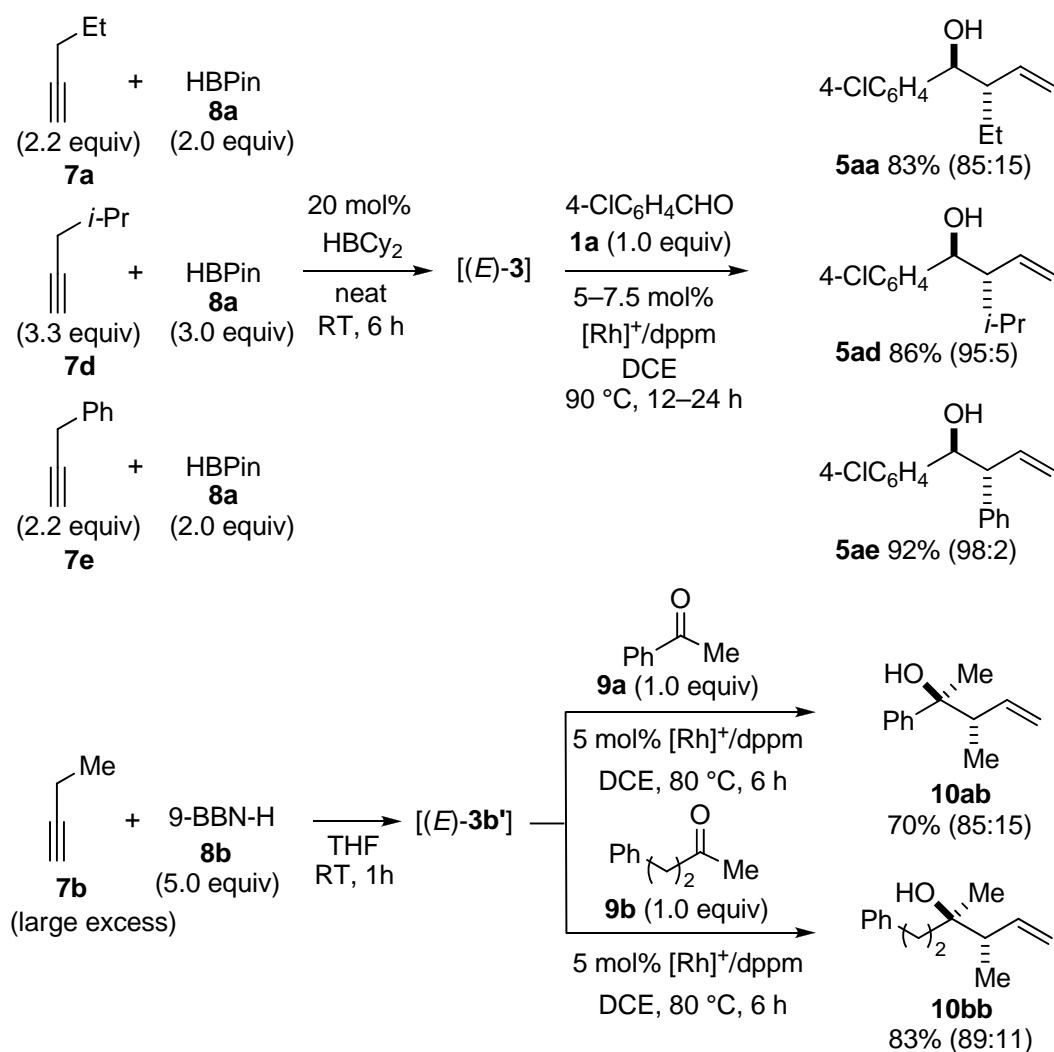

Figure 2. Proposed isomerization pathways throgh π-allyl rhodium intermediates.

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 **3**.[13] 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 **5aa**, **5ad**, and **5ae** were isolated in high yields with good to high diastereoselectivities. Interestingly, even the ketones **9a** and **9b** 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.[17]

Conclusion

  In summary, the author has been demonstrated that 1-alkenylboronates, which are readily synthesized by hydroboration of terminal alkynes,[14,15] act as the synthetic equivalent to γ-substituted allylboronates in the presence of a cationic rhodium(I) catalyst. The present reaction provides a unique method for the diastereoseletive 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. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 500 (^1H at 500 MHz and ^{13}C at 125 MHz) spectrometer using tetramethylsilane (^1H, $\delta = 0.00$) 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[TM] 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$_6$
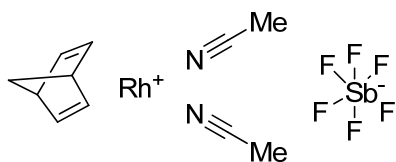
To a solution of [RhCl(nbd)]$_2$ (1.3 g, 2.82 mmol) in CH$_3$CN (8.5 mL) and CH$_2$Cl$_2$ (35 mL) was added AgSbF$_6$ (2.03 g, 5.92 mmol). The reaction mixture was stirred at room temperature for 30 min. Then, the precipitate was removed by filtration through Celite[®]. The filtrate was poured into Et$_2$O (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}; ^1H 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, $J_{Rh-C} = 2.6$ Hz), 60.5 (d, $J_{Rh-C} = 10.1$ Hz), 62.5 (d, $J_{Rh-C} = 6.3$ 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.*[14]

(*E*)-But-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane   ((*E*)-3b)
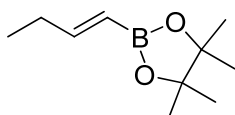
To an oven-dried flask was added (*E*)-1-butenylboronic acid (0.83 g, 8.31 mmol), pinacol (0.98g, 8.31 mmol), MgSO$_4$ (2.50 g, 20.8 mmol), CH$_2$Cl$_2$ (8 mL). The reaction mixture was stirred at room temperature overnight. Then, MgSO$_4$ was removed by filtration. The filtrate was concentrated under 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).

IR (neat): 2978, 1638, 1401, 1325, 1260, 1211, 1146, 1021 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 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); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 12.3, 24.7, 28.5, 82.9, 117.3 (br), 156.0; HRMS (EI$^+$): Calcd for C$_{10}$H$_{19}$O$_2$B (M$^+$) 182.1478. Found m/z 182.1474.

(*E*)-3-Phenylprop-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((*E*)-3e)
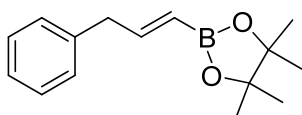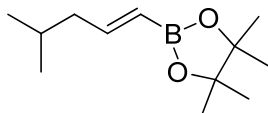

To an oven-dried flask was added (*E*)-3-phenylpropen-1-yl-boronic acid (1.17 g, 7.22 mmol), pinacol (0.90 g, 7.58 mmol), and benzene (30 mL). The reaction mixture was stirred at reflux temperature for 6 h, during which H$_2$O was removed azeotropically. Then, the solvent was removed under reduced pressure. 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).

IR (neat): 2979, 2931, 1637, 1495, 1396, 1363, 1323, 1146 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 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); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 24.7, 42.2, 83.0, 119.7 (br), 126.1, 128.4, 128.9, 139.0,

152.4; HRMS (APCI): Calcd for $C_{15}H_{22}O_2B$ ([M+H]$^+$) 245.1707. Found m/z 245.1704.

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

To an oven-dried flask was added Cy_2BH (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^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.90 (d, *J* = 6.7 Hz, 6H), 1.27 (s, 12H), 1.65–1.76 (m, 1H), 2.04 (dt, *J*=1.4 Hz, 6.8 Hz, 2H), 5.41 (dt, *J*=17.9 Hz, 1.5 Hz, 1H), 6.60 (dt, *J*=17.9 Hz, 6.9 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 22.4, 24.8, 27.7, 45.5, 82.9, 119.8 (br), 133.5; HRMS (EI$^+$): Calcd for $C_{12}H_{23}O_2B$ (M$^+$) 210.1791. Found m/z 210.1790.

(*E*)-3-Methyl-but-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3i)
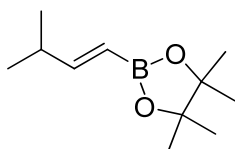
The compound **3i** was prepared according to the same procedure as that of the synthesis of (*E*)-**3d**. The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 20:1) to give **3i** (84% yield).
IR (neat): 2979, 2932, 2870, 1638, 1464, 1356, 1323, 1215, 1148 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 1.01 (d, *J* = 6.8 Hz, 6H), 1.27 (s, 12H), 2.30–2.41 (m, 1H), 5.38 (dd, *J* = 18.1 Hz, 1.5 Hz, 1H), 6.62 (dd, *J* = 18.1 Hz, 6.1 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 21.4, 24.7, 33.5, 82.9, 115.3 (br), 160.9; HRMS (EI$^+$): Calcd for $C_{11}H_{21}O_2B$ (M$^+$) 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.*[15] The pinacolate (*Z*)-**3b** was prepared by borylation of

(*Z*)-butenylbromide[19] because 1-butyne is low boiling substance.

(*Z*)-Pent-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((*Z*)-3a)
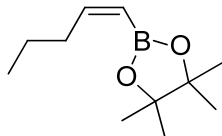
To a two-neck flask was charged [RhCl(cod)]$_2$ (0.148 g, 0.300 mmol) and Cy$_3$PHBF$_4$ (0.442 g, 1.20 mmol). The flask was evacuated and refilled with argon. Then, cyclohexane (60 mL), Et$_3$N (13.94 mL, 100 mmol), and pinacolborane (2.90 mL, 20.0 mmol) were added at room temperature. After 1 h, 1-pentyne (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, 1259, 1147 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 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); ^{13}C NMR (125 MHz, CDCl$_3$, the boron-bound carbon was not detected due to quadrupolar relaxation): δ = 13.5, 22.6, 24.8, 34.2, 82.7, 154.9; HRMS (APCI): Calcd for C$_{11}$H$_{22}$O$_2$B ([M+H]$^+$) 197.1707. Found m/z 197.1705.

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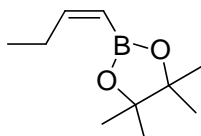

To a solution of (*Z*)-butenylbromide[19] (2.90 g, 21.48 mmol) in Et$_2$O (100 mL) was added *tert*-BuLi (1.6 M in pentane, 26.9 mL, 43.0 mmol) at −75°C. After 1 h, triisopropylborate (5.95 mL, 25.8 mol) was added, and the reaction temperature was gradually raised to 5 °C. After 4 h, pinacol (3.05 g, 25.8 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with aqueous NH$_4$Cl. The organic layer was separated and 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 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^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 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): δ = 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.
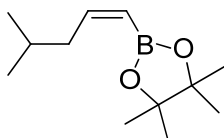
(Z)-3-Cyclopentylprop-1-en-1-yl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane ((Z)-3c)
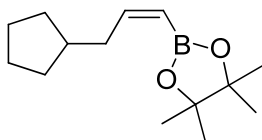
(Z)-**3c** was prepared according to the same procedure as that of the synthesis of (Z)-**3a**. The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 100:0 ~ 98:2) to give (Z)-**3c** (43 % yield).
IR (neat): 2978, 2949, 2868, 1628, 1425, 1373, 1323, 1259, 1146 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 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$_3$): δ = 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)

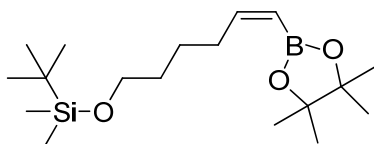(Z)-**3d** was prepared according to the same procedure as that of the synthesis of (Z)-**3a**. The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 100:0 ~ 99:1) to give (Z)-**3d** (58 % yield).
IR (neat): 2979, 2958, 2871, 1628, 1425, 1373, 1321, 1259, 1147 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 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): δ = 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)
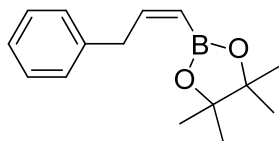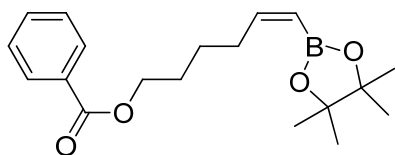

(*Z*)-**3e** was prepared according to the same procedure as that of the synthesis of (*Z*)-**3a**. The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 100:0 ~ 99:1) to give (*Z*)-**3e** (30 % yield).

IR (neat): 2979, 2931, 1628, 1419, 1373, 1325, 1261, 1144 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 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): δ = 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$_3$): δ = 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): δ = –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, 1146, 1115 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 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): δ = 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)
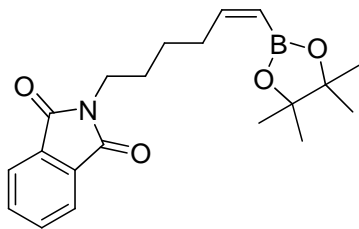
To a two-neck flask was charged [RhCl(cod)]$_2$ (0.065 g, 0.132 mmol) and Cy$_3$PHBF$_4$ (0.194 g, 0.528 mmol). The flask was evacuated and refilled with argon. Then, cyclohexane (20 mL), Et$_3$N (6.13 mL, 44.0 mmol), and pinacolborane (1.28 mL, 8.80 mmol) were added at room temperature. After 1 h, a 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$_3$): δ = 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): δ = 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**[20], **5ab**[21], **5ae**[21], **5ai**[22], **5aj**[23], **5ba**[24], **5ia**[24], **9ab**[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)]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)]$_2$ (2.3 mg, 0.005 mmol), dppf (5.5 mg, 0.01 mmol), 4-chlorobenzaldehyde (**1a**) (28.1 mg, 0.200 mmol), (*E*)-1-butenylboronic acid (**2a**, 34.2 mg, 0.300 mmol). The tube was evacuated and refilled with argon three times. Then, 1,4-dioxane/H$_2$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® (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).

1-(4-Chlorophenyl)hexan-1-one (4aa)[20]
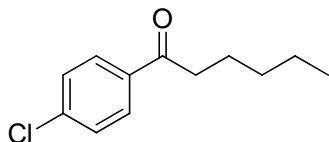
^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.86–0.97 (m, 3H), 1.32–1.40 (m, 4H), 1.68–1.78 (m, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 7.41–7.46 (m, 2H), 7.88–7.92 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 13.9, 22.5, 24.0, 31.5, 38.5, 128.8, 129.5, 135.4, 139.3, 199.3.

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$_3$CN)$_2$]SbF$_6$ (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® (1.5 x 5 cm) and eluted with ethyl acetate (50 mL). The filtrate was concentrated under reduced
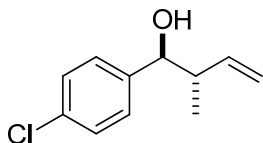
pressure and the residue was purified by flash diol-SiO$_2$ column chromatography (hexane:ethyl acetate = 97:3 ~ 90:10) to give **5aa** (72.7 mg, 86% yield, *anti/syn* = 96:4).

(1S*,2S*)-1-(4-Chlorophenyl)-2-ethylbut-3-en-1-ol (5aa)
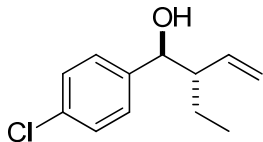
IR (neat): 3416, 2968, 1639, 1597, 1491, 1412, 1383, 1089 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): *anti*-form δ = 0.79 (t, *J* = 7.5 Hz, 3H), 1.11–1.29 (m, 2H), 2.10–2.17 (m, 1H), 2.18 (d, *J* = 2.4 Hz, 1H), 4.39 (dd, *J* = 7.9 Hz, 2.3 Hz, 1H), 5.20 (ddd, *J* = 17.1 Hz, 1.9 Hz, 0.6 Hz, 1H), 5.29 (dd, *J* = 10.3 Hz, 1.9 Hz, 1H), 5.62 (ddd, *J* = 17.1 Hz, 10.3 Hz, 9.3 Hz, 1H), 7.25–7.29 (m, 2H), 7.39–7.33 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): *anti*-form δ = 11.7, 23.3, 54.6, 75.8, 119.3, 128.26, 128.32, 133.2, 138.6, 141.0; HRMS (FAB$^+$): Calcd for C$_{12}$H$_{14}$OCl ([M–H]$^+$) 209.0739. Found m/z 209.0741.
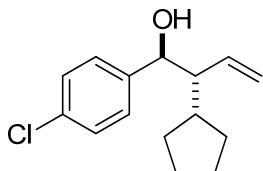
(1S*, 2S*)-1-(4-Chlorophenyl)-2-methylbut-3-en-1-ol (5ab)[21]

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).

^{1}H NMR (500 MHz, CDCl$_3$): *anti*-form δ = 0.87 (d, *J* = 6.8 Hz, 3H), 2.15 (d, *J* = 2.6 Hz, 1H), 2.39–2.47 (m, 1H), 4.35 (dd, *J* = 7.8 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); ^{13}C NMR (125 MHz, CDCl$_3$): *anti*-form δ = 16.4, 46.4, 77.1, 117.3, 128.2, 128.4, 133.3, 140.2, 140.8.

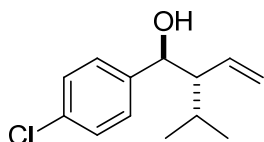**(1S*, 2R*)-1-(4-Chlorophenyl)-2-cyclopentylbut-3-en-1-ol (5ac)**

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).

IR (neat): 3423, 2949, 2866, 1489, 1412, 1308, 1192, 1088, 1053, 1009 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): *anti*-form δ = 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 Hz, 6.7

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 δ = 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$^+$): Calcd for C$_{15}$H$_{19}$OCl ([M–H]$^+$) 250.1124. Found m/z 250.1128.
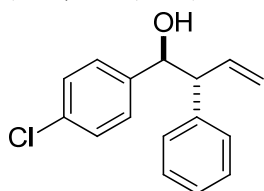
(1S*, 2S*)-1-(4-Chlorophenyl)-2-isopropylbut-3-en-1-ol (5ad)

  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 δ = 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 δ = 17.5, 21.8, 27.5, 58.9, 73.9, 120.5, 128.2, 128.4, 133.2, 135.3, 141.3; HRMS (EI$^+$): Calcd 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)[21]

  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).

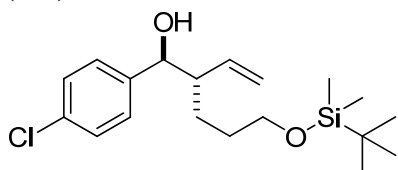^{1}H NMR (500 MHz, CDCl$_3$): *anti*-form δ = 2.37 (brs, 1H), 3.47 (t, *J* = 8.5 Hz, 1H), 4.80 (d, *J* = 7.9 Hz, 1H), 5.24 (dd, *J* = 17.1 Hz, 0.8 Hz, 1H), 5.28 (dd, *J* = 10.1 Hz, 1.3 Hz, 1H), 6.22 (ddd, *J* = 17.1 Hz, 10.1 Hz, 9.1 Hz, 1H), 7.01–7.07 (m, 4H), 7.14–7.18 (m, 3H), 7.19–7.24 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): *anti*-form δ = 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$_2$ column chromatography (hexane:ethyl acetate = 97:3 ~ 95:5) to give **5af** (129.6 mg, 91% yield, *anti/syn* = 97:3, Table 1, entry 10).

IR (neat): 3431, 2929, 2856, 1491, 1468, 1387, 1254, 1092, 1009 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): *anti*-form δ = −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); ^{13}C NMR (125 MHz, CDCl$_3$): *anti*-form δ = −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$^+$): Calcd for C$_{19}$H$_{31}$O$_2$ClSi (M$^+$) 354.1782. Found m/z 354.1799.

(S*)-4-((S*)-(4-Chlorophenyl)(hydroxy)methyl)hex-5-enyl benzoate (5ag)
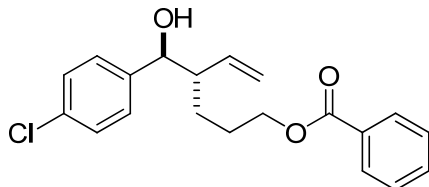
The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 90:10 ~ 85:15) to give **5ag** (133.2 mg, 97% yield, *anti/syn* = 99:1, Table 1, entry 11).

IR (neat): 3484, 1719, 1601, 1491, 1453, 1277, 1117, 1092 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): *anti*-form δ = 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); ^{13}C NMR (125 MHz, CDCl$_3$): *anti*-form δ = 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$^+$): Calcd for C$_{20}$H$_{21}$O$_3$Cl (M$^+$) 344.1179. Found m/z 344.1186.
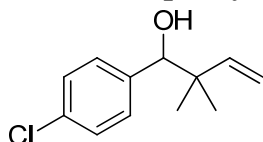
2-((S*)-4-((S*)-(4-Chlorophenyl)(hydroxy)methyl)hex-5-enyl)isoindoline-1,3-dione (5ah)
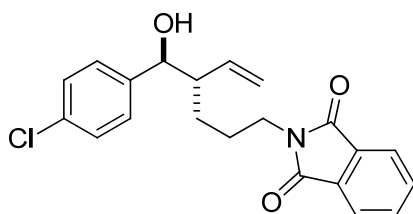
The crude mixture was purified by flash diol-SiO$_2$ column chromatography (hexane then hexane:ethyl acetate = 80:20) to give **5ah** (138.0 mg, 93% yield, *anti/syn* = 96:4, Table 1, entry 12).

IR (neat): 3496, 2937, 1770, 1712, 1398, 1369, 1088, 1051, 1012 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): *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); ^{13}C NMR (125 MHz, CDCl$_3$): *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 C$_{21}$H$_{20}$O$_3$ClN ([M+Cl]$^+$) 404.0815. Found m/z 404.0816.

1-(4-Chlorophenyl)-2,2-dimethylbut-3-en-1-ol (5ai)[22]

The crude mixture was purified by flash diol-SiO$_2$ column chromatography (hexane:ethyl acetate = 95:5 ~ 90:10) to give **5ai** (78.3 mg, 93% yield, eq. 1).

^{1}H NMR (500 MHz, CDCl$_3$): 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); ^{13}C NMR (125 MHz, CDCl$_3$): δ = 20.8, 24.3, 42.2, 79.9, 114.2, 127.6, 129.1, 133.1, 139.1, 144.7.
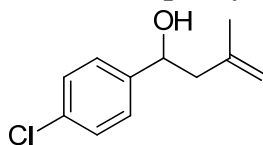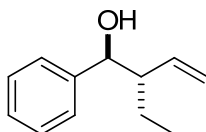
1-(4-Chlorophenyl)-3-methylbut-3-en-1-ol (5aj)[23]

The crude mixture was purified by flash diol-SiO$_2$ column chromatography (hexane:ethyl acetate = 95:5 ~ 90:10) to give **5aj** (65.0 mg, 83% yield, eq. 2).

^{1}H NMR (500 MHz, CDCl$_3$): δ = 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, CDCl$_3$): δ = 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)[24]

The crude mixture was purified by flash diol-SiO$_2$ 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, CDCl$_3$): *anti*-form δ = 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, CDCl$_3$): *anti*-form δ = 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)
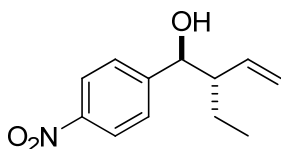
The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 90:10 ~ 85:15) to give **5ca** (83.5 mg, 94% yield, *anti/syn* = 99:1, Table 2, entry 2).

IR (KBr): 3518, 3078, 2966, 2873, 1603, 1520, 1344, 1219, 1105, 1051 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): *anti*-form δ = 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 (dd, *J* = 7.2 Hz, 2.6 Hz, 1H), 5.17 (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, CDCl$_3$): *anti*-form δ = 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.

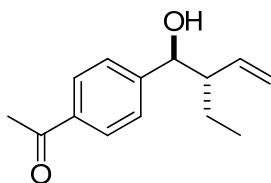### (1S*, 2S*)-2-Ethyl-1-(4-methoxycarbonylphenyl)but-3-en-1-ol (5da)
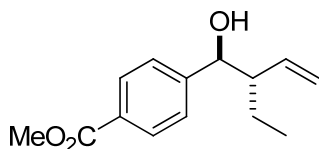
The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 90:10 ~ 85:15) to give **5da** (90.4 mg, 96% yield, *anti*/*syn* = 98:2, Table 2, entry 3).

IR (neat): 3457, 2961, 1722, 1611, 1437, 1281, 1113, 1042 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): *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 (dd, 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); ^{13}C NMR (125 MHz, CDCl$_3$): *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 C$_{14}$H$_{18}$O$_3$ (M$^+$) 234.1256. Found m/z 234.1258.

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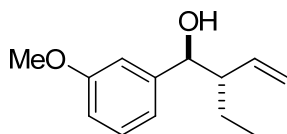

The crude mixture was purified by flash silica gel column chromatography (hexane:ethyl acetate = 90:10 ~ 85:15) to give **5ea** (71.6 mg, 82% yield, *anti*/*syn* = 97:3, Table 2, entry 4).

IR (neat): 3437, 2964, 2931, 2875, 1680, 1606, 1414, 1360, 1271, 1041 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): *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); ^{13}C NMR (125 MHz, CDCl$_3$): *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 C$_{14}$H$_{19}$O$_2$ ([M+H]$^+$) 219.1380. Found m/z 219.1373.

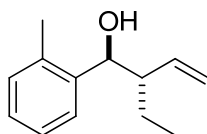## (1S*, 2S*)-2-Ethyl-1-(3-methoxyphenyl)but-3-en-1-ol (5fa)

The crude mixture was purified by flash diol-SiO$_2$ 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}; ^{1}H NMR (500 MHz, CDCl$_3$): *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); ^{13}C NMR (125 MHz, CDCl$_3$): *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 C$_{13}$H$_{19}$O$_2$ ([M+H]$^+$) 207.1380. Found m/z 207.1374.

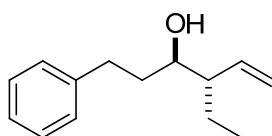## (1S*, 2S*)-2-Ethyl-1-o-tolylbut-3-en-1-ol (5ga)

The crude mixture was purified by flash diol-SiO$_2$ 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}; ^{1}H NMR (500 MHz, CDCl$_3$): *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); ^{13}C NMR (125 MHz, CDCl$_3$): *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 C$_{13}$H$_{18}$O (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-SiO$_2$ 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}; ^{1}H NMR (500 MHz, CDCl$_3$): *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); ^{13}C NMR (125 MHz, CDCl$_3$): *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 C$_{14}$H$_{20}$O (M$^+$) 204.1514. Found m/z 204.1509.

(1R*, 2S*)-1-Cyclohexyl-2-ethylbut-3-en-1-ol (5ia)[24]
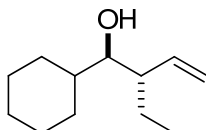
The crude mixture was purified by flash diol-SiO$_2$ column chromatography (hexane:ethyl acetate = 98:2 ~ 96:4) to give **5ia** (45.5 mg, 62 % yield, *anti/syn* = 91:9, Table 2, entry 8).

IR (neat): ^{1}H NMR (500 MHz, CDCl$_3$): *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); ^{13}C NMR (125 MHz, CDCl$_3$): *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).
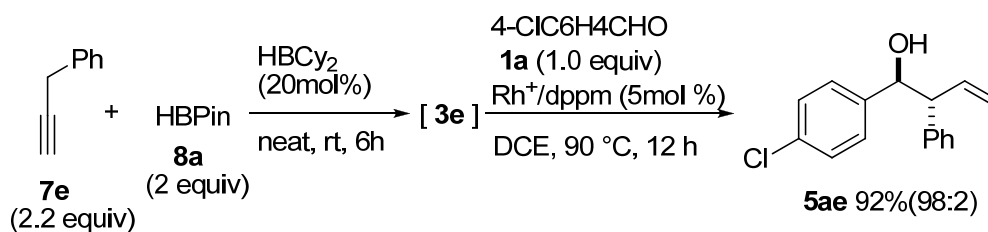
To an oven-dried flask was added Cy$_2$BH (0.1 M in THF, 0.8 mL, 0.08 mmol). The solvent was removed under reduced pressure, and the flask was filled with argon. Then,

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)(CH$_3$CN)$_2$]SbF$_6$ (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 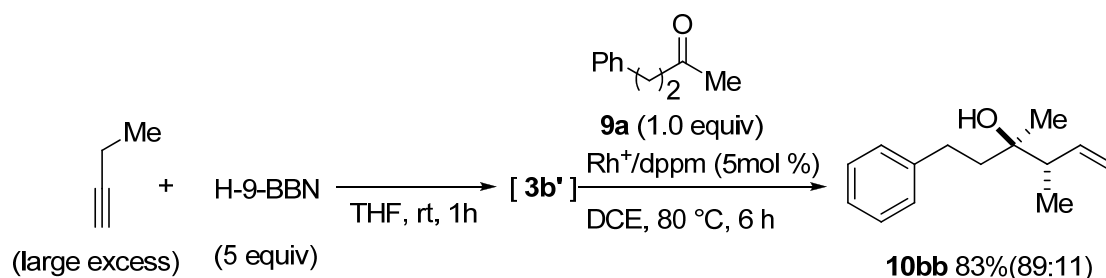the residue was purified by flash diol-SiO$_2$ column chromatography (hexane:ethyl acetate = 95:5) to give **5ae** (95.0 mg, 92% yield, *anti/syn* = 98:2, scheme 2).

(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)(CH$_3$CN)$_2$]SbF$_6$ (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]
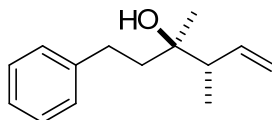
^{1}H NMR (500 MHz, CDCl$_3$): *anti*-form δ = 1.05 (d, *J* = 6.9 Hz, 3H), 1.18 (s, 3H), 1.54 (brs, 1H), 1.76–1.81 (m, 2H), 2.29–2.38 (m, 1H), 2.62–2.80 (m, 2H), 5.12–5.17 (m, 2H), 5.86 (ddd, *J* = 17.9 Hz, 9.7 Hz, 8.6 Hz, 1H), 7.16–7.23 (m, 3H), 7.28 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl$_3$): *anti*-form δ = 14.9, 23.5, 29.8, 42.0, 47.4, 73.5, 116.6, 125.7, 128.3 (two signals overlapping), 140.1, 142.7.

(2S*, 3S*)-3-Methyl-2-phenylpent-4-en-2-ol (10ab)[25]
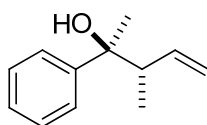
The crude mixture was purified by flash NH-silica gel column chromatography (hexane:ethyl acetate = 95:5 ~ 90:10) to give **10ab** (49.5 mg, 70% yield, *anti/syn* = 85:15).

^{1}H NMR (500 MHz, CDCl$_3$): *anti*-form δ = 0.97 (d, *J* = 6.9 Hz, 3H), 1.53 (s, 3H), 1.94 (s, 1H), 2.56–2.65 (m, 1H), 5.08–5.14 (m, 2H), 5.71 (ddd, *J* = 17.1 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); ^{13}C NMR (125 MHz, CDCl$_3$): *anti*-form δ = 14.1, 25.9, 48.8, 75.7, 116.6, 125.5, 126.6, 127.9, 139.9, 147.0.

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 ^{1}H 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 postions 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 CDCl$_3$ (3 mL). The filtrates were concentrated under reduced pressure and the residues were monitored by ^{1}H NMR. The resulting NMR spectra are shown in Figure 1S and 2S. The product ratio estimated from the integral value of the ^{1}H NMR spectrum is shown in Scheme 1.

Figure 1S. The time course of ¹H NMR spectrum (0.3-7.1 ppm) for a control experiment in the absence of aldehyde.
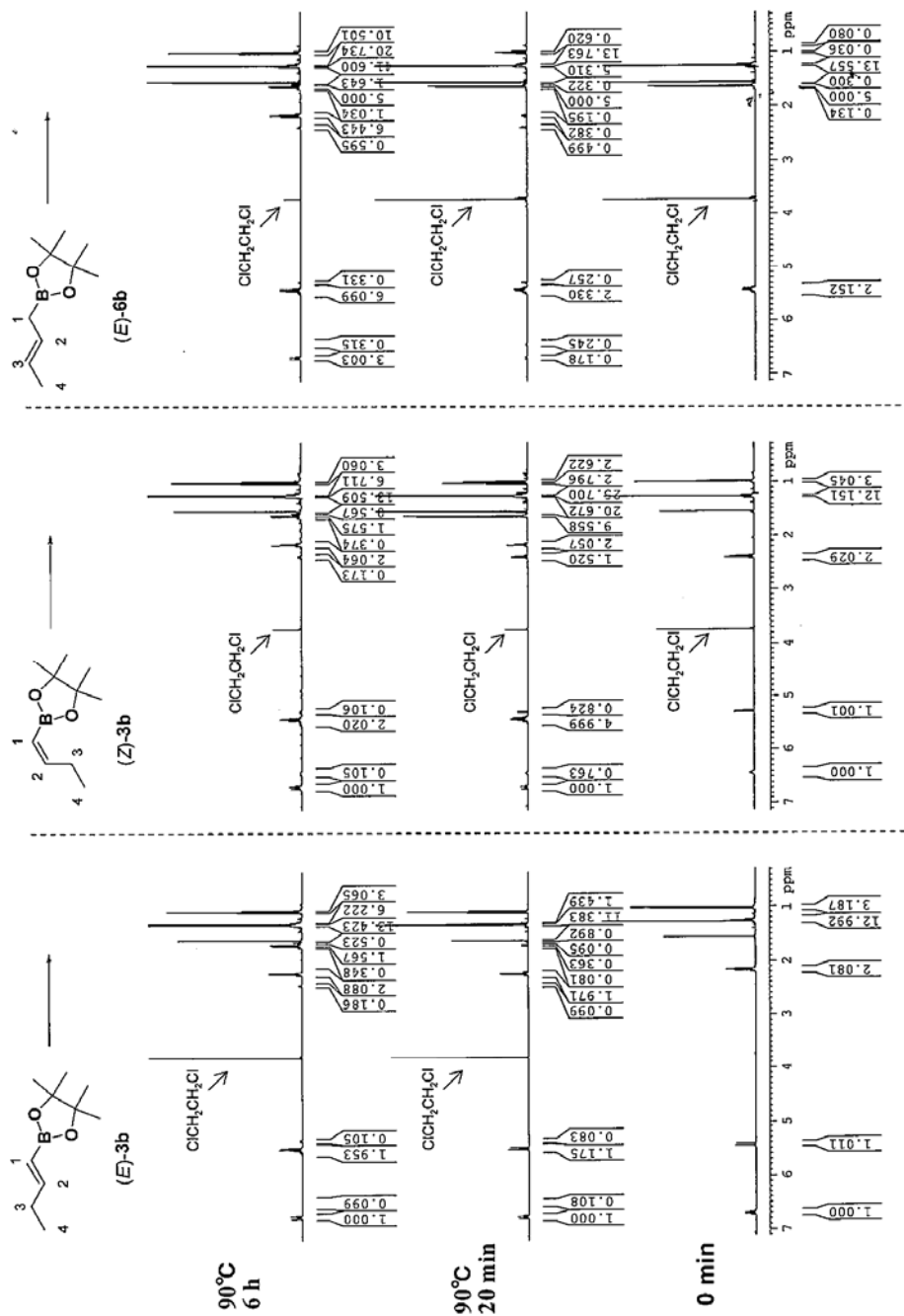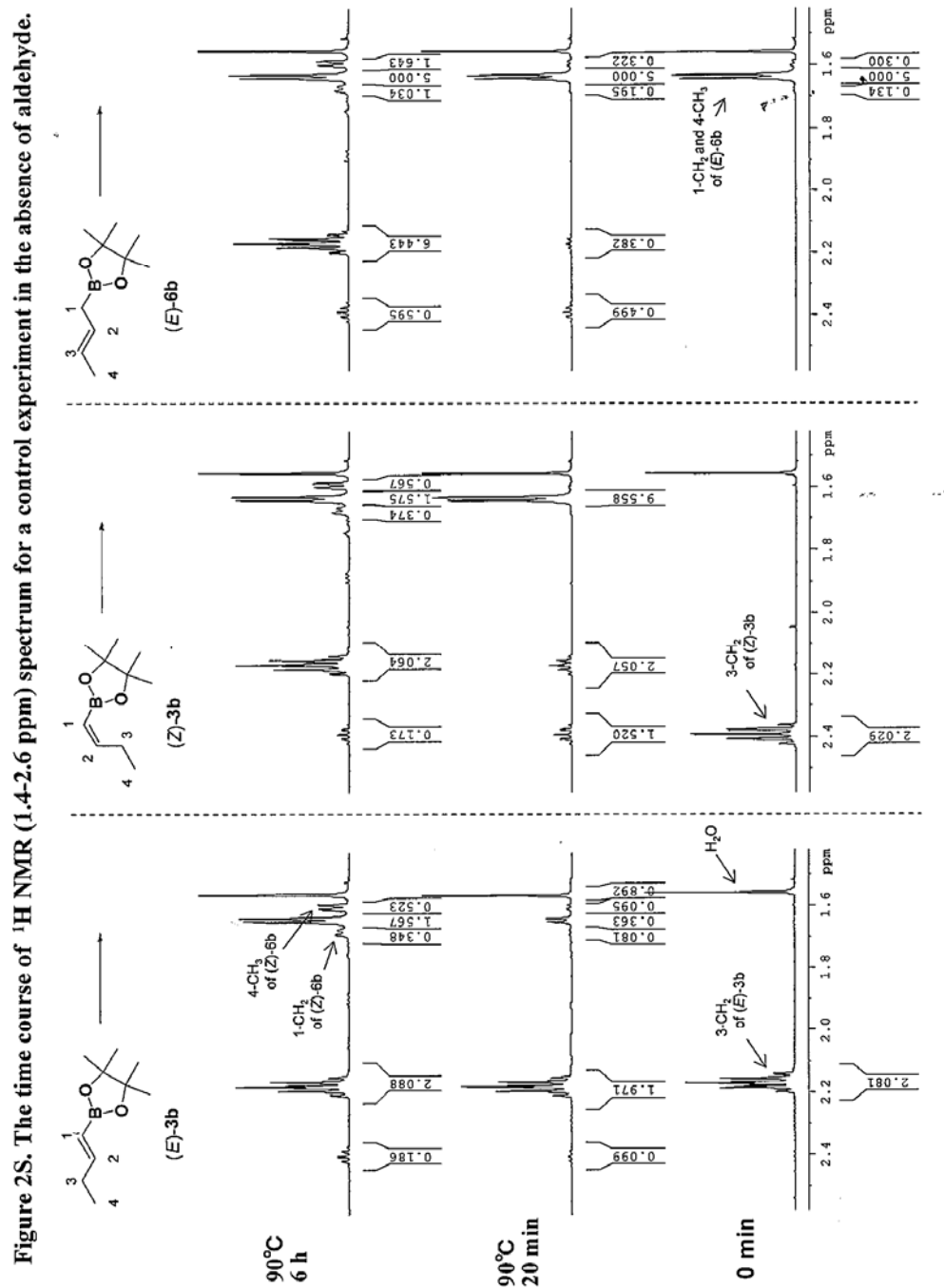
Figure 2S. The time course of ¹H NMR (1.4-2.6 ppm) spectrum for a control experiment in the absence of aldehyde.

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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).

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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
Chem. Commun. **2007**, 2855-2857.

Chapter 2   Synthesis of Functionalized Isoindoles by the Rhodium-Catalyzed Reaction of Cyanoformates with *ortho*-Borylbenzalacetone Derivatives
Hiroshi Shimizu, Tomohiro Igarashi and Masahiro Murakami
Bull. Korean Chem. Soc. **2010**, *31*, 1461-1462.

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
Org. Biomol. Chem. **2010**, *8*, 4074-4076.

Chapter 5   Rhodium-Catalyzed Reaction of 1-Alkenylboronates with Aldehydes Leading to Allylation Products
Hiroshi Shimizu, Tomohiro Igarashi, Tomoya Miura, and Masahiro Murakami
Angew. Chem. Int. Ed. **2011**, *50*, 11465-11469.