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**Studies on Novel Asymmetric Allylic Substitution
and Asymmetric Polymerization Catalyzed by
Planar-Chiral Cyclopentadienyl-Ruthenium Complex**

A Doctoral Thesis

by

Naoya Kanbayashi

Submitted to

the Graduate School of Science

Osaka University

February, 2013

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This thesis presents the research that the author performed at Graduate School of Science, Osaka University from 2008 to 2013 under direction of Professor Kiyotaka Onitsuka. The author would like to express his sincere gratitude to Professor Kiyotaka Onitsuka for his continuing guidance, helpful suggestion and warm encouragement. The author also wishes to express his sincere gratitude to Associate Professor Taka-aki Okamura for his numerous helpful suggestions and the X-ray measurement.

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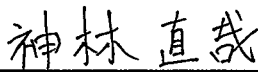
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Chapter 1: General Introduction

Background

In the early days of synthetic organic chemistry, many researchers were interested in the development of new synthetic methods for simple organic molecules, and then their interest has moved to the synthesis of highly complicated molecules. The growth of the organometallic chemistry has brought rapid progress in synthetic organic chemistry and a variety of efficient methods for organic synthesis using organometallic catalysts have been found. Recently many researches have focused their interest on *precise synthesis* including the control of stereochemistry such as enantio- and diastereo-selectivity as well as control of chemo-, and regio-selectivity.¹

In the past decades, there has been a dramatic increase in the demand for enantiopure compounds as fine-chemicals such as biological agrochemicals and pharmaceuticals, and for material science such as liquid crystals and polymers. These demands have been reflected in the advance of asymmetric synthesis. One of the most famous synthetic methods is *catalytic asymmetric synthesis*,² which has appeared in a large number of publications, and the 2001 Nobel Prize in Chemistry awarded to W. S. Knowles,³ R. Noyori,^{3,4} and K. B. Sharpless.⁵ One of the main advantages of asymmetric catalysis in asymmetric synthesis can be selective synthesis of optically active materials from cheap, commercially available prochiral starting materials without undesirable products. In the field, combinations of a transition metal and a chiral ligand are most commonly used for organometallic catalysts, because they promote the reaction by activation of small molecules which are not reactive toward organic molecules under normal conditions. Thus, many researchers have studied asymmetric synthesis using asymmetric organometallic catalysis to develop a wide variety of catalytic systems.² Until now, a great effort has been made for the research of chiral organometallic complexes. Thus, many of them possessing various chiral ligands such as chiral phosphines and amines have been developed as effective asymmetric catalysts. Noyori and co-workers reported axial-chiral 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) ligand (Figure 1-1a), which is one of the most effectively chiral ligands coordinating to transition metals, and Rh-BINAP complexes were used as an excellent catalyst for asymmetric hydrogenations.⁶ After the invention, many chiral ligands, such as chiral phosphine and amines containing a binaphthyl backbone with axial chirality, have been studying to achieve various enantioselective reaction systems.⁷ Recently, Suginome reported a novel type of phosphine

ligands with helical chirality, and high enantioselectivity was achieved in the asymmetric reactions (Figure 1-1b).⁸

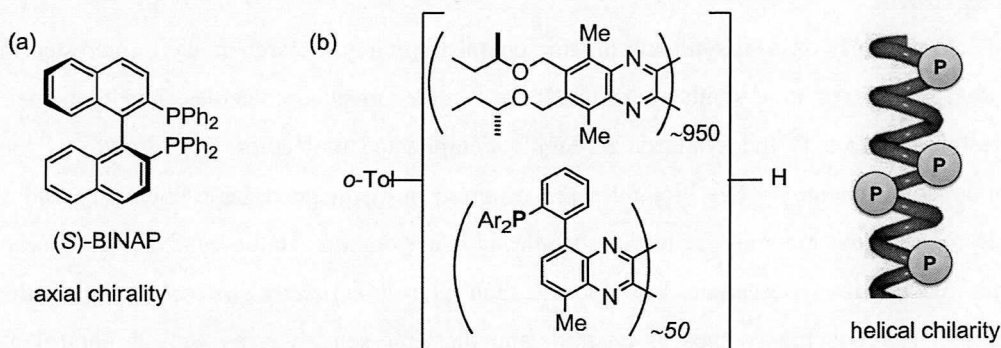


Figure 1-1. Examples of Chiral Ligand

1-1 Planar-Chiral Organometallic Catalyst

A large number of chiral organometallic complexes have been synthesized with the aim of applying to asymmetric reactions as a catalyst. Most of all commonly contain chiral ligands such as chiral phosphines, phosphites, amines, heterocycles etc.,² which can coordinate to a central metal atom playing as an active site as mentioned above.

On the other hand, cyclopentadienyl-metal complexes such as bis(cyclopentadienyl)-metal complexes (metallocene) and half-sandwich cyclopentadienyl-metal complexes have been widely known as representative organometallic complexes, and many of them exhibit highly efficient catalytic activities for a broad range of organic transformation reactions.¹⁰ Despite of favorable characteristics of cyclopentadienyl-metal complexes as stability and robustness, there are few reports on asymmetric organometallic complex containing chiral cyclopentadienyl (Cp) ligand due to difficulty of the design and synthesis of chiral cyclopentadienyl-metal complexes as well as chiral cyclopentadienyl ligands.¹¹ Planar-chiral organometallic compound is a good

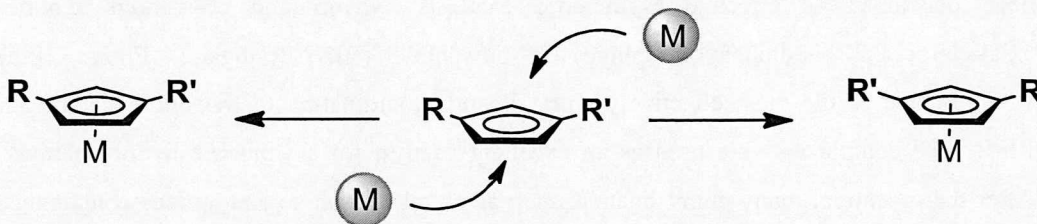


Figure 1-2. Planar-Chiral Cyclopentadienyl Organometallic Complex

solutions of the synthetic problems.¹² The planar chirality arises from organometallic π -coordination of prochiral ligands such as unsymmetrically substituted cyclopentadienyls (Figure 1-2), arenes, olefins, π -allyls, and dienes toward metals. Cyclopentadienyl ligand has been widely used for planar-chiral complexes because racemization arising from a change in coordination mode from η^5 into η^1 or dissociation of the cyclopentadienyl ligand is unlikely to occur.

In 1959, Thomson reported the first planar-chiral complex, disubstituted ferrocene derivatives.¹³ Since then, many researchers have reported various types of planar-chiral cyclopentadienyl metal complexes, which can be classified into two types: Type 1 and Type 2 (Figure 1-3).¹⁴ One has an active site separately from the metal atom with planar-chiral ligand (Type 1), and the planar-chiral complex simply acts as an optically active ligand. On the other hand, in the other type, a central metal inducing planar-chirality acts as a catalytic active site (Type 2).

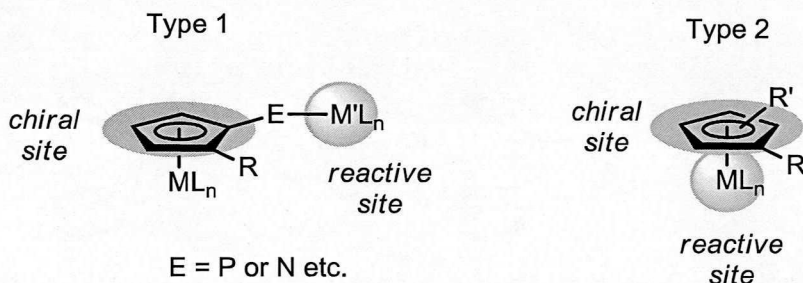


Figure 1-3. Planar-Chiral Complexes Classified into Type1 and Type 2

Hayashi reported in 1973 planar-chiral ferrocenylphosphine complexes,¹⁵ which are classified as Type 1. In this case, the iron atom of planar-chiral ferrocenyl moiety does not react with substrate, which simply serves as bulky substituents, and the other metal atom, such as palladium, coordinated by chiral ferrocenylphosphine ligand,

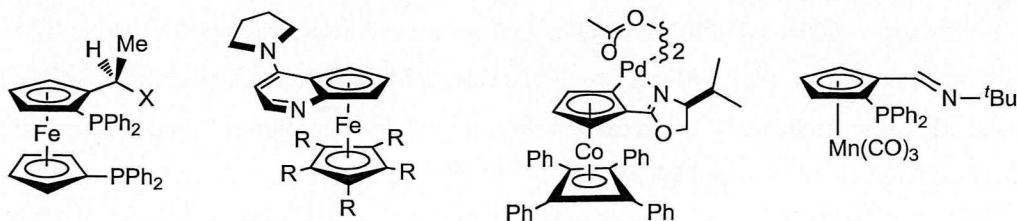
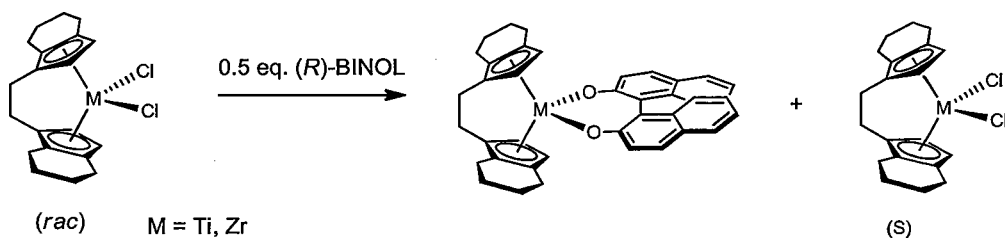


Figure 1-4. Examples of Planar-Chiral Complex of Type 1

acts as an active site. After this work, many planar-chiral complexes of Type 1 have been reported, such as planar-chiral heterocycle complexes reported by Fu,¹⁶ planar-chiral cobalt complexes¹⁷ and manganese complexes,¹⁸ which realized several asymmetric reactions with high enantioselectivity (Figure 1-4).

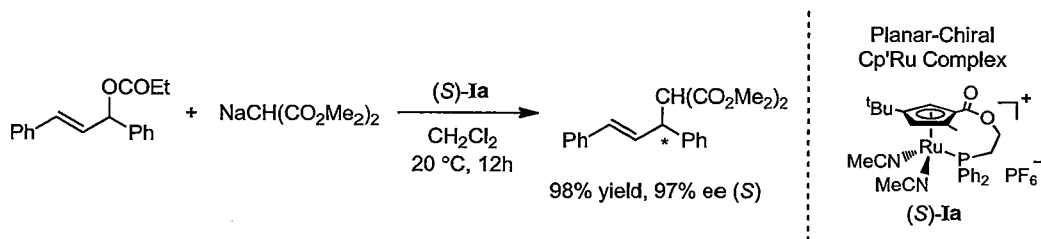
In Type 2, the central metal atom that generates planar chirality simultaneously acts as a reactive site, it is expected that strongly asymmetric environment should be constructed around the active metal center. However, there are a limited number of reports on planar-chiral complex of Type 2 because it is difficult to resolve enantiomers. In 1980's, this type of complex, *ansa*-metallocene, has been synthesized by use of early transition metals and led to planar-chiral metallocene complex, which have been used to control tacticity in the polymerization of propylene and butylene. In 1982, Brintzinger and co-workers reported the synthesis of chiral titanocene derivatives,¹⁹ which were resolved as binaphtholate derivatives (Scheme 1-1),^{19a} and these enantiopure complexes were used as an asymmetric catalyst for enantioselective carbon-carbon and carbon-hydrogen bond formation reactions.²⁰



Scheme 1-1. Resolution of Metallocene Enantiomers

In contrast to bis(cyclopentadienyl)-metal complexes, half-sandwich cyclopentadienyl-metal complexes such as Cp-Rh(III),²¹ -Ir(III),²² -Ru(II),²³ and -Co(I)²⁴ catalyze a range of important reactions which can not be achieved using metal-phosphine and -amine complexes, however, there have been only few reports on the synthesis of planar-chiral complexes of Type 2, especially with late transition metals, because it is difficult to control the arrangement of the three other ligands around the central metal.^{9,25} Recently, we have reported the synthesis of planar-chiral cyclopentadienyl-ruthenium complexes,²⁶ and found that the ruthenium complexes with an anchor phosphine ligand can control metal-centered chirality with high selectivity.²⁷ Then, we have reported the first example of Ru-catalyzed asymmetric allylic amination and alkylation of allyl carbonates using planar-chiral cyclopentadienyl-ruthenium (Cp'Ru) complex **I** (Scheme 1-2).²⁸ This system has

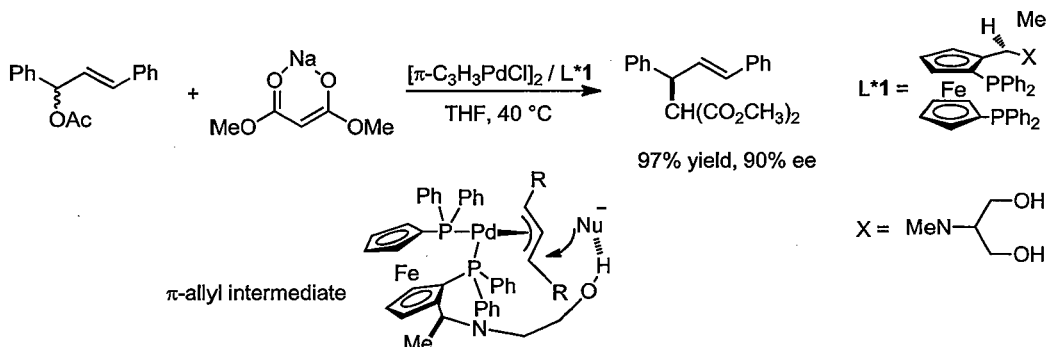
been successfully extended to the regio- and enantioselective allylic substitution of monosubstituted allylic halides with oxygen and carbon nucleophiles.²⁹



Scheme 1-2. Asymmetric Allylic Alkylation Catalyzed Cp*Ru Complex I

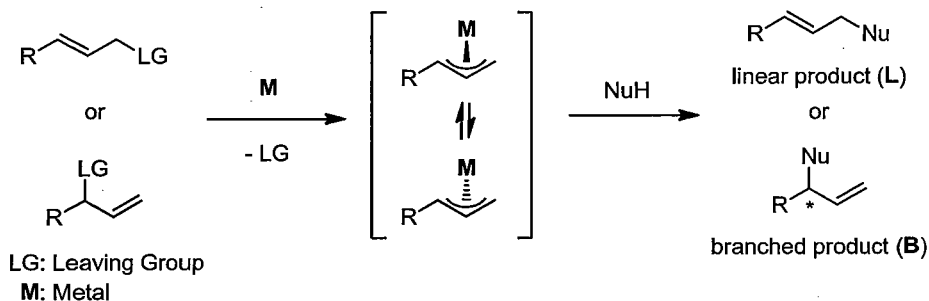
1-2 Asymmetric Allylic Substitutions of Monosubstituted Allylic Substrate

Asymmetric allylic substitution catalyzed by an organometallic complex is a powerful method to create carbon-carbon and carbon-heteroatom bonds with high enantioselectivity, and is frequently applied to the synthesis of pharmaceutical and natural products.³⁰ In 1965, Tuji reported palladium-mediated allylic substitution as stoichiometric reaction.³¹ Since then many reactions have been reported. Trost developed the reaction into asymmetric catalytic system in 1977.³² In order to attain asymmetric allylic substitutions, the reaction via a π -allylpalladium intermediate bearing symmetrical π -allyl ligand has been widely studied using a variety of chiral ligands.³⁰ In allylic substitution reactions, asymmetric induction arises from a preferential attack by a nucleophile to either of the two diastereotopic π -allyl carbon atoms in the meso π -allylpalladium(II) intermediate which was formed by oxidative addition of an allylic substrate to palladium(0) species.^{30,33} To lead such palladium-mediated allylic substitution reactions to asymmetric ones, several efforts have been done by the use of chiral ligands which can coordinate to the π -allylpalladium species. For examples, Hayashi reported that a chiral ferrocenylphosphine-palladium complex catalyzes effectively an asymmetric allylic substitution of symmetrical allylic substrates with sodium acetylacetonate to give an alkylation product with enantioselectivity of up to 92% ee (Scheme 1-3).³⁴ The ferrocenylphosphine ligand on the palladium complex has a pendant side chain bearing a hydroxy group at the terminal position which interacts with the acetylacetonate nucleophile and controls the attack of nucleophile to the π -allyl group on palladium (Scheme 1-3). Many analogous reaction systems involving symmetrically substituted π -allylpalladium intermediates have been reported until now.^{35,36}



Scheme 1-3. Asymmetric Allylic Alkylation Catalyzed by Ferrocenylphosphine π -Allyl Palladium Complex

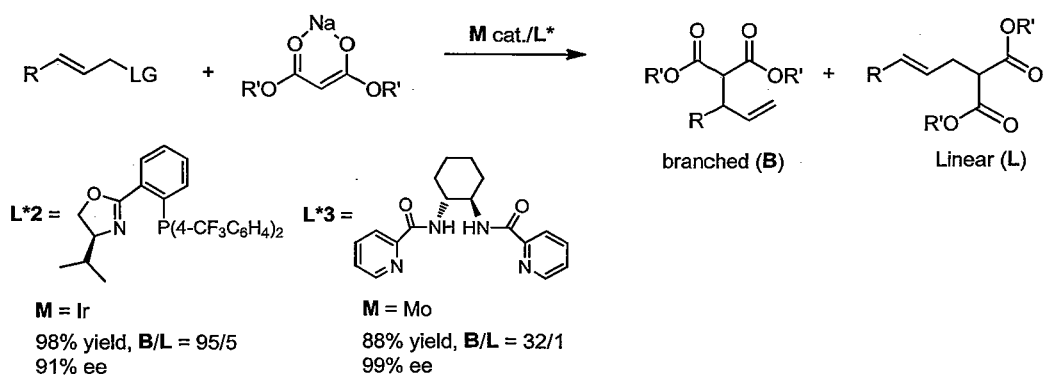
However, the asymmetric reaction of unsymmetrically substituted allylic compounds still remains as a challenging research subject, because nucleophilic attack generally takes place at the less hindered allylic carbon to give a linear product (**L** in Scheme 1-4) in the monosubstituted allylic substrate. Recently, some reaction systems have shown that a branched allylic product (**B** in Scheme 1-4), which has a stereogenic carbon and a terminal double bond, is obtained as a main product by the substitution at the hindered allylic carbon. In the reaction, the π -allyl intermediate formed via oxidative addition to the metal atom is asymmetric, so that in order to realize high enantioselectivity in the reaction, it is important to



Scheme 1-4. Schematic Representation for General Asymmetric Allylic Substitutions of Monosubstituted Substrate

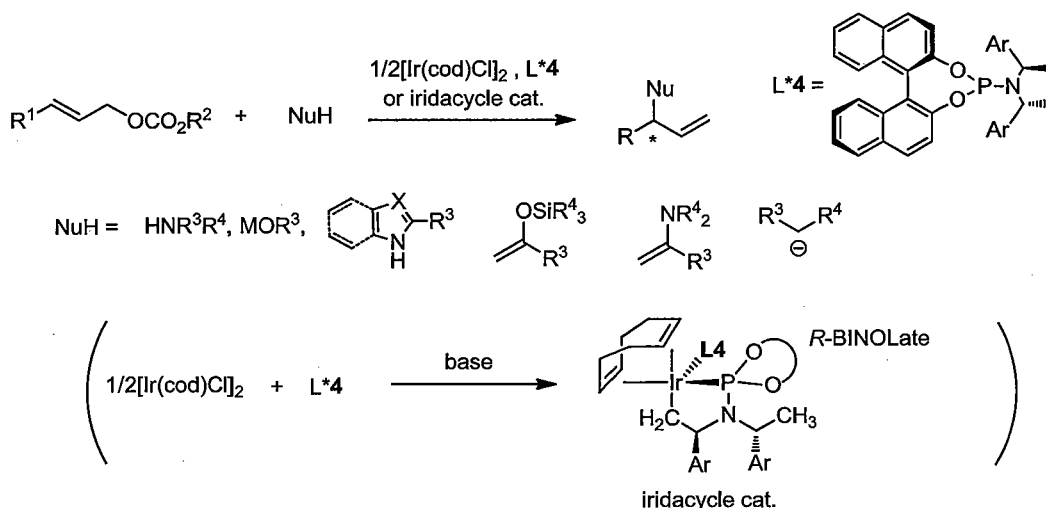
control the coordination plane of a π -allyl ligand and the positional selectivity of π -allyl carbon atoms receiving the attack of nucleophile. Until now, the asymmetric allylic substitutions of unsymmetrical allylic substrates have been reported, which catalyzed by various metal complexes, such as Ir, Mo, Ru, Cu and Pd complexes.³⁷ The reactions largely depend on the nature of the metal and nucleophile.

In 1997, Helmchen reported asymmetric allylic alkylation of monosubstituted allylic alkylation with methylmalonate catalyzed by an Ir complex containing phosphine-oxazoline ligand (**L*2**) to give branched allylic alkylation products with high regio- and enantioselectivity (Scheme 1-5).³⁸ Trost reported regio- and enantioselective allylic alkylation catalyzed by a molybdenum complex combined with bispyridylamide ligands (**L*3**).³⁹



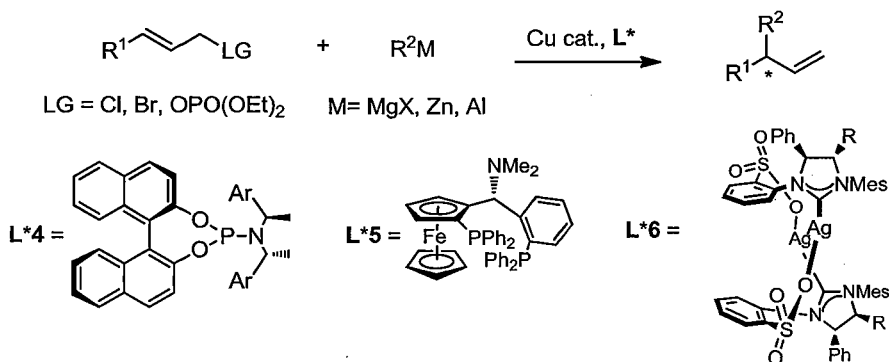
Scheme 1-5. Asymmetric Allylic Alkylation of Monosubstituted Substrate

In asymmetric allylic alkylation of monosubstituted allylic substrates using sodium malonates nucleophile, many reaction systems have been extensively studied. On the other hand, asymmetric allylic substitution using other nucleophiles, such as heteroatom nucleophiles and carbon atom nucleophiles other than malonates, were much less developed.^{37,40} Comparing all of the above described transition metal catalysts, Ir complexes have been widely used in the reaction. Phosphoramidite ligand **L*4**, which was originally prepared and applied to copper-catalyzed processes by Feringa,⁴¹ was used in Ir-catalyzed asymmetric allylic substitutions. The asymmetric reactions using different types of nucleophiles such as carbon, nitrogen, oxygen, and sulfur atoms were achieved by Hartwig et al. (Scheme 1-6).⁴² The reaction mechanism studied by Hartwig group and others led to the identification of an active catalyst, which was an iridacycle formed via C-H bond activation of methyl group of the phosphoramidate. In 2009, Hartwig and Helmchen separately reported the allyliridium intermediate at the same time, and the reaction mechanism have also been studied.^{43,44}

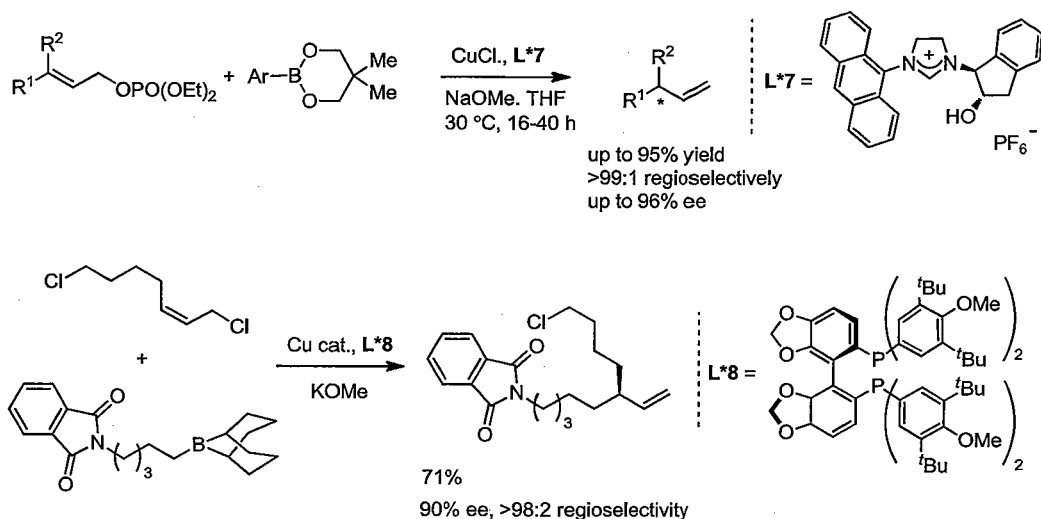


Scheme 1-6. Iridium-Catalyst for Asymmetric Allylic Substitution (Hartwig' Work)

In the enantioselective allylic alkylation with hard carbon nucleophiles such as organometallic reagents of Mg, Li, Zn, and Al, copper complexes with chiral phosphine and amine ligands were used as a catalyst. For examples, Feringa and Alexiakis used phosphoramidate and ferrocenylphosphine ligands.^{45,46} Recently, the reaction using *N*-heterocyclic carben (NHC) ligand was reported by Hoveyda etc. (Scheme 1-7).⁴⁷ In contrast, most recently Hayashi and Sawamura separately reported enantioselective allylic substitution reactions using organoboron compounds catalyzed by copper complexes (Scheme 1-8).^{48,49}

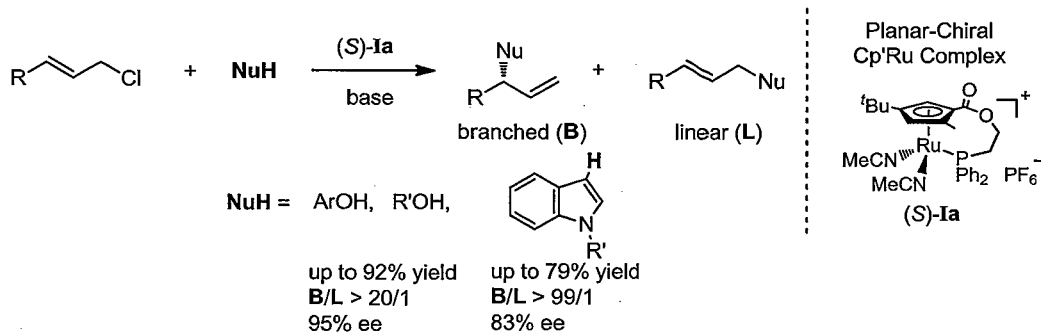


Scheme 1-7. Asymmetric Allylic Substitutions with Hard Carbon Nucleophile



Scheme 1-8. Asymmetric Allylic Substitutions with Organoboron Nucleophile

Regarding ruthenium catalysts, there are few reports on asymmetric allylic substitutions with unsymmetrically allylic substrates in compared with other metal catalysts.^{50,51} On the other hand, our conception is based on that planar-chiral cyclopentadienyl metal complexes may offer strong asymmetric environment around metal atoms suitable well for asymmetric reactions as already described in section 1-2. As the central metal atoms in the cyclopentadienyl-metal complexes, we have chosen “ruthenium” because ruthenium metal atom has a relatively variety of redox properties which are desired for a catalyst. Half-sandwich cyclopentadienyl-ruthenium complexes are thermally stable, and are handled without special care. We have selected, therefore, planar-chiral cyclopentadienyl-ruthenium complexes for our present research on asymmetric allylic substitution. Previously we reported

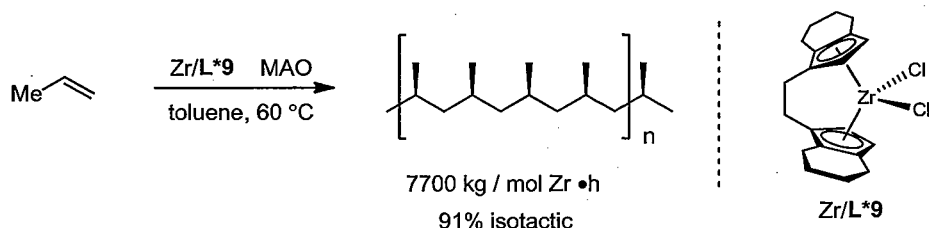


Scheme 1-9. Asymmetric Allylic Substitution Catalyzed by Cp*Ru Complex I

the enantioselective allylic substitution of 1,3-disubstituted allylic carbonate with amine and carbon nucleophiles catalyzed by planar-chiral cyclopentadienyl-ruthenium (Cp'Ru) complexes.²⁸ Recently, we have studied the regio- and enantioselective allylic substitution of monosubstituted allylic halides with oxygen and carbon nucleophiles using Cp'Ru catalyst (Scheme 1-9).²⁹

1-3 Asymmetric Polymerization

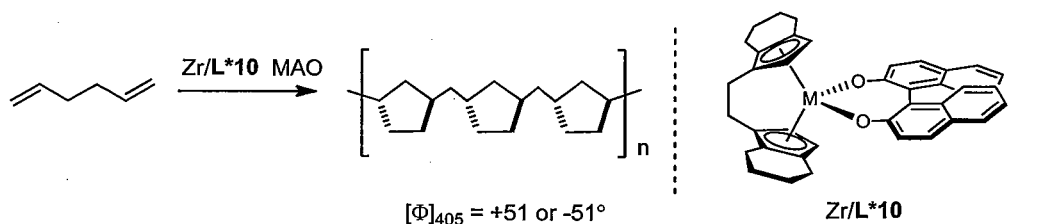
As described above, in the research field of synthetic organic chemistry, one of current topics is *precise synthesis* of various organic molecules, especially of structurally interested and optically active chiral molecules. The concept grown up in the field is now directed toward the field of polymer synthesis, and nowadays so-called "*precise polymer synthesis*," is attracting much interest of synthetic chemists. Although numerous numbers of excellent methods and techniques for polymer synthesis are known,⁵²⁻⁵⁶ there are limited numbers of reports on precise macromolecular synthesis, because it should be very difficult to attain precise synthesis of very large molecules compared with usual organic molecules. On the other hand, in 1954 Natta discovered the isotactic polymerization of propylene using heterogeneous metal catalysts which have multiple active sites,⁵⁷ and showed isotactic polypropylene to have highly thermal and crystalline properties compared with atactic ones. Since then, stereoregular polymerization of vinyl monomers has been attracted much attention in both industrial and academic fields. In 1980s, the stereoselective polymerization by single-site organometallic catalysts, *ansa*-metallocene, were reported by Kaminsky et al., which can control the molecular weight, molecular weight distribution, and both the relative and absolute stereochemistry of polymer.^{19,58} Such control in the polymerization is often impossible using conventional multi-site catalysts (Scheme 1-10).⁵⁹



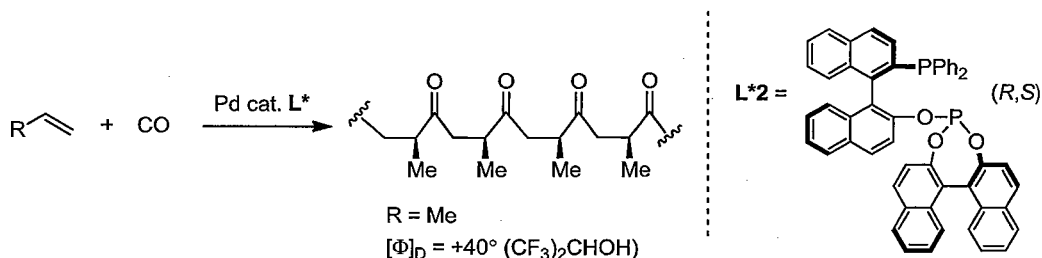
Scheme 1-10. Stereoselective Polymerization by Single Site Organometallic Catalysts

Optically active polymers have been much attention because they are considered as candidate for new and valuable materials.⁶⁰ On the other hand, in order to attain asymmetric

polymerization, highly enantioselective reaction of monomer at the active site of a chiral catalyst should be maintained throughout propagation steps of the polymerization reaction. It seems to be quite difficult to attain the aim, and indeed there are few reports on asymmetric polymerization reaction, although a number of highly controlled enantioselective organic reactions have already been developed as mentioned above.^{2,60} In 1991, some efficient systems for asymmetric polymerization of achiral monomer have been reported. Waymouth reported a novel asymmetric polymerization of 1,5- and 1,6-dienes by use of enantiomerically pure single-site metallocene catalyst (*R,R*)-Zr/L*10-MAO and (*S,S*)-Zr/L*10-MAO, which gives a completely saturated polymer with 72% *trans* rings and a molar optical rotation of $[\Phi]_{405} = +51^\circ$ and -51° , respectively.⁶¹ Nozaki and Takaya reported the asymmetric co-polymerization of α -olefins with CO using palladium and a chiral phosphine-phospite ligand which gives polymers with high regio- and stereoselectivity (Scheme 1-12).⁶² The success of asymmetric co-polymerization is based on the recent development of organometallic chemistry. Despite of these efforts, most of known asymmetric polymerizations of achiral monomers are confined almost exclusively to vinyl monomers. Effective syntheses of optically active polymers require new chiral organometallic catalysts applicable to the polymerization of a variety of monomers other than vinyl ones.



Scheme 1-11. Asymmetric Polymerization of 1,5-Dienes Using Chiral Metallocene Catalysts

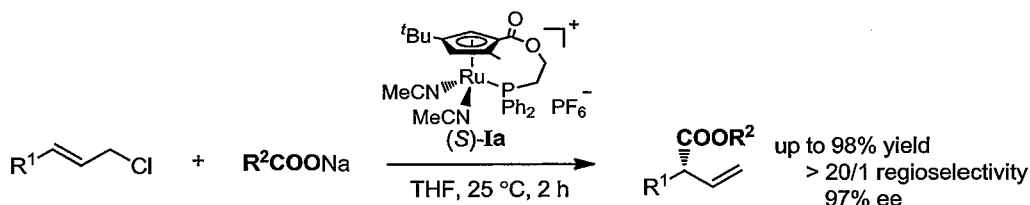


Scheme 1-12. The Asymmetric Polymerization of α -Olefin with CO

1-4 Outline of This Thesis

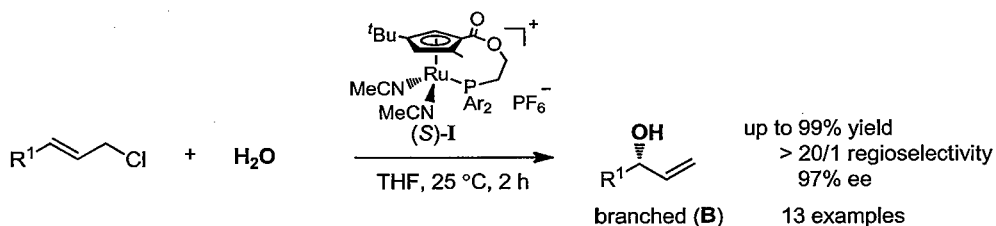
As above stated, many reactions aimed at *precise synthesis* have been developed so far, and one of them belongs to asymmetric synthesis which particularly influences the development of precise synthesis. Also we have shown a novel asymmetric catalytic system with planar-chiral cyclopentadienyl ruthenium (Cp*Ru) complexes, which are a proficient catalyst for asymmetric allylic substitutions. Recently we succeeded in the development of regio- and enantioselective reactions of monosubstituted allylic halides with oxygen and carbon nucleophiles,²³ which produce enantiomerically enriched branched allylic compounds in good yields. In this thesis, investigations of novel asymmetric allylic substitutions and the development of a new reaction system using planar-chiral Cp*Ru catalyst are described.

In Chapter 2, an asymmetric allylic substitution with sodium carboxylate using a planar-chiral cyclopentadienyl ruthenium complex will be described. Optically active allylic esters are prepared in good yields with high regio- and enantioselectivities.



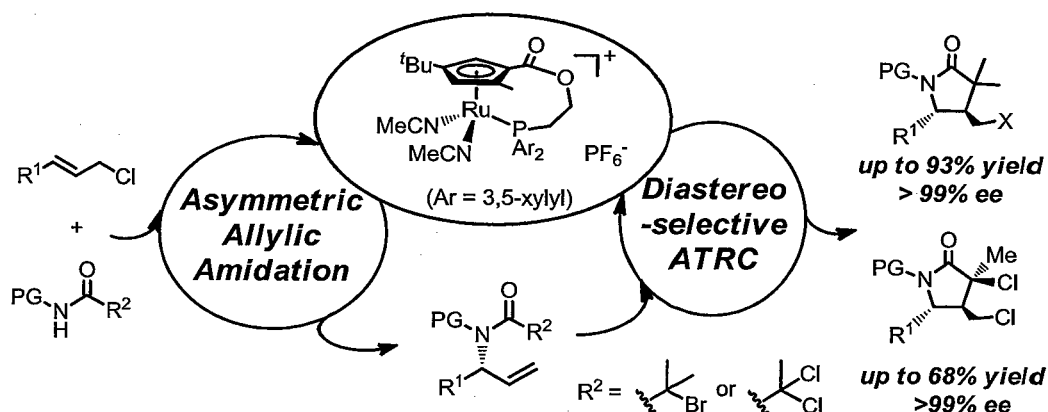
Scheme 1-13. Asymmetric Allylic Carboxylation Using Cp*Ru Catalyst

In Chapter 3, a new route to access to chiral allylic alcohols through the regio- and enantioselective substitution of monosubstituted allylic chlorides with water has been developed. The reaction is catalyzed effectively by planar-chiral cyclopentadienyl ruthenium complexes. This novel reaction is rare example that the enantioselection is based on the direct nucleophilic attack of water.



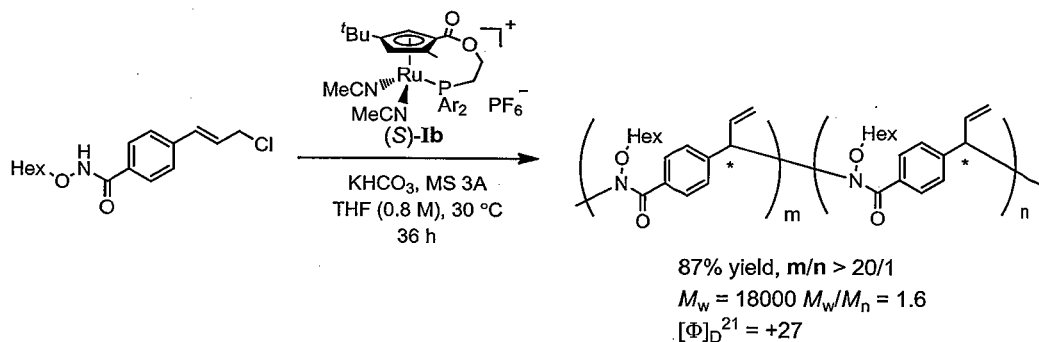
Scheme 1-14. Asymmetric Allylic Carboxylation Using Cp*Ru Catalyst

In Chapter 4, the example of asymmetric auto-tandem reaction catalyzed by planar-chiral cyclopentadienyl-ruthenium complex is described. The reaction of allylic chloride with α -haloamides provides a synthetically useful γ -lactam having multiple stereogenic centers in a diastereomerically and enantiomerically enriched form via sequential allylic amidation/atom transfer radical cyclization, both of which are promoted by the single ruthenium catalyst in one-pot, which is, to best our knowledge, the first example asymmetric auto-tandem catalysis.



Scheme 1-15. The First Asymmetric Auto-Tandem Catalysis Catalyzed by Cp^{*}Ru Catalyst

In Chapter 5, the asymmetric allylic substitution reaction is applied to asymmetric polymerization using the planar-chiral cyclopentadienyl-ruthenium complex. The resulting polymer is characterized by optical rotation power, circular dichroism and ^1H NMR analyses. The results strongly suggest that the system works in highly stereoselective manner to give optically active polyamides.



Scheme 1-16. Asymmetric Polymerization Catalyzed by Cp^{*}Ru Catalyst

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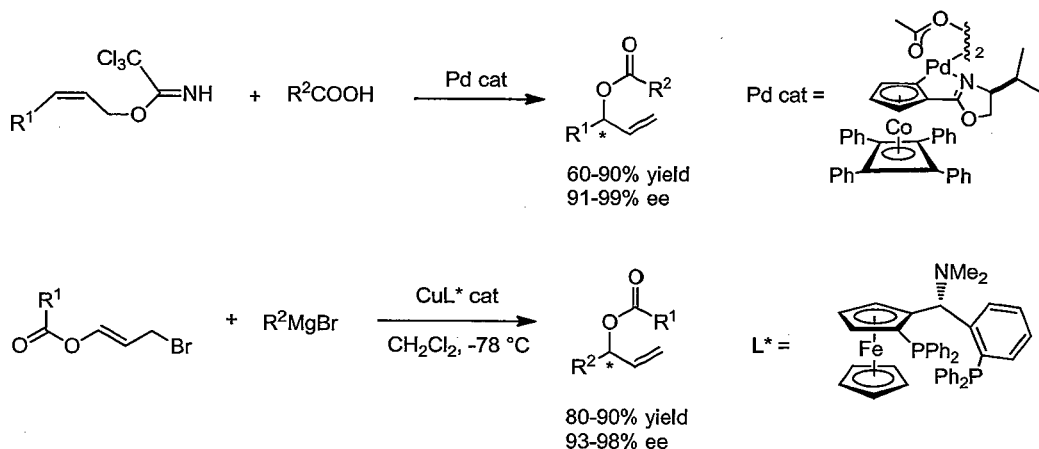
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Chapter 2: Asymmetric Allylic Substitution with Carboxylates Catalyzed by Planar-Chiral Cyclopentadienyl-Ruthenium Complex: Enantioselective Synthesis of Allylic Esters

2-1 Introduction

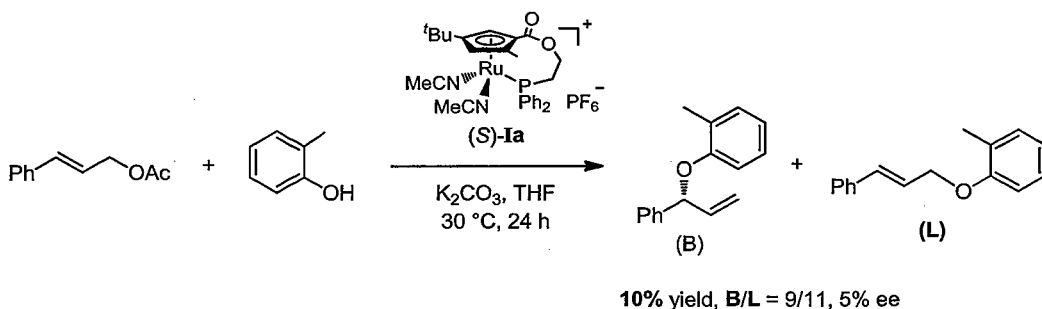
Optically active allylic alcohols and their derivatives are valuable building blocks for organic synthesis.¹ An efficient approach to these compounds involves transition-metal-catalyzed allylic substitution with oxygen nucleophiles.^{2,3} However, most of these processes are limited to the synthesis of allylic ethers. Although asymmetric allylic substitution with carboxylates seems to be a fascinating direct process, few reports are available,⁴ probably because of the high reactivity of the resulting allylic esters which undergo further reaction with metal catalysts. Overman disclosed the Pd-catalyzed asymmetric synthesis of chiral allylic esters from (*Z*)-allylic trichloroacetimidates and carboxylic acid.⁵ However, this system is not applicable to the *E* isomer, and the relatively large leaving group is unfavorable from the viewpoint of atom economy (Scheme 2-1).⁶ Feringa and co-workers offered another route to allylic esters via Cu-catalyzed asymmetric allylic alkylation of 3-bromopropenyl esters, but the use of a Grignard reagent led to some limitations.⁷



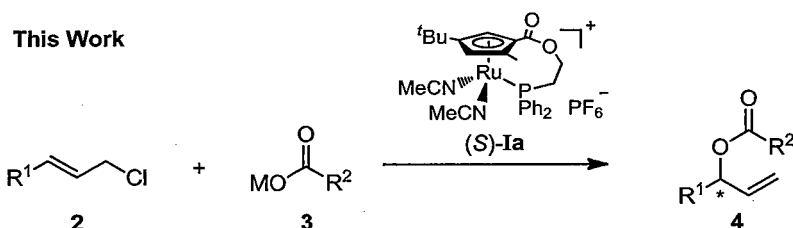
Scheme 2-1. Enantioselective Synthesis of Allylic Esters via Asymmetric Allylic Substitution

2-2 Asymmetric Allylic Carboxylation

As an extension of our study of asymmetric allylic substitution catalyzed by planar-chiral cyclopentadienyl ruthenium (Cp^{*}Ru) complexes (**I**),^{8,9} we recently reported the regio- and enantioselective reaction of monosubstituted allylic halides with phenol and indole.¹⁰ When allylic acetate was used as the substrate in these reactions, the desired allylation products were furnished in low yields, and most of the starting allylic acetate was recovered (Scheme 2-2).^{10a} The low reactivity of Cp^{*}Ru catalysts **I** with allylic esters prompted us to examine the allylic substitution using carboxylate as the nucleophile. We present herein the catalytic asymmetric allylic substitution with sodium carboxylates to give allylic esters with high regio- and enantioselectivities (Scheme 2-3).



Scheme 2-2. Reaction of Cinnamyl Acetate with *o*-Cresol



Scheme 2-3. This Work

2-3 Optimization of Reaction Conditions

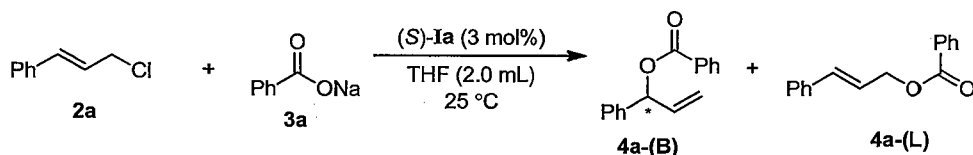
We started investigation by optimizing the reaction conditions using cinnamyl chloride (**2a**) with sodium benzoate (**3a**) in THF at 25 °C in the presence of 3 mol % (*S*)-**Ia** (R = *t*Bu). The reaction proceeded with almost quantitative conversion after 12 h to produce linear allylic ester in 97% yield. On the other hand, when the reaction was carried out without (*S*)-**Ia** catalyst, the reactivity of the system was reduced to produce linear allylic ester only 30%

yield. Therefore, the Cp'Ru complex **I** works as a catalyst in the reaction system. To improve the regioselectivity in the system, we conducted optimization of reaction conditions.

Effect of the Ratio of Cinnamyl Chloride (**2a**) to Sodium Benzoate (**3a**)

Initially, we investigate the effect of ratio of substrate to nucleophile on the reaction between **2a** and **3a** with the (*S*)-**Ia** catalyst in THF (Table 2-1). Controlling the substrate ratio (**2a**/**3a**) was crucial to achieving high regioselectivity. The reaction of **3a** with an equimolar amount of **2a** produced branched and linear allylic esters in 97% yield in 13:7 ratio with 89% ee for **4a-(B)** (entry 1). The reaction with 0.5 equivalent of **2a** showed similar regioselectivity but lower enantioselectivity (entry 2). Extension of the reaction time decreased the regioselectivity of **4a-(B)**, and unexpectedly **4a-(L)** was obtained as sole product in the reaction conducted for 7 h (entry 4), indicating that **4a-(B)** was converted into **4a-(L)** under these conditions. Use of 1.3 equivalents of **2a** slightly improved the regioselectivity to **4a-(B)**/**4a-(L)** = 18:2 (entry 5). The reaction with 2.0 equivalents of **2a** selectively produced **4a-(B)** in 98% yield with 95% ee (entry 6), and no loss of region- and enantioselectivity was observed when the reaction was conducted for 12 h (entry 7). These results suggest that the presence of excess **2a** prevented the isomerization of **4a-(B)** into **4a-(L)**. We decided to conduct all of the reactions, described below, to be performed with 2.0 equivalents of **2a** for a

Table 2-1. Effect of the Ratio of Cinnamyl Chloride (**2a**) to Sodium Benzoate (**3a**)^a



entry	2a (mmol)	3a (mmol)	reaction time (h)	yield (%) of 4a ^b	4a-(B) / 4a-(L) ^c	ee (%) of 4a-(B) ^d
1	0.5	0.5	2	97	13/7	89 (<i>R</i>)
2	0.5	1.0	2	98	13/7	69 (<i>R</i>)
3	0.5	1.0	5	98	4/16	65 (<i>R</i>)
4	0.5	1.0	7	98	<1/20	-
5	0.75	0.5	2	98	18/2	82 (<i>R</i>)
6	1.0	0.5	2	98	>20/1	95 (<i>R</i>)
7	1.0	0.5	12	98	>20/1	94 (<i>R</i>)

^a (*S*)-**Ia** (0.01 mmol), **2a**, and **3a** in THF (2.0 mL), stirred at 25 °C. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic esters. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

reaction time of 2 h.

Effect of Reaction Temperature

To investigate the influence of reaction temperature, the reaction between **2a** (1.0 mmol) and **3a** (0.5 mL) with (*S*)-**1a** catalyst in THF (2.0 mL) was carried out. The results are summarized in Table 2-2. The reaction at lower temperature than 25 °C caused to reduce the reactivity, regio- and enantioselectivity (entries 1-5). On the contrary, increasing the reaction temperature to 30 °C improved the reactivity, and the reaction was completed in only one hour (entries 7 and 8), but the enantioselectivity was reduced in comparison with that at 25 °C. Thus, the best reaction temperature has been determined to be 25 °C.

Table 2-2. Effect of Reaction Temperature^a

Run	Temperature (°C)	Reaction time (h)	Yield (%) of 4a ^b	4a-(B)/4a-(L) ^c	ee (%) of 4a-(B) ^d
1	0	40	15	17/3	-
2	5	40	98	>20/1	87 (<i>R</i>)
3	10	18	98	>20/1	91 (<i>R</i>)
4	15	5	98	>20/1	93 (<i>R</i>)
5	20	5	98	>20/1	93 (<i>R</i>)
6	25	2	98	>20/1	95 (<i>R</i>)
7	30	1	99	>20/1	94 (<i>R</i>)
8	40	1	99	>20/1	91 (<i>R</i>)

^a (*S*)-**1a** (0.01 mmol), **2a** (1.0 mmol), and **3a** (0.5 mmol) in THF (2.0 mL). ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic esters. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

Effect of Reaction Time

To investigate the influence of reaction time, the reaction between **2a** and **3a** with (*S*)-**1a** catalyst in THF at 25 °C was conducted. The results are summarized in Table 2-3. The reaction time gave no influence on the regio- and enantioselectivity. The reaction for 1 h slightly decreased the yield (entry 1). When the reaction time was prolonged to 12 h, isomerization of branched allylic ester **4-(B)** to linear allylic ester **4-(L)** was not observed. These results indicated that the presence of excess **2a** prevented the isomerization of **4a-(B)** to **4a-(L)**, even as extension of the reaction time. We decided to conduct all of the reaction mixture described below to be stirred for 2 h.

Table 2-3. Effect of Reaction Temperature^a

entry	Reaction time (h)	Yield (%) of 4a ^b	4a-(B)/4a-(L) ^c	ee (%) of 4a-(B) ^d
1	1	92	>20/1	94 (<i>R</i>)
2	2	98	>20/1	95 (<i>R</i>)
3	3	98	>20/1	95 (<i>R</i>)
4	5	98	>20/1	94 (<i>R</i>)
5	12	98	>20/1	94 (<i>R</i>)

^a (*S*)-**1a** (0.01 mmol), **2a** (1.0 mmol), and **3a** (0.5 mmol) in THF (2.0 mL), stirred at 25 °C for 2 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic esters. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

Effect of Counter Cation

The reaction between **2a** and benzoic acid in the presence of (*S*)-**1a** did not proceed at all, suggesting that carboxylate anion works as nucleophile, and we investigated the influence of counter cation of carboxylate for the reaction between **2a** and **3a** with (*S*)-**1a** in THF for a reaction time of 2 h. Results obtained from the optimization of reaction are summarized in Table 2-4. Changing the counter cation from sodium to potassium and lithium reduced the yield and enantioselectivity (entries 2 and 3). When ammonium benzoate was used as nucleophile, the reaction proceeded with moderate enantioselectivity and yield (entry 4). Although the reaction with benzoic acid in presence of ^tPr₂NEt as a base proceeded with quantitative conversion, the enantioselectivity of **4-(B)** was drastically reduced (entry 5). As described below, the reaction seems to proceed via π -allyl intermediates (*S*)-**II** that are generated by the oxidative addition of allylic chloride to the central Ru atom with high diastereoselectivity, therefore silver(I) benzoate was used as nucleophile due to accelerate the extraction of chlorine. As a result, the reaction gave moderate yield and regioselectivity, but any products showing an optical activity were not obtained (entry 6). The fact indicated that the counter cation of carboxylate is crucial for achieving high selectivity of the reaction. Thus, in the present allylic carboxylation the most suitable counter cation has been determined to be sodium. However, the reason why sodium is the best counter cation is not yet clear.

Table 2-4. Effect of Counter Cation^a

2a 1.0 mmol	3a 0.5 mmol		4a (B)	4a (L)
entry	M	Yield (%) of 4a ^b	4a-(B)/4a-(L) ^c	ee (%) of 4a-(B) ^d
1	Na	98	>20/1	95 (<i>R</i>)
2	K	63	>20/1	91 (<i>R</i>)
3	Li	74	20/1	76 (<i>R</i>)
4	NH ₄	63	20/1	83 (<i>R</i>)
5	<i>i</i> Pr ₂ NEt	97	18/2	31 (<i>R</i>)
6	Ag	71	1/20	0 (<i>R</i>)

^a (*S*)-**Ia** (0.01 mmol), **2a** (1.0 mmol), and **3a** (0.5 mmol) in THF (2.0 mL), stirred at 25 °C for 2 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic esters. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

Effect of Solvent

To know the influence of solvent, we examined the reaction between **2a** and **3a** in a variety of solvents in the presence of (*S*)-**Ia** catalyst at 25 °C. The results obtained from the reaction in a good solvent for the catalyst are summarized in Table 2-5. The reaction in THF gave the best result with 98% yield and 95% ee (entry 1). When acetone was used as a solvent, the reaction proceeded with quantitative conversion, but the enantioselectivity was reduced

Table 2-5. Effect of Solvent^a

entry	solvent	reaction time (h)	yield (%) of 4a ^b	4a-(B)/4a-(L) ^c	ee (%) of 4a-(B) ^d
1	THF	2	98	>20/1	95 (<i>R</i>)
2	Acetone	2	99	>20/1	86 (<i>R</i>)
3	DMF	2	90	14/6	49 (<i>R</i>)
4	CH ₂ Cl ₂	24	99	10/10	56 (<i>R</i>)
5	Toluene	24	57	11/9	47 (<i>R</i>)

^a (*S*)-**Ia** (0.01 mmol), **2a** (1.0 mmol), and **3a** (0.5 mmol) in solvent (2.0 mL), stirred at 25 °C for 2 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic esters. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

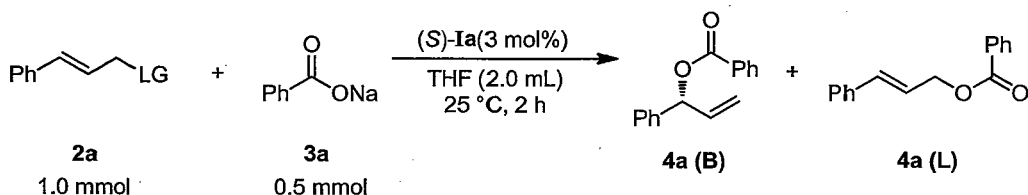
(entry 2). The use of dimethylformamide as a polar solvent resulted in a good yield, but the

regio- and enantioselectivity were decreased (entry 3). The use of dichloromethane resulted in a poor yield and a low enantioselectivity (entry 4). Hydrocarbons like toluene are not a suitable solvent for the reaction because the ruthenium catalyst showed a low solubility in common hydrocarbons (entry 5).

Effect of Leaving Group on Allylic Chloride

To investigate the influence of leaving group on the allylic carboxylation, we examined the reactivity of cinnamyl bromide, which also produced branched allylic ester **4a-(B)** in good yield, but the enantioselectivity was considerably reduced (entry 2). When cinnamyl carbonate was used as a substrate, the reaction did not proceed at all (entry 3). Thus, in the allylic carboxylation reaction the most suitable substrate has been determined to be allylic chloride.

Table 2-6. Effect of Leaving Group on Allylic Chloride ^a



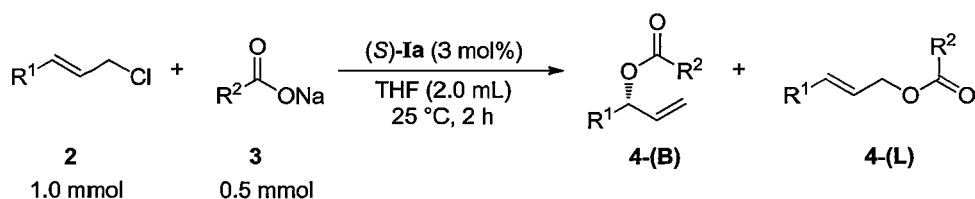
entry	LG	yield (%) of 4a ^b	4a-(B)/4a-(L) ^c	ee (%) of 4a (B) ^d
1	Cl	98	>20/1	95 (<i>R</i>)
2	Br	98	>20/1	70 (<i>R</i>)
3	OCO ₂ Et	0	-	-

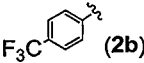
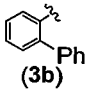
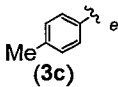
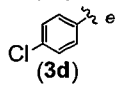

^a (S)-**Ia** (0.01 mmol), **2a** (1.0 mmol), and **3a** (0.5 mmol) in THF (2.0 mL), stirred at 25 °C for 2 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic esters. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

From the experimental results described above, the optimal reaction conditions of the present allylic amidation have been determined as follows: Catalyst, Cp*₂Ru complex **Ia** (3 mol%); Counter Cation, Na; Ratio of **2/3** = 2:1; Reaction temperature, 25 °C; Leaving Group on allylic substrate, Cl; Solvent, THF.

2-4 Screening of Substrate

Table 2-7. Reaction of Allyl Chloride Derivatives **2** with Sodium Carboxylates **3**^a

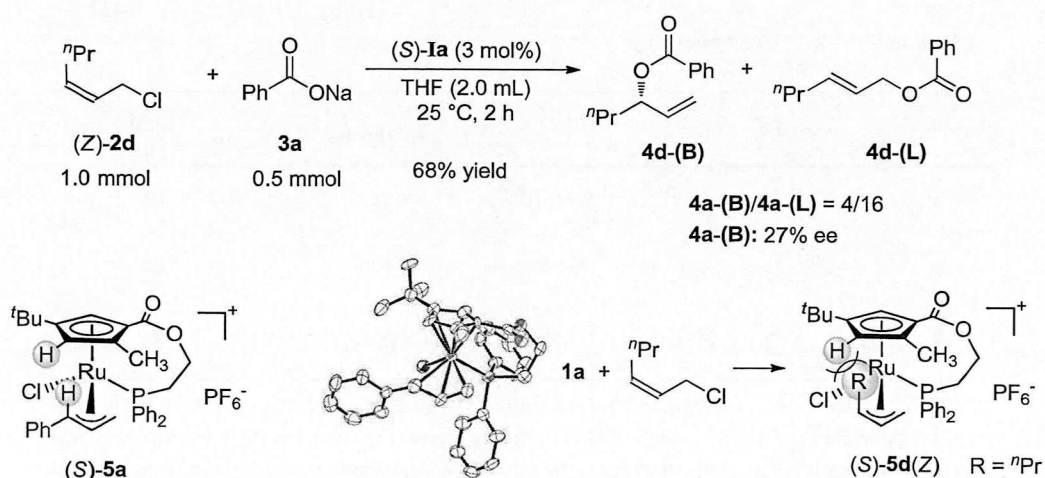


entry	R ¹	R ²	yield (%) of 4 ^b	4a-(B)/4a-(L) ^c	ee (%) of 4a-(B) ^d
1	Ph (2a)	Ph (3a)	98 (4a)	> 20/1	95 (<i>R</i>)
2	 (2b)	Ph (3a)	98 (4b)	> 20/1	97 (<i>R</i>)
3	Me (2c)	Ph (3a)	99 (4c)	> 20/1	82 (<i>S</i>)
4	<i>n</i> Pr (2d)	Ph (3a)	88 (4d)	> 20/1	81 (<i>S</i>)
5	Ph (2a)	 (3b)	99 (4e)	> 20/1	91 (<i>R</i>)
6	Ph (2a)	 (3c)	80 (4f)	> 20/1	93 (<i>R</i>)
7	Ph (2a)	 (3d)	97 (4g)	> 20/1	88 (<i>R</i>)
8	Ph (2a)	Me (3e) ^e	99 (4h)	> 20/1	92 (<i>R</i>)
9	Ph (2a)	<i>n</i> Pr (3e) ^e	64 (4i)	> 20/1	84 (<i>R</i>)
10	Ph (2a)	<i>t</i> Bu (3g) ^e	97 (4j)	> 20/1	91 (<i>R</i>)
11	Ph (2a)	 (3h) ^e	99 (4k)	> 20/1	93 (<i>R</i>)

^a (*S*)-**Ia** (0.01 mmol), **2** (1.0 mmol), and **3** (0.5 mmol) in THF (2.0 mL), stirred at 25 °C for 2 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic esters. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses. ^e Sodium carboxylates were generated in situ from carboxylic acids with Na₂CO₃.

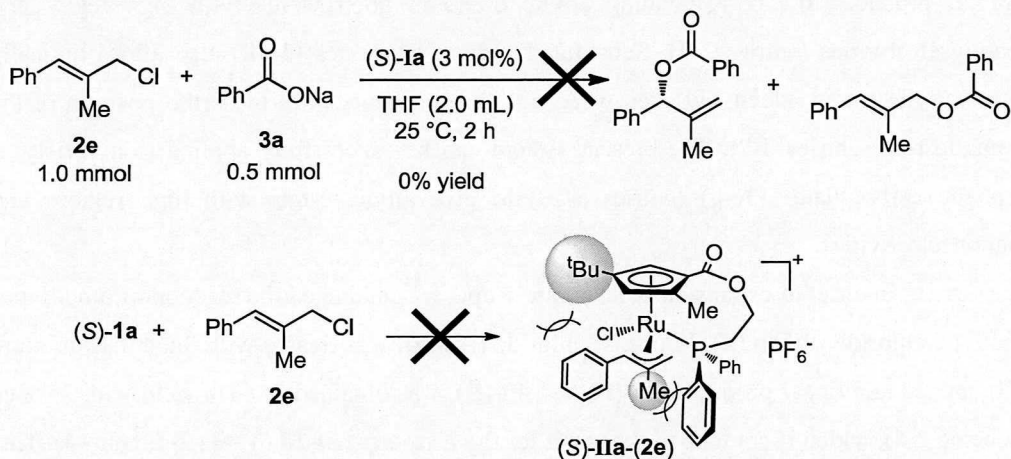
Under the optimized conditions determined above, reactions of several other allylic chloride derivatives **2b-d** with sodium benzoates and aliphatic carboxylates (**3a-g**) were carried out in the presence of catalyst **I**. The results are summarized in Table 2-7, suggesting that not only aryl-substituted allylic chloride **2b** but also alkyl substituted allylic chlorides **2c** and **2d** produced the corresponding allylic esters in good yields with high regio- and enantioselectivities (entries 2-4). Substituted sodium benzoates (**3b-d**) also afford optically active allylic esters selectively even when a bulky group occupies the ortho position of the aromatic ring (entries 5-7). The present system can be successfully applied to a variety of aliphatic carboxylates (**3e-g**) (entries 8-10) to give allylic esters with high region- and enantioselectivities.

Next, in order to expansion of substrate scope, we conducted the reaction of other types of allylic chloride. When (*Z*)-2-hexenyl chloride ((*Z*)-**2d**) was treated with **3a**, a 4:16 mixture of branched and linear products, **4d-(B)** and **4d-(L)**, was obtained in 63% yield with 27% ee (Scheme 2-4), which is contrast to the result for the *E* isomer (*E*)-**2d** (Table 2-7, entry 4). This result showed that the present system is applicable to only (*E*)-allylic chloride and is complementary to the Pd-catalyzed system.⁵ Our previous studies,¹⁰ as described below, show that the reaction system proceeds via π -allyl intermediates (*S*)-**IIa**. When (*Z*)-**2d** was used as allylic chloride, oxidative addition of the halide producing a π -allyl intermediate is prevented by steric repulsion between the ^{*n*}Pr group on the π -allyl ligand and the Cp' ring, and the product yield is reduced.



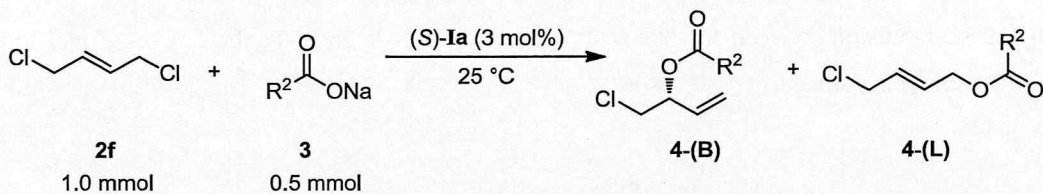
Scheme 2-4. Reaction of (*Z*)-2-Hexenyl Chloride ((*Z*)-**2d**) with Sodium Benzoate (**3a**)


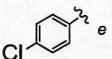
Moreover, when cinnamyl derivative **2e** bearing methyl group on 2-position was used as a substrate, the reaction did not proceed at all (Scheme 2-5). The methyl group on 2-position in **2e** may disturb the oxidative addition of **2e** to the central Ru by steric barrier between the methyl group and a phenyl group on the anchor phosphine ligand as illustrated in Scheme 2-5.



Scheme 2-5. Reaction of Cinnamyl Derivative **2e** with Sodium Benzoate (**3a**)

Table 2-8. Reaction of bifunctional allylic **2f** with Sodium Carboxylates **3^a**



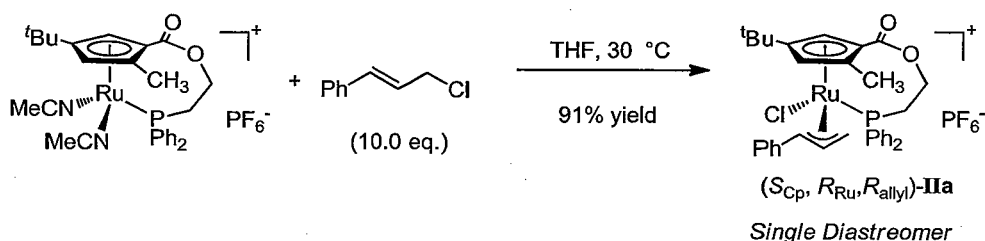
entry	R ²	yield (%) of 4 ^b	4-(B) / 4-(L) ^c	ee (%) of 4-(B) ^d
1	Ph (3a)	90 (4l)	> 20/1	88
2	 (3b)	90 (4m)	> 20/1	88
3	 (3d)	93 (4n)	> 20/1	78

^a (S) -**1a** (0.01 mmol), **2f** (1.0 mmol), and **3** (0.5 mmol) in THF (2.0 mL), stirred at 25 °C for 2 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic esters. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses. ^e Sodium carboxylates were generated in situ from carboxylic acids with Na₂CO₃.

We also examined the reaction of a bifunctional allylic substrate.¹¹ Treatment of (*E*)-1,4-dichloro-2-butene (**2f**) with **3a** resulted in the formation of branched product **4l-(B)** in 90% yield with **4l-(B)**/**4l-(L)** > 20:1 and 88% ee for **4l-(B)** (Table 2-8, entry 1). Substituted sodium benzoates **3b** and **3d** similarly reacted with **2f** to give **4m** and **4n**, respectively, in good yields with high selectivities. Thus prepared allylic esters **4l**, **4m**, and **4n** should be useful as a highly tunable chiral synthon, because they have three functional groups of unsaturated C=C bond and chloro groups as well as ester group in a molecule.

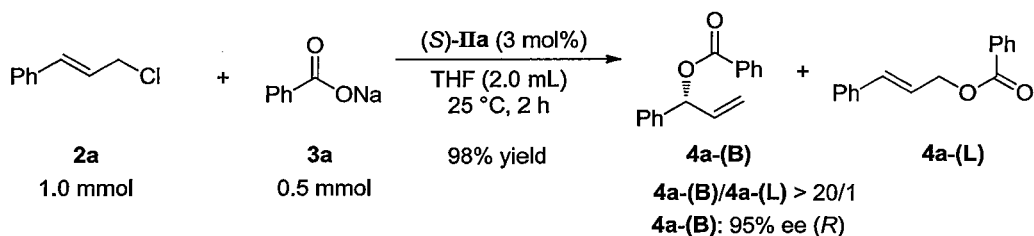
2-5 Investigation on Reaction Mechanism

Our previous studies have shown that Cp*Ru-catalyzed allylic substitutions of monosubstituted allylic halides with phenol and indole proceeds via π -allyl intermediate ((*S*)-**IIa**) bearing an η^3 -cinnamyl ligand.¹⁰ Although chirality was generated not only at the Ru center (atom-centered chirality) but also on the η^3 -allyl ligand (planar chirality), the NMR spectra of the reaction mixture suggested that Cp*Ru (η^3 -cinnamyl) complex, (*S*)-**IIa**, to be a single diastereomer (Scheme 2-6). The configuration of (*S*)-**IIa** has been determined by an X-ray crystallographic analysis to be (*S*^{*}_{Cp}, *R*^{*}_{Ru}, *R*_{allyl})-**IIa**.



Scheme 2-6. Synthesis of π -Allyl Complex **IIa**

It appears that in the present system the asymmetric allylic substitution proceeds via π -allyl complex (*S*)-**IIa**, similar to that proposed for the previous reaction.^{10a} In order to demonstrate the reaction mechanism, we examined the reaction of **2a** with **3a** in the presence of (*S*)-**IIa** as a catalyst instead of (*S*)-**Ia**. The reaction smoothly proceeded to give branched allylic ester **4a-(B)** in good yield with high regio- and enantioselectivities, which are similar to the case for (*S*)-**Ia** catalyst (Scheme 2-7). The result suggests that (*S*)-**IIa** complex also works as an intermediate of the present allylic carboxylation reaction, affording a useful information on the reaction mechanism.



Scheme 2-7. Reaction of Cinnamyl Chloride with Sodium Benzoate Catalyzed by (*S*)-IIa

A plausible reaction mechanism is illustrated in Figure 2-1. Oxidative addition of **2a** to (*S*)-Ia produces π -allyl (*S*)-IIa. Then, nucleophilic attack by carboxylate **3a** to (*S*)-IIa takes place to give product (*R*)-4a-(B) and regenerated (*S*)-Ia catalyst. The absolute configuration of product (*R*)-4a-(B) should be determined by diastereoselective formation of (*S*)-IIa, followed by inside attack of the carboxylate nucleophile on Ru in (*S*)-IIIa and subsequent reductive elimination to give the product. In the reaction using an excess amount of allylic chloride, the catalytic cycle would stop at the stage involving (*S*)-IIa, which does not react further with the reaction product, branched allylic esters 4a-(B). On the other hand, when the amount of allylic chloride in the system is insufficient, regenerated (*S*)-Ia would slowly react with branched allylic ester 4a-(B) to provide thermodynamically stable linear allylic ester 4-(L) (Figure 2-1).

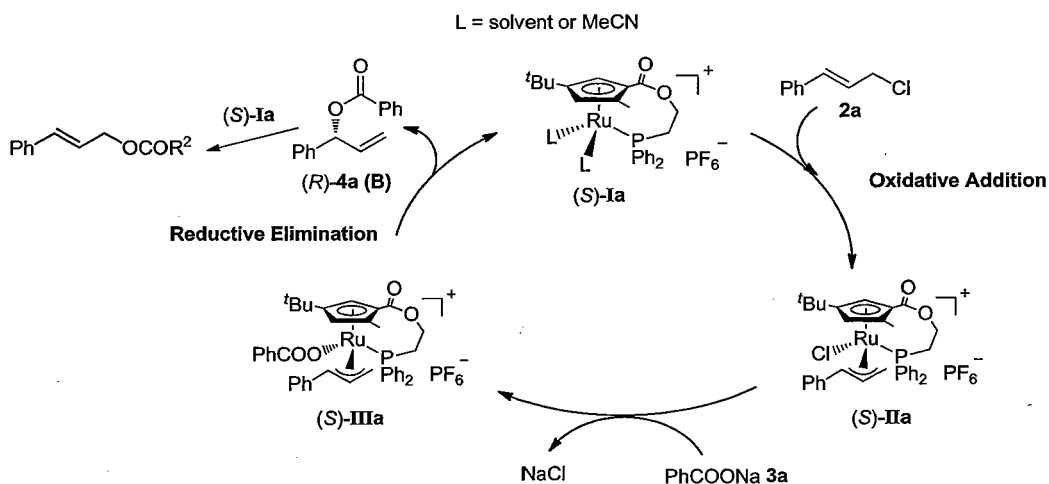
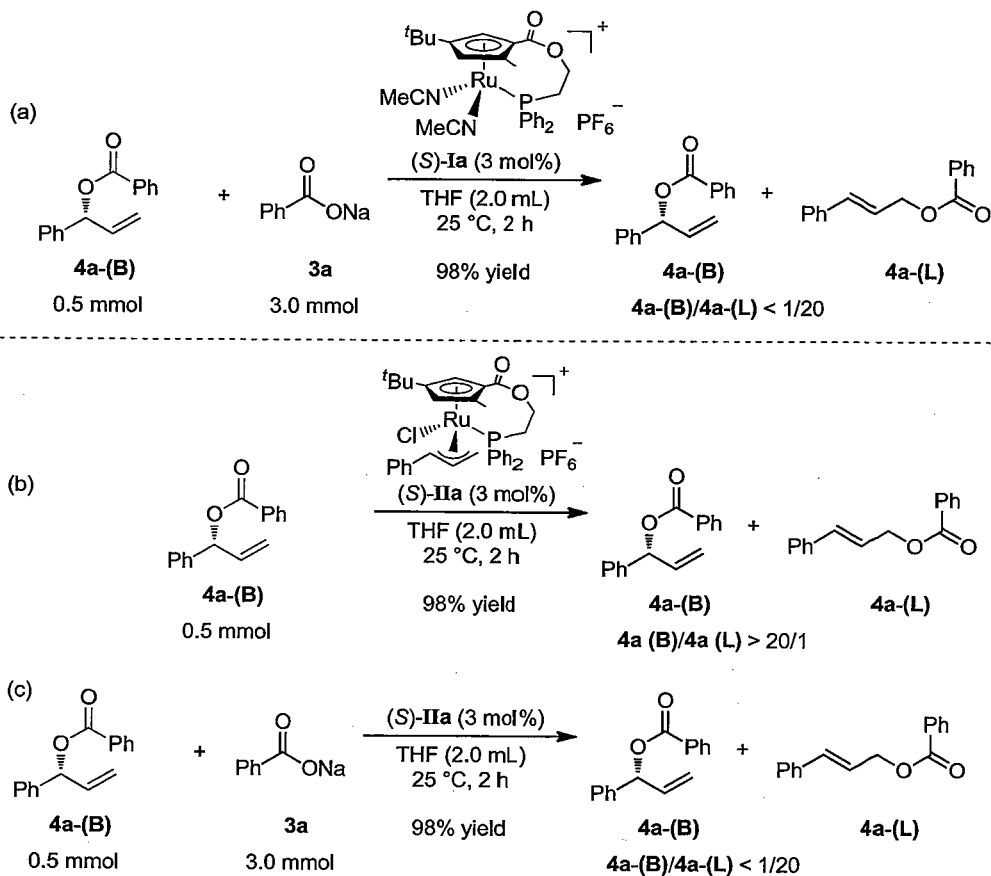


Figure 2-1. Plausible Reaction Mechanism

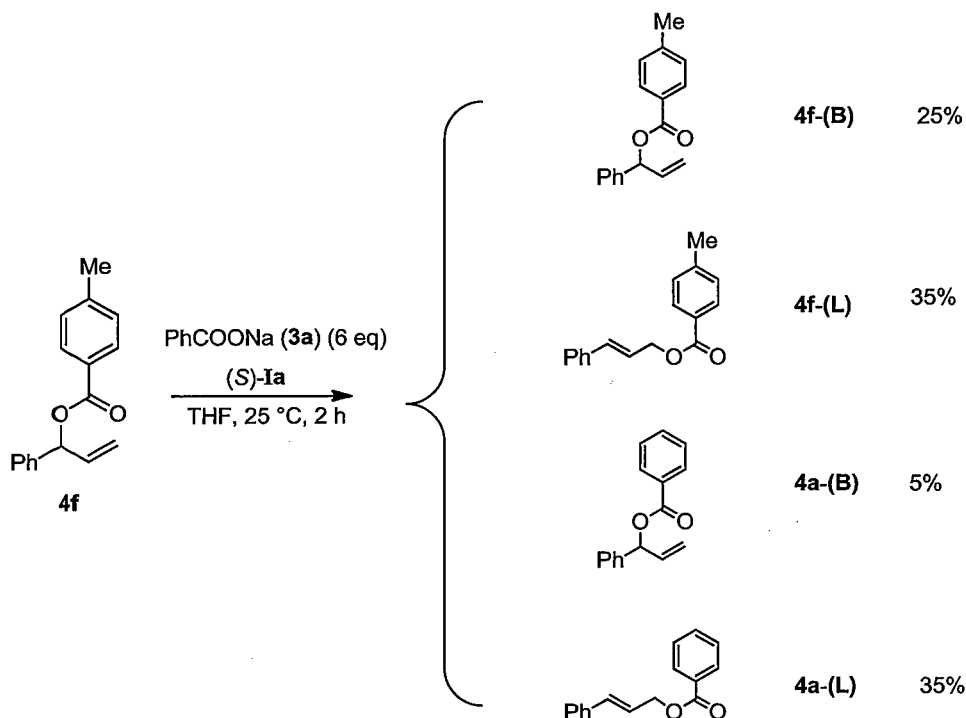
The reaction mechanism may be supported by the following experimental results. The reaction of 4a-(B) with 3a in the presence of (*S*)-Ia in THF at 25 °C was conducted. After the

reaction for 7 h, linear allylic esters **4a-(B)** was selectively formed via the isomerization of **4a-(B)** to **4b-(L)** (**4a-(B)**/**4a-(L)** < 1:20) (Scheme 2-8a). On the other hand, when **4a-(B)** was used as substrate in the presence of catalytic amount of (*S*)-**Ia**, any isomerization of **4a-(B)** was not observed. The addition of **3a** to the system resulted in quantitative formation of **4a-(L)** for 2 h (Scheme 2-8(b) and (c)). These experimental studies suggest that the isomerization of **4a-(B)** to **4b-(L)** is caused by, which is regenerated via (*S*)-**IIa** and then (*S*)-**IIIa**-(**3a**).



Scheme 2-8. The Reaction of Branched Allylic Ester **4a-(B)**.

To learn the isomerization mechanism of **4a-(B)**, crossover reactions were conducted, thus the reaction of **4g-(B)** with **Ia** was performed in the presence of **3a**. The resulting products are not only **4g-(L)** but also **4a-(L)**, and branched **4a-(B)** was also formed. The crossover experiment indicates the isomerization of **4-(B)** to proceed through an inter- or intramolecular reversible reaction pathway, involving ligand-exchange reactions (Scheme 2-9).



Scheme 2-9. Crossover Reaction

In Figure 2-2, a tentative isomerization mechanism is shown. From the experimental results, we assume that the isomerization of **4-(B)** proceeds through an intramolecular mechanism. Initially, η^3 -cinnamyl moiety on $(S)\text{-IIIa-(3f)}$ is generated by oxidative addition of **4f-(B)** (Figure 2-2(a)). Such the oxidative addition of allylic esters to palladium complex is well-known.² The η^3 -cinnamyl moiety in **IIIa-(3f)** rotates around the axis of allyl-ruthenium bound and transforms into a stereoisomer of **IIIa'-(3f)**. Subsequent reductive elimination (inside attack) gives linear allylic ester **4f-(L)**. In the mechanism, carboxylate-ligand exchange between **IIIa-(3f)** and **IIIa-(3a)** gives **IIIa'-(3f)** and **IIIa'-(3a)**, which give **4f-(L)** and **4a-(L)** by reductive elimination (Figure 2-2(b)). Similarly, the crossover products may be derived from the ligand exchange reaction. The mechanism would be most suitable for understanding the isomerization mechanism of **4-(B)** to **4-(L)**.

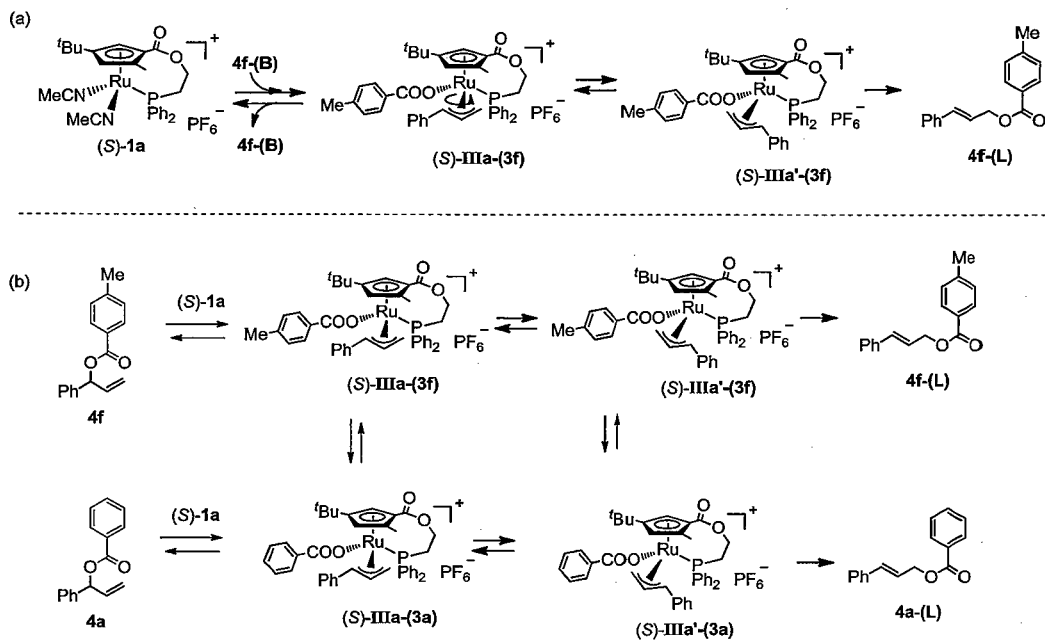
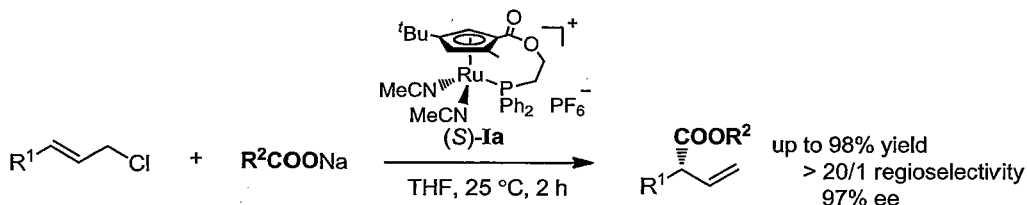


Figure 2-2. Plausible Mechanism of Isomerization of 4-(B)

2-6 Conclusions

We have demonstrated the efficient synthesis of optically active allylic esters by means of asymmetric allylic substitution with carboxylates catalyzed by planar-chiral Cp'Ru complex. In the reaction, controlling the ratio of substrate to catalyst is crucial to achieving high regioselectivity and enantioselectivity of the allylic carboxylation reaction. Synthetic methods using other transition-metal catalysts like palladium complexes may be difficult to realize the selective allylic carboxylation because the resulting allylic esters react again with metal catalysts via oxidative addition. To our best knowledge, this is the first example of a regio- and enantioselective allylic carboxylation using metal carboxylate nucleophile.



2-7 Experimental Procedure

General. All reactions were carried out under Ar atmosphere using Schlenk technique, whereas the workup was performed in air. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on Varian Mercury 300, JEOL GSX400 and JEOL ECA500 spectrometers. Enantiomeric excess was obtained by HPLC analysis using Shimadzu LC-10 and SPD-10AV equipped with DAICEL Chiralcel OJ-H, OD-H and OB-H columns. Optical rotation was measured on JASCO DIP-1000. Absolute configuration of the products was determined by the CD spectra of products¹² or the HPLC elution time of the corresponding allylic alcohols prepared by hydrolysis under basic conditions.

Materials. All solvents used for reactions were passed through purification columns just before use. Cp*Ru complexes **I** were prepared as reported previously.¹³ *p*-Trifluoromethyl- cinnamyl chloride **2b** was prepared according to the known method.¹⁴ The other cinnamyl chloride derivatives **2c**, **2d** were prepared by the similar method to that for analogous bromides,¹⁵ and were purified by distillation using glass tube oven. Carboxylic acids and **2f** were available from commercial source and used without further purification.

Standard method of the catalytic reaction. To a solution of allylic chloride (1.0 mmol) and Cp*Ru catalyst (15 μmol , 3 mol%) in THF (2.0 mL) were added sodium carbonate (1.5 mmol) and carboxylic acid (0.5 mmol), and the reaction mixture was stirred for 2 h at 25 °C. After dilution with *n*-hexane, the insoluble parts were filtered off. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography with *n*-hexane/diethyl ether = 20/1 to give colorless oil. Metal and ammonium benzoates commercially available were used for optimization of the reaction conditions, and the workup was performed in the same manner. The reaction using sodium benzoate gave the same result as the reaction generated from sodium carbonate and benzoic acid in situ as described above.

Characterization of Allylic Esters

(*R*)-1-Phenyl-2-propenyl benzoate (4a).¹² ^1H NMR (CDCl_3 , 500 MHz): δ 8.10–8.09 (m, 2H, Ar), 7.56 (tt, 1H, J = 7.5, 1.3 Hz, Ar), 7.46–7.29 (m, 4H, Ar), 7.39–7.36 (m, 2H, Ar), 7.31 (tt, 1H, J = 7.3, 1.3 Hz, Ar), 6.52 (d, 1H, J = 5.9 Hz, CH), 6.13 (ddd, 2H, J = 17.2, 10.5, 5.9 Hz, CH=), 5.40 (dd, 1H, J = 17.2, 1.3 Hz, CH=), 5.30 (dd, 1H, J = 10.5, 1.3 Hz, CH=). ^{13}C NMR (CDCl_3 , 126 MHz): δ 165.4, 138.9, 136.3, 132.3, 130.3, 129.7, 128.6, 128.3, 128.1, 127.1, 117.0, 76.6. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*PrOH = 100/1 (v/v), 1.0 mL/min, 254 nm; major enantiomer *R*: t = 17.3 min, minor enantiomer *S*: t = 25.1 min, 95% ee.

(*R*)-1-(4-Trifluoromethylphenyl)-2-propenyl benzoate (4b). ^1H NMR (CDCl_3 , 400 MHz): δ 8.10 (d, 2H, J = 7.8 Hz, Ar), 7.66–7.54 (m, 4H, Ar), 7.46 (t, 2H, J = 7.8 Hz, Ar), 6.52 (d, 1H, J = 6.1 Hz, CH), 6.13 (ddd, 2H, J = 17.0, 10.7, 6.1 Hz, CH=), 5.40 (d, 1H, J = 17.0 Hz, CH=), 5.30 (d, 1H, J = 10.7 Hz, CH=). ^{13}C NMR (CDCl_3 , 100 MHz): δ 165.2, 142.9, 135.5, 133.2, 130.5 (q, J = 32 Hz), 129.9, 129.7, 128.4,

127.3, 125.2 (q, $J = 4$ Hz), 118.5 (q, $J = 273$ Hz), 117.9, 75.6. $[\alpha]_D^{27} = -21.1$ ($c = 0.66$, CHCl_3) for 97% ee. Anal Calcd for $\text{C}_{17}\text{H}_{13}\text{F}_3\text{O}_2$: C, 66.67; H, 4.28. Found; C, 66.48; H, 4.18. HPLC analysis: Chiralcel OJ-H column, n -hexane/ $\text{PrOH} = 100/1$ (v/v), 0.5 mL/min, 254 nm; major enantiomer R : $t = 16.5$ min, minor enantiomer S : $t = 19.3$ min, 97% ee.

(S)-2-But-3-enyl benzoate (4c).¹⁶ ^1H NMR (CDCl_3 , 500 MHz): δ 8.07–8.05 (m, 2H, Ar), 7.55 (tt, 1H, $J = 7.3, 1.3$ Hz, Ar), 7.43 (t, 2H, $J = 7.7$ Hz, Ar), 5.97 (ddd, 1H, $J = 17.3, 10.6, 5.8$ Hz, CH=), 5.60 (m, 1H, CH), 5.34 (dd, 1H, $J = 17.3, 1.3$ Hz, CH=), 5.19 (dd, 1H, $J = 10.6, 1.3$ Hz, CH=), 1.45 (d, 3H, $J = 6.6$ Hz, CH_3). ^{13}C NMR (CDCl_3 , 126 MHz): δ 165.8, 137.7, 132.8, 130.6, 129.6, 128.3, 115.7, 71.5, 20.0. HPLC analysis: Chiralcel OB-H column, n -hexane/ $\text{PrOH} = 1000/1$ (v/v), 0.8 mL/min, 254 nm; major enantiomer S : $t = 11.5$ min, minor enantiomer R : $t = 13.0$ min, 82% ee.

(S)-4-Hex-5-enyl benzoate (4d).¹⁷ ^1H NMR (CDCl_3 , 400 MHz): δ 8.05 (d, 2H, $J = 7.6$ Hz, Ar), 7.54 (t, 1H, $J = 7.6$ Hz, Ar), 7.43 (t, 2H, $J = 7.6$ Hz, Ar), 5.89 (ddd, 1H, $J = 17.3, 10.6, 6.4$ Hz, CH=), 5.50 (q, 1H, $J = 6.4$ Hz, CH), 5.31 (d, 1H, $J = 17.3$ Hz, CH=), 5.19 (d, 1H, $J = 10.6$ Hz, CH=), 1.83–1.65 (m, 2H, CH_2), 1.49–1.38 (m, 2H, CH_2), 0.96 (t, 3H, $J = 7.4$ Hz, CH_3). ^{13}C NMR (CDCl_3 , 126 MHz): δ 165.8, 136.6, 132.8, 130.6, 129.5, 128.3, 116.5, 75.1, 36.4, 18.4, 13.9. HPLC analysis: Chiralcel OB-H column, n -hexane/ $\text{PrOH} = 1000/1$ (v/v), 0.8 mL/min, 254 nm; major enantiomer S : $t = 8.7$ min, minor enantiomer R : $t = 11.8$ min, 81% ee.

(R)-1-Phenyl-2-propenyl biphenyl-2-carboxylate (4e). ^1H NMR (CDCl_3 , 500 MHz): δ 7.85 (dd, 1H, $J = 7.7, 1.0$ Hz, Ar), 7.52 (dt, 1H, $J = 7.5, 1.4$ Hz, Ar), 7.40 (dt, 1H, $J = 7.6, 1.3$ Hz, Ar), 7.36 (dd, 1H, $J = 7.7, 0.9$ Hz, Ar), 7.32–7.25 (m, 8H, Ar), 7.12–7.09 (m, 2H, Ar), 6.27 (d, 1H, $J = 6.0$ Hz, CH), 5.78–5.74 (m, 1H, CH=), 5.14 (dt, 1H, $J = 7.0, 1.3$ Hz, CH=), 5.12 (d, 1H, $J = 1.3$ Hz, CH=). ^{13}C NMR (CDCl_3 , 126 MHz): δ 167.5, 142.4, 141.2, 138.5, 135.9, 131.1, 131.0, 130.8, 129.9, 128.5, 128.3, 128.0, 127.9, 127.1, 127.1, 127.0, 117.1, 77.1. $[\alpha]_D^{26} = +9.34$ ($c = 0.46$, CHCl_3) for 91% ee. Anal Calcd for $\text{C}_{22}\text{H}_{18}\text{O}_2$: C, 84.05; H, 5.77. Found; C, 83.78; H, 5.67. HPLC analysis: Chiralcel OJ-H column, n -hexane/ $\text{PrOH} = 100/1$ (v/v), 1.0 mL/min, 254 nm; major enantiomer R : $t = 17.4$ min, minor enantiomer S : $t = 23.6$ min, 91% ee.

(R)-1-Phenyl-2-propenyl 4-chlorobenzoate (4g).¹⁸ ^1H NMR (CDCl_3 , 400 MHz): δ 8.02–8.01 (m, 2H, Ar), 7.44–7.30 (m, 7H, Ar), 6.49 (d, 1H, $J = 5.9$ Hz, CH), 6.11 (ddd, 2H, $J = 17.1, 10.4, 5.9$ Hz, CH=), 5.37 (dd, 1H, $J = 17.1, 1.2$ Hz, CH=), 5.30 (dd, 1H, $J = 10.4, 1.2$ Hz, CH=). ^{13}C NMR (CDCl_3 , 100 MHz): δ 164.5, 139.5, 138.7, 136.0, 131.0, 128.7, 128.6, 128.2, 127.1, 117.2, 77.4, 77.2. $[\alpha]_D^{27} = +64.7$ ($c = 0.51$, CHCl_3) for 88% ee. HPLC analysis: Chiralcel OD-H column, n -hexane/ $\text{PrOH} = 1000/1$ (v/v), 0.4 mL/min, 254 nm; major enantiomer R : $t = 38.3$ min, minor enantiomer S : $t = 42.1$ min, 88% ee.

(R)-1-Phenyl-2-propenyl 4-methylbenzoate (4f). ^1H NMR (CDCl_3 , 400 MHz): δ 7.99–7.97 (m, 2H, Ar), 7.45–7.42 (m, 2H, Ar), 7.38–7.34 (m, 2H, Ar), 7.31–7.27 (m, 1H, Ar), 7.24–7.21 (m, 2H, Ar), 6.50 (d, 1H, $J = 5.7$ Hz, CH), 6.12 (ddd, 2H, $J = 17.2, 10.5, 5.7$ Hz, CH=), 5.38 (dd, 1H, $J = 17.2, 1.3$ Hz, CH=),

5.29 (dd, 1H, $J = 10.5, 1.3$ Hz, CH=), 2.41 (s, 3H, CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 165.5, 143.7, 139.0, 136.4, 129.7, 129.1, 128.5, 128.1, 127.5, 127.1, 116.9, 76.4, 21.6. $[\alpha]_D^{27} = -11.0$ ($c = 0.45$, CHCl₃) for 93% ee. Anal Calcd for C₁₇H₁₆O₂: C, 80.93; H, 6.39. Found; C, 81.11; H, 6.45. HPLC analysis: Chiralcel OD-H column, *n*-hexane/ⁱPrOH = 1000/1 (v/v), 0.5 mL/min, 254 nm; major enantiomer *R*: $t = 45.4$ min, minor enantiomer *S*: $t = 48.8$ min, 93% ee.

(*R*)-1-Phenyl-2-propenyl acetate (4h).¹⁹ ¹H NMR (CDCl₃, 500 MHz): δ 7.36–7.28 (m, 5H, Ar), 6.27 (d, 1H, $J = 6.0$ Hz, CH), 6.01 (ddd, 2H, $J = 17.0, 10.5, 6.0$ Hz, CH=), 5.30 (dd, 1H, $J = 17.0, 1.3$ Hz, CH=), 5.24 (dd, 1H, $J = 10.5, 1.3$ Hz, CH=), 2.11 (s, 3H, CH₃). ¹³C NMR (CDCl₃, 126 MHz): δ 170.0, 139.0, 136.4, 128.6, 128.2, 127.2, 117.0, 76.9, 21.3. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/ⁱPrOH = 93/7 (v/v), 0.5 mL/min, 254 nm; major enantiomer *R*: $t = 25.2$ min, minor enantiomer *S*: $t = 28.3$ min, 92% ee.

(*R*)-1-phenyl-2-propenyl butyrate (4i).¹H NMR (CDCl₃, 500 MHz): δ 7.37–7.25 (m, 5H, Ar), 6.28 (dt, 1H, $J = 6.0, 1.3$ Hz, CH), 6.00 (ddd, 2H, $J = 17.1, 10.5, 6.0$ Hz, CH=), 5.29 (dt, 1H, $J = 17.1, 1.3$ Hz, CH=), 5.23 (dt, 1H, $J = 10.5, 1.3$ Hz, CH=), 2.35 (td, $J = 7.5, 1.6$, 2H, CH₂), 1.67 (dt, $J = 7.5, 7.5$, 2H, CH₂), 0.93 (t, $J = 7.5$, 3H, CH₃). ¹³C NMR (CDCl₃, 126 MHz): δ 172.4, 139.4, 136.4, 128.5, 128.0, 127.0, 116.7, 75.8, 36.4, 18.4, 13.6. $[\alpha]_D^{27} = +41.0$ ($c = 0.72$, CHCl₃), for 84% ee. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/ⁱPrOH = 100/1 (v/v), 0.5/min, 254 nm; major enantiomer: $t = 17.4$, minor enantiomer: $t = 18.8$ min.

(*R*)-1-Phenyl-2-propenyl pivaloate (4j).²⁰ ¹H NMR (CDCl₃, 500 MHz): δ 7.35–7.32 (m, 4H, Ar), 7.31–7.26 (m, 1H, Ar), 6.22 (dt, 1H, $J = 5.7, 1.4$ Hz, CH), 5.99 (ddd, 2H, $J = 17.1, 10.5, 5.7$ Hz, CH=), 5.29 (dd, 1H, $J = 17.1, 1.4$ Hz, CH=), 5.22 (dd, 1H, $J = 10.5, 1.4$ Hz, CH=), 1.23 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 126 MHz): δ 177.2, 139.2, 136.6, 128.5, 128.0, 126.8, 116.4, 75.7, 38.8, 27.2. $[\alpha]_D^{27} = +51.0$ ($c = 0.31$, CHCl₃) for 91% ee. HPLC analysis: Chiralcel OJ-H column, hexane/ⁱPrOH = 100/1 (v/v), 0.5 mL/min, 254 nm; major enantiomer *R*: $t = 10.5$ min, minor enantiomer *S*: $t = 11.5$ min, 91% ee.

(*R*)-1-Phenyl-2-propenyl cyclohexanecarboxylate (4k).¹H NMR (CDCl₃, 400 MHz): δ 7.37–7.25 (m, 5H, Ar), 6.25 (d, 1H, $J = 6.1$ Hz, CH), 5.99 (ddd, 2H, $J = 17.1, 10.5, 6.1$ Hz, CH=), 5.28 (dd, 1H, $J = 17.1, 1.2$ Hz, CH=), 5.22 (dd, 1H, $J = 10.5, 1.2$ Hz, CH=), 2.40–2.32 (m, 1H, CH), 1.96–1.93 (m, 2H, Cy), 1.77–1.72 (m, 2H, Cy), 1.65–1.61 (m, 1H, Cy), 1.49–1.41 (m, 1H, Cy), 1.33–1.20 (m, 4H, Cy). ¹³C NMR (CDCl₃, 100 MHz): δ 174.8, 139.2, 136.5, 128.5, 128.0, 127.0, 116.6, 75.5, 43.3, 28.9, 28.9, 25.7, 25.4. $[\alpha]_D^{23} = -36.6$ ($c = 0.40$, CHCl₃) for 93% ee. Anal Calcd for C₁₆H₂₀O₂: C, 78.65; H, 8.25. Found; C, 78.49; H, 8.18. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/ⁱPrOH = 100/1 (v/v), 0.5 mL/min, 254 nm; major enantiomer *R*: $t = 12.5$ min, minor enantiomer *S*: $t = 15.4$ min, 93% ee.

1-Chloro-2-but-3-enyl benzoate (4l).¹H NMR (CDCl₃, 400 MHz): δ 8.10–8.07 (m, 2H, Ar), 7.57 (tt, 1H, $J = 7.4, 1.5$ Hz, Ar), 7.47–7.43 (m, 2H, Ar), 5.96 (ddd, 2H, $J = 17.1, 10.5, 6.3$ Hz, CH=), 5.70 (ddt,

1H, $J = 6.3, 1.2, 1.2$ Hz, CH), 5.47 (dd, 1H, $J = 17.1, 1.2$ Hz, CH=), 5.36 (dd, 1H, $J = 10.5, 1.2$ Hz, 1H, CH=), 3.79–3.72 (m, 2H, CH₂). ¹³C NMR (CDCl₃, 100 MHz): δ 165.3, 133.2, 132.8, 129.7, 129.7, 128.3, 119.3, 74.0, 45.5. $[\alpha]_D^{27} = +41.0$ ($c = 0.43$, CHCl₃) for 88% ee. Anal Calcd for C₁₁H₁₁ClO₂: C, 62.72; H, 5.26. Found; C, 62.69; H, 5.12. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 1000/1 (v/v), 0.5 mL/min, 254 nm; major enantiomer: $t = 31.0$ min, minor enantiomer: $t = 28.8$ min, 88% ee.

1-Chloro-2-but-3-enyl biphenyl-2-carboxylate (4m). ¹H NMR (CDCl₃, 300 MHz): δ 7.89–7.86 (m, 1H, Ar), 7.53 (dt, 1H, $J = 7.5, 1.5$ Hz, Ar), 7.45–7.30 (m, 7H, Ar), 5.62 (ddd, 1H, $J = 17.2, 10.6, 6.5$ Hz, CH=), 5.47–5.40 (m, 1H, CH=), 5.25 (dd, 1H, $J = 17.3, 1.2$ Hz, CH=), 5.22 (dd, 1H, $J = 10.6, 1.2$ Hz, CH=), 3.36 (d, 2H, $J = 5.9$ Hz, CH₂). ¹³C NMR (CDCl₃, 75 MHz): δ 167.2, 142.6, 141.3, 132.5, 131.3, 130.7, 130.5, 129.9, 128.5, 128.0, 127.2, 127.1, 119.4, 74.2, 44.9. $[\alpha]_D^{27} = +22.6$ ($c = 0.29$, CHCl₃) for 88% ee. Anal Calcd for C₁₇H₁₅ClO₂: C, 71.20; H, 5.27. Found; C, 71.08; H, 5.21. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH = 100/1 (v/v), 0.5 mL/min, 254 nm; major enantiomer: $t = 33.2$ min, minor enantiomer: $t = 28.7$ min, 88% ee.

1-Chloro-2-but-3-enyl 4-chlorobenzoate (4n). ¹H NMR (CDCl₃, 500 MHz): δ 8.01 (dd, 2H, $J = 8.7, 2.1$ Hz, Ar), 7.42 (dd, 2H, $J = 8.7, 2.1$ Hz, Ar), 5.95 (ddd, 1H, $J = 17.1, 10.7, 6.2$ Hz, CH=), 5.70–5.67 (m, 1H, CH), 5.47 (dd, $J = 17.1, 1.1$ Hz, 1H, CH=), 5.38 (dd, 1H, $J = 10.7, 1.1$ Hz, CH=), 3.78–3.71 (m, 2H, CH₂). ¹³C NMR (CDCl₃, 126 MHz): δ 164.6, 139.8, 132.7, 131.1, 128.8, 128.3, 119.6, 74.3, 45.3. $[\alpha]_D^{27} = +59.4$ ($c = 0.29$, CHCl₃) for 78% ee. Anal Calcd for C₁₁H₁₀Cl₂O₂: C, 53.90; H, 4.11. Found; C, 53.76; H, 4.07. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH = 100/1 (v/v), 0.5 mL/min, 254 nm; major enantiomer: $t = 17.2$ min, minor enantiomer: $t = 16.4$ min, 78% ee.

2-8 References

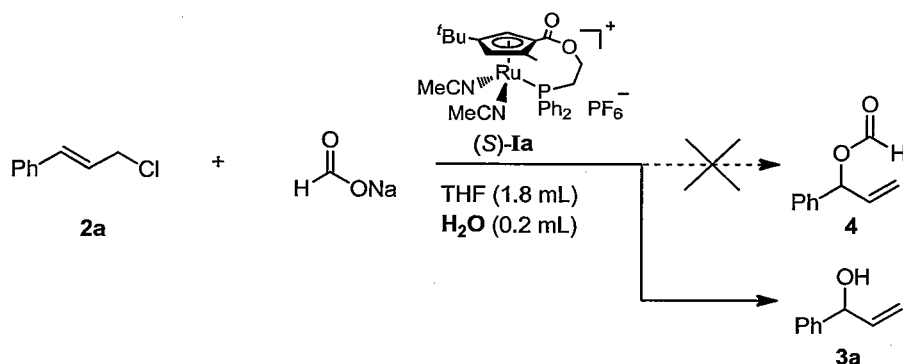
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Chapter 3: Regio- and Enantio-selective Allylic Substitution with Water Catalyzed by Planar-Chiral Cyclopentadienyl-Ruthenium Complex: Direct Synthesis of Chiral Allylic Alcohols

3-1 Introduction

We have shown, in Chapter 2,^{1c} the effective catalysis of planar chiral Cp*Ru complexes (**I**) for the asymmetric allylic carboxylation of allylic chlorides. In the screening of several carboxylic substrates as a nucleophile in the asymmetric reaction, we have attempted to use sodium formate. However sodium formate was insoluble in THF, so that a small amount of water was added to the reaction system to dissolve sodium formate (Scheme 3-1). The reaction proceeded with quantitative conversion of cinnamyl chloride **2a**, but the resulting product was not branched allylic ester **4**, and instead unexpected branched allylic alcohol (**3a**) was formed. From this experimental result, we have learned that water can act as a nucleophile in the allylic substitution reaction to give useful allylic alcohol **3a**. In this chapter, we describe the direct and stereoselective synthesis of optically active allylic alcohols by the catalysis of planar-chiral Cp*Ru complex using water as a nucleophile.



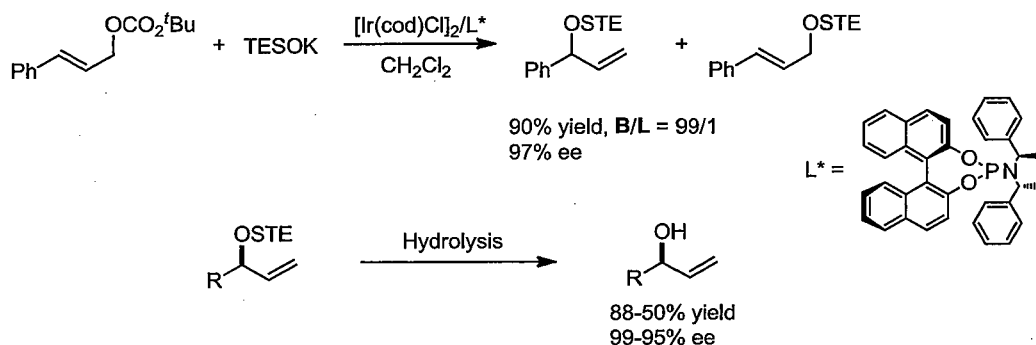
Scheme 3-1. Reaction of Cinnamyl Chloride (**2a**) with Sodium Formate

3-2 Synthesis of Optically Active Allylic Alcohol

Optically active branched allylic alcohols, which serve as useful chiral building blocks, are usually synthesized via many processes,² such as the hydrogenation of α,β -unsaturated ketones,³ the nucleophilic addition of vinylmetal reagents to aldehyde and ketones,⁴ and the kinetic resolution of racemic allylic alcohols.⁵ Recently, new ways to access these compounds have been developed, and one of them is the way involving allylic substitution by a two-step transforming from allylic alcohol derivatives.⁶ In 2006, Carreira reported a reaction with a

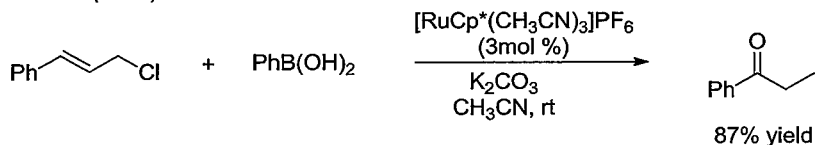
silanolate as nucleophile in the presence of iridium-chiral phosphoramidite catalyst yielding optically active branched allylic silyl ethers. The products readily are transformed to enantioenriched allylic alcohols via a hydrolysis reaction (Scheme 3-2).⁷ In 2008, Bruneau reported the reaction of allylic chloride with boronic acid as an oxygen source in the presence of a ruthenium catalyst to give the allylic alcohols, but high regio- and enantioselectivities were not achieved (Scheme 3-3).⁸

Carreira (2006)



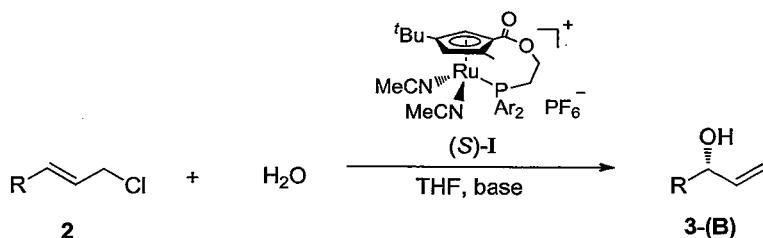
Scheme 3-2. Reaction of Cinnamyl Carbonate with Silanolate

Bruneau (2008)



Scheme 3-3. Reaction of Cinnamyl Chloride with Boronic Acid

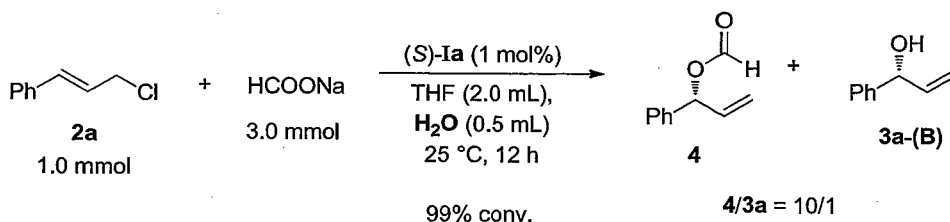
We have already shown that planar-chiral cyclopentadienyl ruthenium (Cp^*Ru) complex **I** is a proficient catalyst for allylic substitutions. This system was successfully extended to the regio- and enantioselective allylic substitution of monosubstituted allylic halides with oxygen nucleophiles.¹ During the experiment on allylic substitution with a carboxylic acid nucleophile, we have found unexpectedly that water also acts as a nucleophile to give branched alcohols from allylic halides by the catalysis of Cp^*Ru complexes. Herein, we describe the direct synthesis of chiral allylic alcohols from allylic halide with water, which provides a useful and practical method for the synthesis of optically active branched allylic alcohols (Scheme 3-4).



Scheme 3-4. Reaction of Allylic Chloride **2** with Water Catalyzed by Cp^{*}Ru Complex **I**

3-3 Optimization of Reaction Conditions

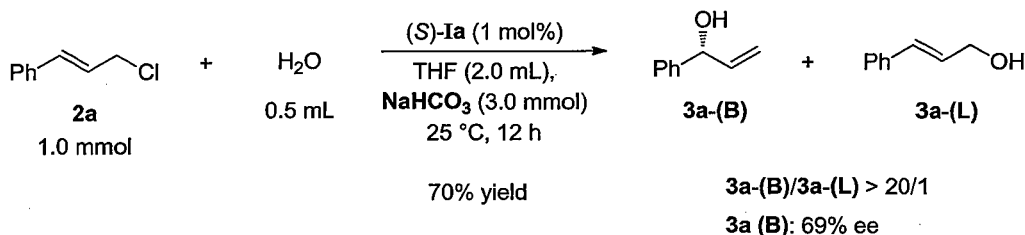
In an attempt of allylic carboxylation with sodium formate, cinnamyl chloride (**2a**, 1.0 mmol) was reacted with sodium formate (3.0 mmol) and water (0.5 mL), of which the latter was added to dissolve the formate, in the presence of 1 mol% of (*S*)-**Ia** (Ar = Ph) in THF (2.0 mL) for a reaction time of 12 h as shown in Schemes 3-1 and 3-4. The reaction proceeded with almost quantitative conversion of **2a** to give allylic ester **4** along with branched allylic alcohol **3a-(B)** (**3a-(B)**/**4** = 10/1) (Scheme 3-5).



Scheme 3-5. Reaction of Cinnamyl Chloride **2a** with Water in the Presence of Sodium Formate as a Base Catalyzed by Cp^{*}Ru Complex **I**

In this reaction, sodium formate acts as a carboxylic nucleophile as well as a base which behaves as an acceptor for the chloride released from **2a**. In attempt to realize the selective synthesis of optically active allylic alcohols, we chose a combination of an inorganic base with water. When Na₂CO₃ was used as a base, the orange reaction mixture turned black, and after the reaction for 7 h, cinnamyl chloride **2a** was recovered intact. In this reaction system, it is likely that the combination of Na₂CO₃ with water offered relatively stronger basic reaction conditions than that of sodium formate and caused decomposition of catalyst **I** having an ester linkage between the Cp^{*} ligand and the Phosphine. When NaHCO₃ was used as a relatively weak base, the reaction mixture kept orange color after the reaction for 12 h and gave allylic alcohol in 70% yield with high regioselectivity (>20/1) and moderate

enantioselectivity (69% ee (*R*)) (Scheme 3-6). To improve the selectivity of the reaction, we conducted optimization of reaction conditions for the present new type of enantioselective allylic hydroxylation.



Scheme 3-6. Reaction of Cinnamyl Chloride **2a** with Water

Effect of Base

As shown above, the basicity of the reaction system is crucial to achieve high efficiency of the reaction. To attain a practical route to the efficient synthesis of optically active allylic alcohols, the effect of base was carefully examined for the reaction between **2a** and water with (*S*)-**I** catalyst in THF at 25 °C for a reaction time of 4 h. Among bases tested, metal carbonates were found to give good results, and sodium bicarbonate NaHCO_3 is of choice for the allylic hydroxylation. Although use of metal carboxylates like sodium formate also afforded the branched allylic alcohols in 64% yield with 80% ee, a small amount of a branched allylic ester, which is allylic carboxylation product **4**, was also obtained as a by-product.

Table 3-1. Effect of Base

entry	base (eq.)	yield (%) of 3a-(B) ^b	3a-(B)/3a-(L) ^c	ee (%) of 3a-(B) ^d
1	NaHCO_3	>99	>20/1	81 (<i>R</i>)
2	KHCO_3	87	>20/1	77 (<i>R</i>)
3	Na_2CO_3	87	>20/1	77 (<i>R</i>)
4 ^e	Na_2CO_3	0	-	- (<i>R</i>)
5	HCOONa	64	>20/1	80 (<i>R</i>)
6 ^e	HH_2COONa	9 (90) ^f	>20/1	- (<i>R</i>)

^a Under optimized condition determined below, (*S*)-**Ia** (0.01 mmol), **2a** (1.0 mmol), H_2O (0.5 mL), base (1.2 eq.) in THF (4.0 mL) at 25 °C, stirred for 4 h. ^b Isolated yield. ^c Determined by ^1H NMR analysis. ^d The enantiomeric excess of the branched allylic alcohol. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses. ^e The conditions was not optimized, (*S*)-**Ia** (0.01 mmol), **2a** (1.0 mmol), H_2O (0.5 mL), base (3.0 eq.) in THF (2.0 mL) at 25 °C, stirred for 12 h. ^f Yield of allylic ester **4** is indicated in parentheses.

Effect of Equivalence of Base

In aqueous reaction systems, strong basic conditions often cause the decomposition of the catalyst. As we have confirmed that catalyst Cp'Ru **1a** is stable in aqueous THF containing a relatively weak base, NaHCO₃, and exhibits an activity in the allylic hydroxylation, we initially investigated the influence of the amount of base added to the system. The results obtained from the reaction at 25 °C for 12 h are shown in Table 3-2. When the reaction was carried out using 1.0 equivalent of NaHCO₃, to cinnamyl chloride, the desired branched allylic alcohol (**3a-(B)**) was formed in 76% yield with high regioselectivity and enantioselectivity (81% ee) (entry 3). Use of 1.2 equivalents of the base resulted in increase of the yield (85% yield) with high enantioselectivity (81% ee) (entry 4). On the other hand, the yield and enantioselectivity were slightly reduced by the use of 2.0 equivalents of the base (entry 5). When the equivalence was decreased to less than 1.0 equivalent, the branched allylic alcohol was formed in a poor yield with a lower enantioselectivity (entries 1 and 2). Thus, the best equivalency of base has been determined to be 1.2 to 1.0 of **2a**.

Table 3-2. Effect of Equivalence of Base ^a

$ \begin{array}{c} \text{Ph}-\text{CH}=\text{CH}-\text{CH}_2\text{Cl} + \text{H}_2\text{O} \xrightarrow[\text{THF (2.0 ml), NaHCO}_3, 25\text{ }^\circ\text{C, 12 h}]{\text{(S)-1a (1 mol\%)}} \\ \text{2a} \qquad \qquad \qquad 0.5\text{ ml} \\ 1.0\text{ mmol} \end{array} $				
$ \begin{array}{ccc} \text{Ph}-\text{CH}(\text{OH})-\text{CH}=\text{CH}_2 & + & \text{Ph}-\text{CH}=\text{CH}-\text{CH}_2\text{OH} \\ \text{3a-(B)} & & \text{3a-(L)} \end{array} $				
entry	base (eq) ^b	yield (%) of 3a-(B) ^c	3a-(B)/3a-(L) ^d	ee (%) of 3a-(B) ^e
1	0	32	>20/1	51 (<i>R</i>)
2	0.8	75	>20/1	60 (<i>R</i>)
3	1.0	76	>20/1	83 (<i>R</i>)
4	1.2	85	>20/1	81 (<i>R</i>)
5	2.0	76	>20/1	79 (<i>R</i>)
6	3.0	70	>20/1	69 (<i>R</i>)

^a (S)-**1a** (0.01 mmol), **2a** (1.0 mmol), H₂O (0.5 mL), NaHCO₃ in THF (2.0 mL), stirred at 25 °C for 12 h. ^b Equivalent of base for **2a**. ^c Isolated yield. ^d Determined by ¹H NMR analysis. ^e The enantiomeric excess of the branched allylic alcohol. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

Effect of Concentration

As described above, the basicity of the reaction system is very important to achieve high selectivity of the reaction and high efficiency of the catalyst. Then, to improve more the reaction conditions, the effect of concentration was examined in the reaction between **2a** (1.0

mmol) and water in THF. In order to estimate the effect of concentration of the reaction system on the selectivities of the reaction, the amounts of base NaHCO₃ and catalyst (*S*)-**1a** were kept constant to be 1.2 mmol and 0.01 mmol, respectively, and the reaction was performed at 25 °C for 12 h. The results are summarized in Table 3-3. It should be interesting to note that the reactivity depends on the concentration and the ratio of amounts of water to THF. Decreasing the amount of water from 0.5 mL to 0.25 mL caused drastic reduction in the efficiency and enantioselectivity of the system (entry 2; 58% yield, 48% ee). When the amount of water was increased to 0.75 mL, the yield was slightly increased (89% yield), but enantioselectivity was decreased (77% ee). On the other hand, the reaction smoothly proceeded with good yield and high enantioselectivity of the hydroxylation product when the amount of THF was increased to 4.0 mL (entry 3; 99% yield, 81% ee). Based on these experimental results, we decided to conduct all of the reactions described below to be performed in THF (4.0 mL) and water (0.5 mL).

Table 3-3. Effect of Concentration ^a

entry	H ₂ O (ml)	THF (ml)	yield (%) of 3a-(B) ^b	3a-(B)/3a-(L) ^c	ee (%) ^d
1	0.5	2.0	85	>20/1	81 (<i>R</i>)
2	0.25	2.0	58	>20/1	48 (<i>R</i>)
3	0.75	2.0	89	>20/1	77 (<i>R</i>)
4	0.5	4.0	99	>20/1	81 (<i>R</i>)

^a (*S*)-**1a** (0.01 mmol), **2a** (1.0 mmol), H₂O, NaHCO₃ (1.2 eq.) in THF, stirred at 25 °C for 12 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic alcohol. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

Effect of Reaction Temperature

To investigate the effect of reaction time, the reaction between **2a** (1.0 mmol) and water (0.5 mL) with (*S*)-**1a** catalyst in THF (4.0 mL) was carried out for 12 h. The results are summarized in Table 3-4. The reaction at a lower temperature gave almost the same result as that at 25 °C (entry 1), though a longer reaction time was needed for the complete reaction. On the contrary, increasing the reaction temperature to 30 °C improved the reactivity, and the reaction was completed in only four hours (entry 4). On the other hand, further increasing the reaction temperature resulted in decrease of the yield and enantioselectivity (entry 5). The best reaction temperature has been determined to be 25 °C.

Table 3-4. Effect of Reaction Temperature ^a

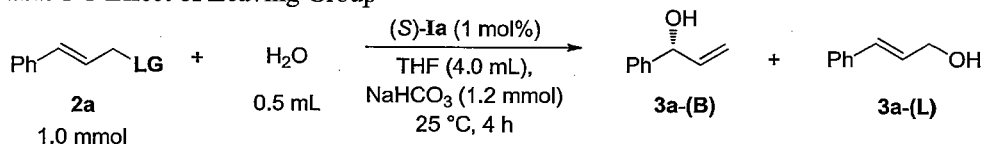
entry	temperature (°C)	reaction time (h)	yield (%) of 3a-(B) ^b	3a-(B)/3a-(L) ^c	ee (%) of 3a-(B) ^d
1	20	12	95	>20/1	80 (<i>R</i>)
2	25	12	99	>20/1	81 (<i>R</i>)
3	25	4	99	>20/1	81 (<i>R</i>)
4	30	4	99	>20/1	81 (<i>R</i>)
5	35	4	88	>20/1	79 (<i>R</i>)

^a (*S*)-**1a** (0.01 mmol), **2a** (1.0 mmol), H₂O (0.5 mL), NaHCO₃ (1.2 eq.) in THF (4.0 mL), stirred for 12 h. ^b Isolated yield.

^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic alcohol. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

Effect of Leaving Group

To investigate the influence of leaving group on the allylic hydroxylation, we examined the reactivity of cinnamyl bromide, and observed the formation of branched allylic alcohol, but the yield and enantioselectivity were considerably reduced (Table 3-5). When cinnamyl carbonate was used as a substrate, the reaction did not proceed at all. Thus, in the allylic hydroxylation reaction the most suitable substrate has been determined to be cinnamyl chloride.

Table 3-5 Effect of Leaving Group

entry	Leaving Group (LG)	yield (%) of 3a-(B) ^b	3a-(B)/3a-(L) ^c	ee (%) of 3a-(B) ^d
1	Cl	>99	>20/1	81 (<i>R</i>)
2	Br	15	>20/1	51 (<i>R</i>)
3	OCOEt	0	-	-

^a (*S*)-**1a** (0.01 mmol), **2** (1.0 mmol), H₂O (0.5 mL), base (1.2 eq.) in THF (4.0 mL) at 25 °C, stirred for 4 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic alcohol. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

Effect of Solvent

Choice of solvent is very important for the catalytic reaction with organometallic complexes. We examined several kinds of solvents in which Cp'Ru complexes are soluble.

The results obtained from reactions between **2a** and water in the presence of (*S*)-**Ia** catalyst and NaHCO₃ at 25 °C for 4 h are summarized in Table 3-6. The use of acetone as a solvent resulted in a poor yield and a low enantioselectivity. When dioxane was used, the branched allylic alcohol was obtained in a moderate yield and enantioselectivity. Thus, THF should be recommended as a solvent for the allylic hydroxylation.

Table 3-6 Effect of Solvent

entry	solvent	yield (%) of 3a-(B) ^b	3a-(B)/3a-(L) ^c	ee (%) of 3a-(B) ^d
1	THF	99	>20/1	81 (<i>R</i>)
2	acetone	50	>20/1	51 (<i>R</i>)
3	dioxane	90	>20/1	81 (<i>R</i>)

^a (*S*)-**Ia** (0.01 mmol), **2** (1.0 mmol), H₂O (0.5 mL), NaHCO₃ (1.2 eq.) in solvent (4.0 mL) at 25 °C, stirred for 4 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic alcohol. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

From the experimental results described above, the optimal reaction conditions for the present allylic substitution with water have been determined as follows:

Catalyst, Cp'Ru complex **Ia**; Additive Base, NaHCO₃; Equivalency of Base to Substrate, 1.2 equivalents; Reaction Concentration, 0.2 M of allylic chloride in a mixture of THF and water with the ratio of THF/Water = 8:1; Reaction Temperature, 25 °C; Leaving Group on Allylic Substrate, Cl; Solvent, THF.

3-4 Screening of Catalyst

(1) Synthesis of New Planar-Chiral Cyclopentadienyl-ruthenium Complexes

In the reaction of allylic chloride using (*S*)-**Ia** under the optimized reaction conditions, we observed the formation of desired branched allylic alcohol **3a-(B)** in >99% yield with 81% ee. However, the enantioselectivity around 80% in the allylic hydroxylation may be unsatisfied in comparison with that (>90% ee) of the allylic carboxylation described in Chapter 2.¹ Our previous studies have shown that the bulkiness of aryl groups on the phosphine ligand in the Cp'Ru complex ((*S*)-**Ib** (Ar = 3,5-Me₂C₆H₅)) plays an important role for the enantioselectivity of allylic substitution reactions.⁹ To attain higher enantioselectivity in the hydroxylation reaction, we have synthesized some new Cp'Ru complexes ((*S*)-**Ic-g**) which have various bulky aryl group on the phosphorus, as described in Section 3-8 (Experimental Section), and examined their catalytic activity in terms of enantioselectivity in

the allylic hydroxylation reaction. Among them, complex **Ic** could not be isolated as a pure form due to its instability.

The Cp*Ru complexes **Ib** and **Id-g** bearing a new type of diarylphosphino group which coordinates to the central ruthenium metal were used in the allylic hydroxylation reaction, and their catalytic activities, especially in terms of the enantioselectivity, were evaluated, and summarized in Table 3-7, which shows that replacement of the aryl group on phosphorus from phenyl (**Ia**) to bulky 3,5-dimethylphenyl (**Ib**) and 4-methoxy-3,5-dimethylphenyl groups (**Id**) led to an increase in enantioselectivity of 88% and 90% ee, respectively (entries 2 and 3). Complex **Ig** having bulkier diisopropylphenyl groups, however, showed enantioselectivity of 81% ee, which is the same as that of complex **Ia**, suggesting that there would be no clear relation between the bulkiness of the phosphine ligand and the enantioselectivity in the reaction. Complexes **Ie** and **If**, which have 3,5-difluorophenyl and 4-fluorophenyl groups, exhibited selectivities of 88% and 87% ee, respectively (entries 4 and 5). Based on these results the enantioselectivity seems to be affected by the electronic properties of the aryl

Table 3-7 Effect of Catalyst Structure

entry	cat.	yield (%) of 3a-(B) ^b	3a-(B) / 3a-(B) ^c	ee (%) of 3a-(B) ^d	Ar =	Ar =
1	(S)- Ia	99	>20/1	81 (R)		
2	(S)- Ib	99	>20/1	88 (R)		
3	(S)- Id	99	>20/1	90 (R)		
4	(S)- Ie	99	>20/1	88 (R)		
5	(S)- If	99	>20/1	87 (R)		
6	(S)- Ig	97	>20/1	81 (R)		

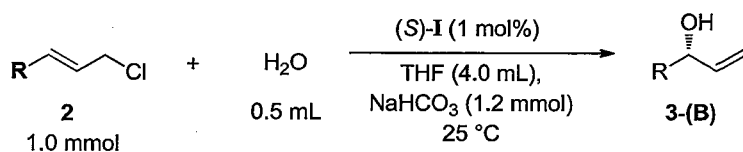
^a (S)-**I** (0.01 mmol), **2** (1.0 mmol), H₂O (0.5 mL), NaHCO₃ (1.2 eq.) in solvent (4.0 mL) at 25 °C, stirred for 4 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic alcohol. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

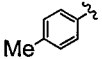
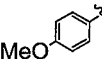
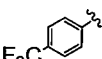
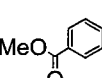
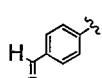
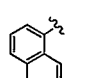
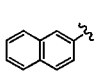
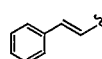
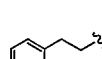
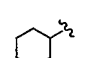
group. Although we could not simply explain the relationship between enantioselectivity and bulkiness as well as basicity of the phosphine ligand from the above experimental results, we have fortunately found complexes **Ib-Ij** to be of choice as a catalyst of the asymmetric allylic hydroxylation.

3-5 Screening of Substrate

Under the optimized conditions determined above, allylic substitution reactions of several other allylic chloride derivatives **2b-m** with water were carried out in the presence of catalyst **I**. The scope of substrate applicable to the present allylic hydroxylation is summarized in Table 3-7. The reaction of a variety of cinnamyl chloride derivatives having substituents on the phenyl group selectively produced corresponding branched allylic alcohols **3-(B)** in good yields with high enantioselectivities, although substrates bearing an electron-withdrawing group such as trifluoromethyl and methoxycarbonyl groups on the phenyl ring required a longer reaction time for complete conversion of starting substrates (entries 4-6). Although Bruneau and co-workers reported that **3c-(B)** easily isomerizes into 1-(4-methoxyphenyl)propanone with a ruthenium catalyst,^{8,10} no isomerization was observed in the present system (entry 3). Moreover, because the reaction conditions are very mild, methoxycarbonyl and formyl groups are well tolerated in the conditions (entries 5 and 6). The reactions of naphthyl and dienyl allylic chloride derivatives **2g-2i** with water also produced the corresponding allylic alcohols in high yield with high selectivity (entries 6-9). The hydroxylation reaction of alkyl-substituted allylic chlorides **2j-2m** also proceeded to give **3j-3m** (entries 10-13), respectively. Although the yields of **3k** and **3l** were not very high, the substrates were completely consumed and no by-products were formed. Technical difficulties in the isolation of **3k** and **3l** due to their relatively low boiling points resulted in lower yields.

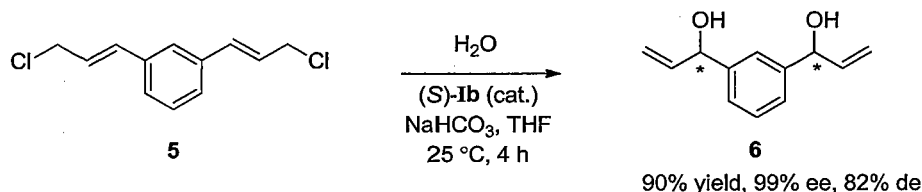
Table 3-8 Screening of Substrate ^a



entry	R	cat.	t (h)	yield (%) of 3a-(B) ^b	ee (%) of 3a-(B) ^d
1	Ph (2a)	(S)- Id	4	99	90 (<i>R</i>)
2	 (2b)	(S)- Ie	4	99	90 (<i>R</i>)
3	 (2c)	(S)- Ib	4	99	76 (<i>R</i>)
4	 (2d)	(S)- Id	12	99	94 (<i>R</i>)
5	 (2e)	(S)- Id	12	99	93 (<i>R</i>)
6	 (2f)	(S)- Id	12	93	93 (<i>R</i>)
7	 (2g)	(S)- Id	4	99	90 (<i>R</i>)
8	 (2h)	(S)- Id	7	95	89 (<i>R</i>)
9	 (2i)	(S)- Ib	4	96	96 (<i>R</i>)
10	 (2j)	(S)- Ie	12	99	85 (<i>S</i>)
11	C ₅ H ₁₁ - (2k)	(S)- Ie	18	78	83 (<i>S</i>)
12	 (2l)	(S)- Ib	18	87	97 (<i>R</i>)
13	Ph ₂ ^t BuSiO- (2m)	(S)- Id	12	99	90 (<i>R</i>)

^a (S)-**I** (0.01 mmol), **2** (1.0 mmol), H₂O (0.5 mL), NaHCO₃ (1.2 eq.) in solvent (4.0 mL) at 30 °C. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic alcohol. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses.

Meanwhile, the reaction of bi-functional *m*-bis(chloropropenyl)benzene (**5**) gave allylic diol (**6**) in 90% yield with 99% ee and 82% de, which have two functional groups of chiral allylic alcohol in the molecular.

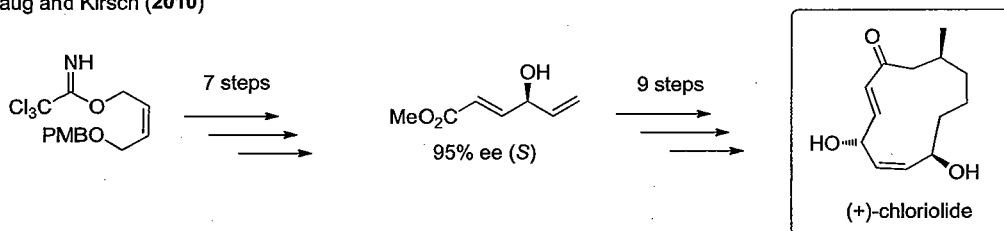


Scheme 3-10. Reaction of Bis(chloropropenyl)benzene (**5**) with Water.

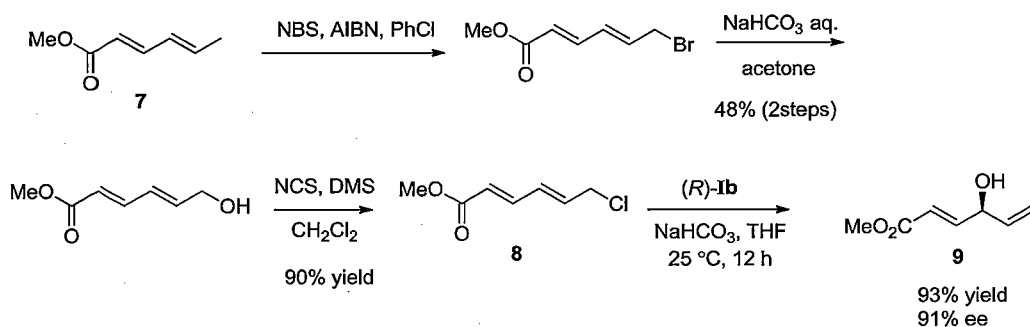
Application to the Synthesis of Intermediate of Natural Product

Branched allylic alcohols **3-(B)** are well recognized to be useful chiral building blocks for the synthesis of a variety of chiral natural products. We have also tried to demonstrate an application of our allylic hydroxylation to the synthesis of a natural product. As our target molecule, we chose (+)-chloriolide of 12-membered macrolide, and tried to prepare the key intermediate, chiral allylic alcohol (**9**) (Scheme 3-11). Kirsh and Hang already prepared chiral allylic alcohol (*S*)-**9** from trichloroacetimidate via seven steps which included Overman allylic esterification (Scheme 3-11).¹¹ Although our attempt at the direct chlorination of

Haug and Kirsch (2010)



Our Work

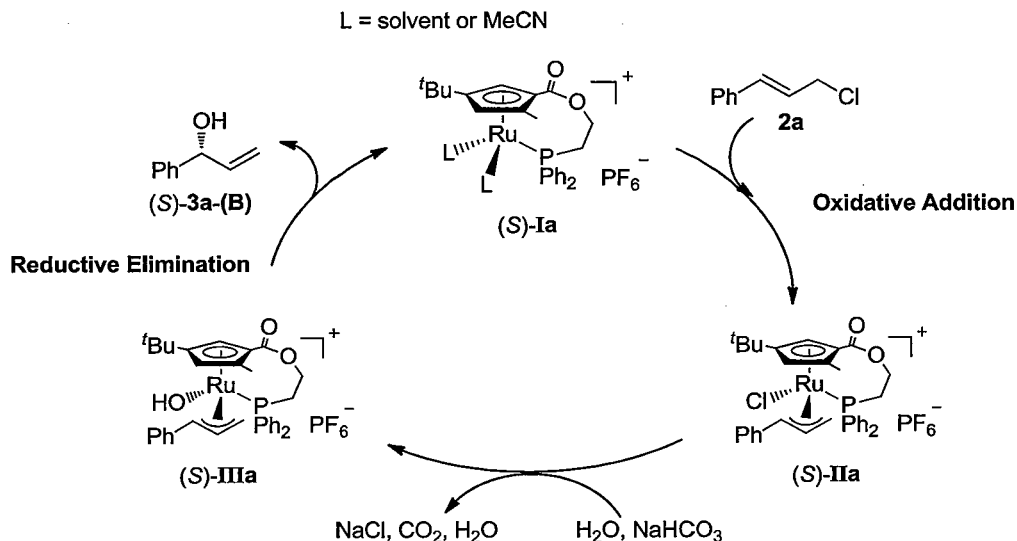


Scheme 3-11. Enantioselective Synthesis of (+)-chloriolide

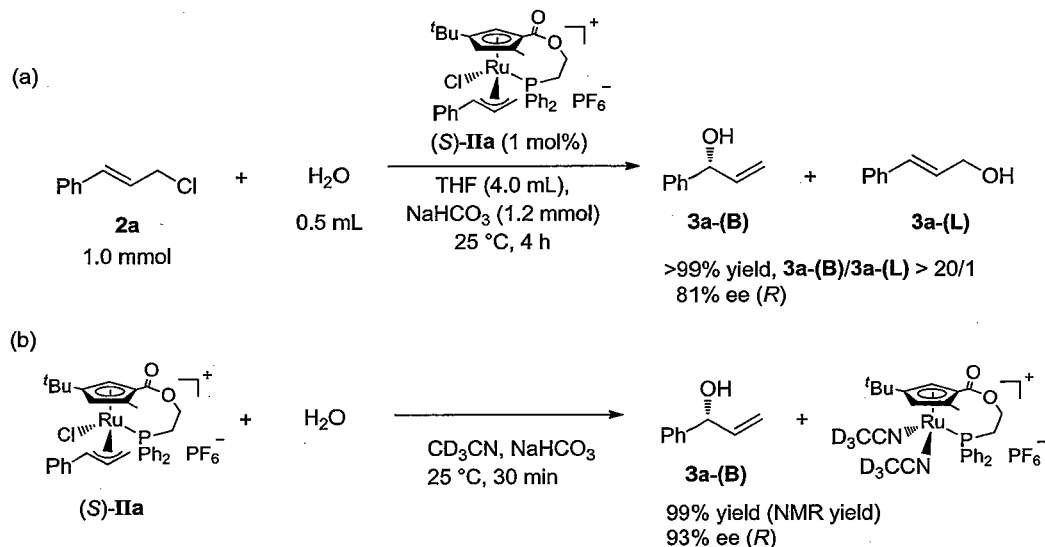
commercially available methylsorbate (**7**) failed, the allylic chloride (**8**) as our starting material was prepared in three steps through the corresponding allylic bromide and alcohol, in 43% overall yield. The allylic hydroxylation of **8** using (*R*)-**Ib** gave target allylic alcohol (*S*)-**9** in 93% yield with 91% ee as expected. Intermediate (*S*)-**9** can be converted into (+)-chloride by known methods.

3-6 Study of the Reaction Mechanism

As described in Chapter 2, Cp*Ru complex-catalyzed asymmetric allylic substitution reactions have been proved to proceed via π -allyl intermediate.¹ In the present allylic hydroxylation reaction, π -allyl complex (*S*)-**II** may be postulated similarly as an active intermediate, which is generated by the oxidative addition of allylic chloride to the central Ru atom with a high diastereoselectivity. To obtain information about the reaction mechanism of the allylic hydroxylation, we have examined the catalytic activity of π -allyl complex **IIa**. By use of thus prepared π -allyl complex (*S*)-**IIa** as a catalyst (1 mol%), a typical hydroxylation of cinnamyl chloride **2a** with water in the presence of NaHCO₃ (1.2 mmol) in THF at 25 °C was performed. As expected, the reaction gave branched allylic alcohol **3a-(B)** in 99% yield with 81% ee (*R*) (Scheme 3-12 (a)). In addition, to trace spectroscopically the behavior of π -allyl intermediate **IIa**, an NMR tube reaction between (*S*)-**IIa** and water in the presence of NaHCO₃ in CD₃CN was carried out (Scheme 3-12 (b)). The quantitative formation of **3a-(B)** with 93% ee (*R*) was observed in the spectrum, and it has been confirmed that the absolute configuration *R* of **3a-(B)** is in agreement with the reaction mechanism which involves an attack of the hydroxy group coordinated on the ruthenium to of the π -allyl moiety in complex (*S*)-**IIIa**. Stereo-controlled reductive elimination from (*S*)-**IIIa** afforded branched allylic alcohol **3a-(B)** with an absolute configuration of (*S*). The latter should be the key-step resulting in the high regio- and enantioselectivity in the present allylic hydroxylation (Scheme 3-13).



Scheme 3-13. Proposed Reaction Pathway for Asymmetric Allylic Hydroxylation

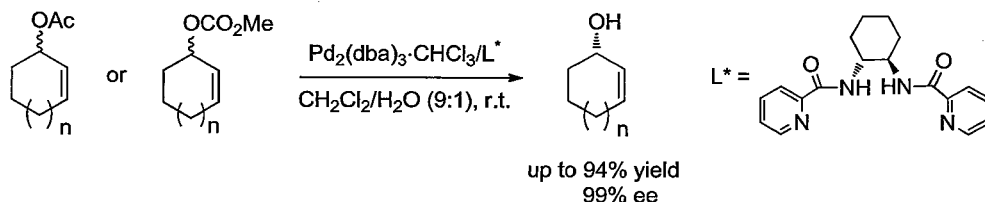


Scheme 3-12. (a) The Reaction Between **2a** and Water Catalyzed by (*S*)-**IIa**. (b) Stoichiometric Reaction of (*S*)-**IIa**

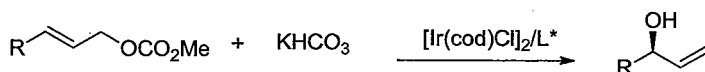
Gais and co-workers reported the palladium-catalyzed deracemization of 1,3-disubstituted allylic carbonates to give chiral allylic alcohols.¹² Recently, Helmchen reported a similar reaction using a chiral iridium catalyst.¹³ On the basis of control experiments, they have concluded that the reaction proceeds through the nucleophilic attack of the hydrogen carbonate ion to a π -allyl intermediate, and followed by decarboxylation. In

contrast, water actually functions as a hydroxide source in our reaction. The reaction using sodium formate instead of sodium hydrogen carbonate also produced **3a-(B)** in 64% yield with 80% ee as mentioned above. Moreover, definite evidence for a direct attack of HO⁻ ion to the π -allyl intermediate was obtained from an isotope labeling experiment. In fact, the reaction using H₂¹⁸O led to the selective formation of [¹⁸O]-**3a-(B)**, which was unequivocally confirmed by mass spectrometry (Scheme 3-15).¹⁴ To best of our knowledge, this is a rare example of an allylic substitution in which water can be used as a nucleophile to give the chiral allylic alcohols.

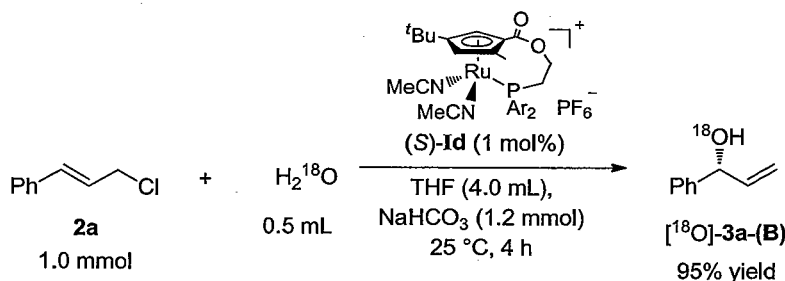
Gais (2003)



Helmchen (2011)



Scheme 3-14. Reaction of Allylic Carbonate with Hydrogen Carbonate ion

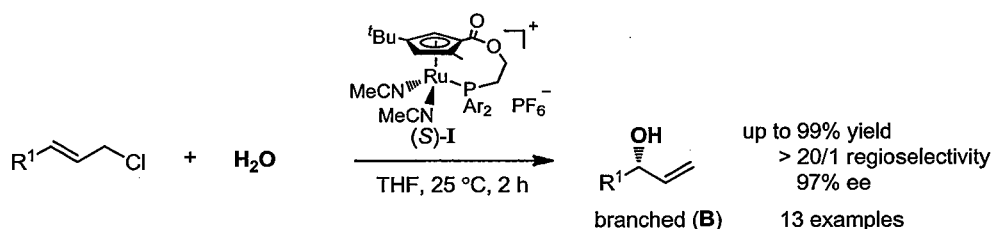


Scheme 3-15. Reaction of **2a** with Water [¹⁸O]

3-7 Conclusions

In conclusion, we have established a synthetic route to chiral allylic alcohols that involves allylic substitution with water, which is more atom economical method for the synthesis of optically active allylic alcohols than the conventional methods. Complete regioselectivity and high enantioselectivity have been achieved by using the planer-chiral Cp^{*}Ru catalysts. This route provides a new method for the synthesis of useful chiral allylic alcohols and is characterized by simplicity and availability in terms of the nucleophile, the

mild reaction conditions, and the wide scope of the allylic chlorides as a starting substrate.

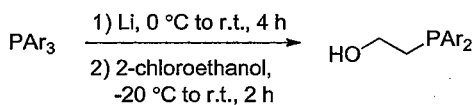


3-8 Experimental Procedure

All reactions were carried out under Ar atmosphere using Schlenk technique, and the workup was performed in air. 1H and ^{13}C NMR spectra were recorded on Varian Mercury 300, JEOL GSX400 and JEOL ECA500 spectrometers. Enantiomeric excess was determined by HPLC analysis using Hitachi L-2130 and L-2455 equipped with DAICEL Chiralcel OJ-H, OD-H and OB-H columns. 1-Octen-3-ol and 1-cyclohexyl-2-propen-1-ol were converted to the corresponding 4-nitrobenzoyl esters for HPLC analysis. Absolute configuration of allylic alcohols was determined by optical rotation and CD spectra. Optical rotation was measured on JASCO DIP-1000. All solvents used for reactions were passed through purification columns just before use. Planar-chiral Cp'Ru complex **1a** was prepared as reported previously.¹⁵ Cinnamyl chloride was available from commercial source. Allylic chlorides **2b–2d** and **2g–2m** were prepared by chlorination of the corresponding allylic alcohols with $SOCl_2$ or NCS/DMS,^{16–18} whereas **2e** was prepared by the method according to that for analogous bromide.¹⁹

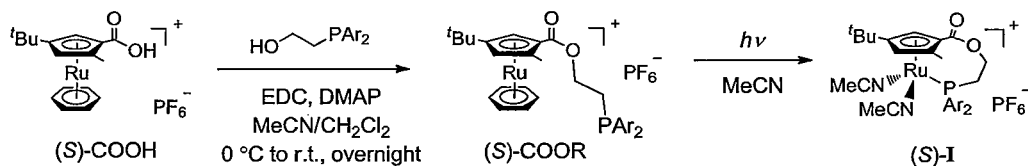
General Procedure for the Synthesis of (S)-Cp'Ru Complexes^{20,21}

Step 1



(S)-**1a**: Ar = Ph,
 (S)-**1b**: Ar = 3,5-Me₂C₆H₃

Step 2

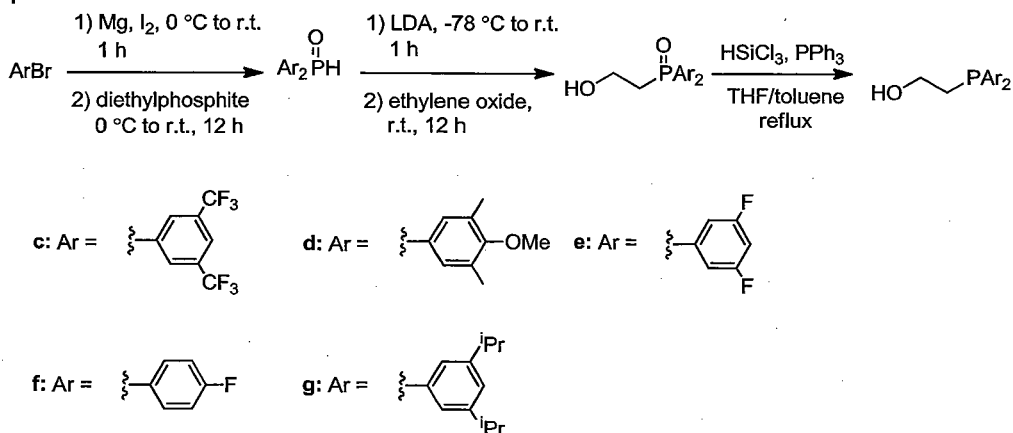


EDC (N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide)

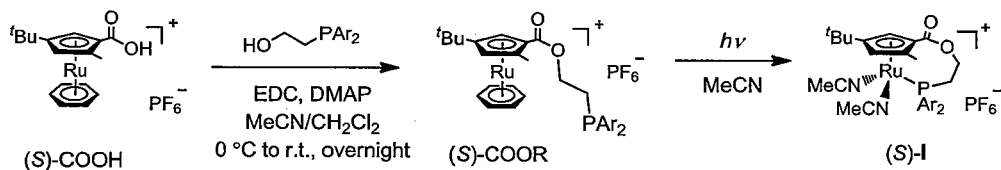
Step 1: Synthesis of 2-Diarylphosphinoethanol

Method A.²² To a solution of triarylphosphine (5.2 mmol) in THF (12 mL) was added Li wire (0.20 g, 26 mmol) at 0 °C, and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The solution was transferred to another flask through cannula, and cooled to -20 °C. After addition of 2-chloroethanol (0.42 g, 5.2 mmol) in THF (10 mL), the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with NH₄Cl aq., and the mixture was extracted with diethyl ether. Combined organic layer was washed with brine, and dried over Na₂SO₄. After removal of the solvent, the residue was purified by silica gel chromatography (*n*-hexane/dichloromethane = 1/1 to dichloromethane/ethyl acetate = 7/3).

Step 1



Step 2



Method B.^{21,21} To a mixture of magnesium (717 mg, 29.7 mmol) and small amounts of iodine in THF (20 mL) was added aryl bromide (24.9 mmol) in THF (5 mL) at 0 °C, and the reaction mixture was allowed to warm to room temperature and stirred for 1 h. After cooling to 0 °C, a solution of diethyl phosphite (8.0 mmol) in THF (10 mL) was added, and the mixture was stirred at room temperature for 12 h. The reaction was quenched with NH₄Cl aq., and the mixture was extracted with diethyl ether. Combined organic layer was washed with brine, and dried over Na₂SO₄. Removal of the solvent gave crude diarylphosphine oxide, which was used without further purification. Crude diarylphosphine oxide was dissolved in THF (10 mL), and the solution was cooled to -78 °C and 2.0 M *n*-hexane solution of lithium diisopropylamide (LDA) (ca. 4.0 mL) was added dropwise. The mixture was stirred for 1 h at the same temperature. After addition of 1.0 M *n*-hexane solution of ethylene oxide (10 mL), the mixture was allowed to warm to room temperature, and stirred for 12 h. The reaction was quenched with NH₄Cl aq., and the mixture was extracted with diethyl ether. Combined organic layer was washed with brine, and dried over Na₂SO₄. Evaporation of the solvent gave 2-diarylphosphorylethanol, which was used without further

purification.

To a solution of crude 2-diarylphosphorylethanol in THF (10 mL) and toluene (10 mL) was added drop-wise trichlorosilane (4.00 g, 30.0 mmol) and triphenylphosphine (1.60 g, 12 mmol) at room temperature, and the reaction mixture was stirred under reflux. Consumption of 2-diarylphosphorylethanol was confirmed by TLC analysis. After dilution with diethyl ether at 0 °C, the mixture was neutralized with 20% NaOH aq., and extracted with diethyl ether. Combined organic layer was washed with brine, and dried over Na₂SO₄. The solvent was removed in vacuo, and the resulting crude product was purified by silica gel chromatography (*n*-hexane/dichloromethane = 1/1 to dichloromethane/ethyl acetate = 7/3).

Step 2: Synthesis of (S)-Cp'Ru Complexes¹⁵

To a dichloromethane solution (6 mL) of *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide (WSCD) (503 mg, 2.63 mmol), 2-diarylphosphinoethanol (700 mg, 1.75 mmol) and a catalytic amount of *N,N*-dimethyl-4-aminopyridine (DMAP) was slowly added an acetonitrile solution (10 mL) of (S)-[Ru{η⁵-C₅H₂(Me)(^tBu)COOH}(η⁶-C₆H₆)](PF₆) (875 mg, 1.75 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. After NH₄PF₆ aq. was added, the reaction mixture was extracted with diethyl ether. Combined organic layer was washed with water and NH₄PF₆ aq., and dried over Na₂SO₄. The solvent was evaporated, and the residue was purified by alumina column chromatography (dichloromethane to acetone) to give yellow oil. Recrystallization from ethanol gave the target ruthenium complex as white powder.

This ruthenium complex was placed in a quartz glass vessel and dissolved in acetonitrile (8.0 mM). This solution was irradiated with a 500 W high-pressure mercury lamp for 18 h. Evaporation of the solvent gave yellow powder in quantitative yield.

(S)-[{η⁵-C₅H₂(Me)(^tBu)CO₂(CH₂)₂P(3,5-Me₂C₆H₃)₂}Ru(CH₃CN)₂](PF₆) (Ie)

The title compound was obtained in 42% yield (step 2), whereas 2-{bis(3,5-dimethylphenyl)phosphino}ethanol was prepared by method A in 77% yield (step 1). ¹H NMR (CDCl₃, 500 MHz): δ 7.34 (s, 1H, Ar), 7.31 (s, 1H, Ar), 7.16 (s, 1H, Ar), 7.03 (s, 1H, Ar), 7.60 (s, 1H, Ar), 6.58 (s, 1H, Ar), 5.15–5.14 (m, 1H, Cp'H), 5.03–4.96 (m, 1H, CH₂), 4.42–4.48 (m, 1H, Cp'H), 3.82–3.76 (m, 1H, CH₂), 2.88–2.81 (m, 1H, CH₂), 2.49–2.42 (m, 1H, CH₂), 2.35 (s, 6H, CH₃), 2.26 (s, 6H, CH₃), 2.20 (d, 3H, *J*_{H-P} = 1.7 Hz, CH₃), 2.16 (d, 3H, *J*_{H-P} = 1.4 Hz, CH₃), 2.04 (s, 3H, CH₃), 1.31 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 126 MHz): δ 168.4, 138.5 (d, *J*_{C-P} = 11 Hz), 137.6 (d, *J*_{C-P} = 10 Hz), 134.1, 133.8, 133.2, 131.8, 131.4 (*J*_{C-P} = 12 Hz), 130.6, 130.2, 128.5 (*J*_{C-P} = 8 Hz), 127.9, 125.1, 118.8, 116.3, 74.3 (d, *J*_{C-P} = 13 Hz), 71.9, 66.2, 60.1, 31.7, 30.6, 21.3, 21.2, 12.5, 3.5 (d, *J*_{C-P} = 12 Hz). ³¹P NMR (CDCl₃, 202 MHz): δ 29.2, –143.8 (sept, *J*_{P-F} = 712 Hz). Anal Calcd for C₃₃H₄₂F₆N₂O₂P₂Ru: C, 51.10; H, 5.46; N, 3.61. Found; C, 50.82; H, 5.24; N, 3.86. [α]_D²⁵ = –105.2 (c 0.08, CHCl₃).

(S)-[{η⁵-C₅H₂(Me)(^tBu)CO₂(CH₂)₂P(3,5-(CF₃)₂C₆H₃)₂}Ru(CH₃CN)₂](PF₆) (Ic)

The title compound could not be isolated as a pure form due to its instability (step 2), whereas 2-{bis(3,5-dimethylphenyl)phosphino}ethanol was prepared by method A in 90% yield (step 1).

(S)-[$\{\eta^5\text{-C}_5\text{H}_2(\text{Me})(\text{tBu})\text{CO}_2(\text{CH}_2)_2\text{P}(4\text{-MeO-3,5-Me}_2\text{C}_6\text{H}_3)_2\}\text{Ru}(\text{CH}_3\text{CN})_2\}\text{[PF}_6\text{]} \text{ (Id)}$

The title compound was obtained in 40% yield (step 2), whereas 2-{bis(4-methoxy-3,5-dimethylphenyl)diarylphosphino}-ethanol was prepared by method B in 48% yield (step 1). ^1H NMR (CDCl_3 , 500 MHz): δ 7.34 (d, 2H, $J_{\text{H-P}} = 10.9$ Hz, Ar), 6.64 (d, 2H, $J_{\text{C-P}} = 9.2$ Hz, Ar), 5.13–5.12 (m, 1H, Cp'H), 5.03–4.95 (m, 1H, CH₂), 4.48 (s, 1H, Cp'H), 3.80 (s, 3H, CH₃), 3.78–3.72 (m, 1H, CH₂), 3.76 (s, 3H, CH₃), 2.84–2.78 (m, 1H, CH₂), 2.46–2.33 (m, 1H, CH₂), 2.30 (s, 6H, CH₃), 2.22 (s, 9H, CH₃), 2.18 (s, 3H, CH₃), 2.04 (s, 3H, CH₃), 1.30 (s, 9H, CH₃). ^{13}C NMR (CDCl_3 , 126 MHz): δ 168.4, 159.6, 158.5, 134.3 (d, $J_{\text{C-P}} = 13$ Hz), 131.8 (d, $J_{\text{C-P}} = 11$ Hz), 131.4 (d, $J_{\text{C-P}} = 8$ Hz), 131.0 (d, $J_{\text{C-P}} = 10$ Hz), 129.0, 128.0, 125.4, 125.1 (d, $J_{\text{C-P}} = 7$ Hz), 118.7, 104.9, 74.3 (d, $J_{\text{C-P}} = 12$ Hz), 71.8, 66.2, 60.1, 59.9, 59.8, 31.7, 30.7, 21.1, 21.0, 16.3, 16.1, 12.5, 3.5. ^{31}P NMR (CDCl_3 , 202 MHz): δ 27.3, –143.9 (sept, $J_{\text{P-F}} = 712$ Hz). Anal Calcd for $\text{C}_{35}\text{H}_{46}\text{F}_6\text{N}_2\text{O}_2\text{P}_2\text{Ru}$: C, 50.30; H, 5.55; N, 3.35. Found; C, 50.02; H, 5.72; N, 3.30. $[\alpha]_{\text{D}}^{25} = -71.3$ (c 0.06, CHCl_3).

(S)-[$\{\eta^5\text{-C}_5\text{H}_2(\text{Me})(\text{tBu})\text{CO}_2(\text{CH}_2)_2\text{P}(3,5\text{-F}_2\text{C}_6\text{H}_3)_2\}\text{Ru}(\text{CH}_3\text{CN})_2\}\text{[PF}_6\text{]} \text{ (Ic)}$

The title compound was obtained in 36% yield (step 2), whereas 2-{bis(3,5-difluorophenyl)phosphino}ethanol was prepared by method B in 31% yield (step 1). ^1H NMR (CDCl_3 , 500 MHz): δ 7.38–7.35 (m, 2H, Ar), 7.10–7.06 (m, 1H, Ar), 6.94–6.90 (m, 1H, Ar), 6.53–6.50 (m, 2H, Ar), 5.27–5.26 (m, 1H, Cp'H), 5.18–5.10 (m, 1H, CH₂), 4.46–4.46 (m, 1H, Cp'H), 3.84–3.79 (m, 1H, CH₂), 2.95–2.89 (m, 1H, CH₂), 2.60–2.53 (m, 1H, CH₂), 2.31 (d, 3H, $J_{\text{H-P}} = 1.2$ Hz, CH₃), 2.28 (d, 3H, $J = 1.4$ Hz, CH₃), 2.06 (s, 3H, CH₃), 1.31 (s, 9H, CH₃). ^{13}C NMR (CDCl_3 , 126 MHz): δ 167.4, 163.2 (m), 162.7 (m), 137.5 (m), 134.3 (m), 128.9, 126.3, 119.8, 117.1 (m), 113.3 (m), 107.8 (d, $J_{\text{C-F}} = 25$ Hz), 107.1, 106.4 (d, $J_{\text{C-F}} = 25$ Hz), 74.7 (d, $J_{\text{C-P}} = 12$ Hz), 71.9, 66.9, 59.3, 31.8, 30.5, 20.0, 19.7, 12.5. 3.6. ^{31}P NMR (CDCl_3 , 202 MHz): δ 37.1, –143.9 (sept, $J_{\text{P-F}} = 712$ Hz). Anal Calcd for $\text{C}_{29}\text{H}_{30}\text{F}_{10}\text{N}_2\text{O}_2\text{P}_2\text{Ru}$: C, 44.00; H, 3.82; N, 3.65. Found; C, 44.23; H, 4.06; N, 3.72. $[\alpha]_{\text{D}}^{25} = -75.8$ (c 0.09, CHCl_3).

(S)-[$\{\eta^5\text{-C}_5\text{H}_2(\text{Me})(\text{tBu})\text{CO}_2(\text{CH}_2)_2\text{P}(4\text{-F-C}_6\text{H}_4)_2\}\text{Ru}(\text{CH}_3\text{CN})_2\}\text{[PF}_6\text{]} \text{ (If)}$

The title compound was obtained in 40% yield (step 2), whereas 2-{bis(4-fluorophenyl)phosphino}ethanol was prepared by method B in 48% yield (step 1). ^1H NMR (CDCl_3 , 500 MHz): δ 7.72–7.67 (m, 2H, Ar), 7.22–7.19 (m, 2H, Ar), 7.13–7.07 (m, 4H, Ar), 5.18–5.17 (m, 1H, Cp'H), 5.01–4.93 (m, 1H, CH₂), 4.42–4.41 (m, 1H, Cp'H), 3.95–3.93 (m, 1H, CH₂), 2.83–2.76 (m, 1H, CH₂), 2.55–2.48 (m, 1H, CH₂), 2.25 (d, 3H, $J_{\text{H-P}} = 1.2$ Hz, CH₃), 2.20 (d, 3H, $J = 1.4$ Hz, CH₃), 2.04 (s, 3H, CH₃), 1.31 (s, 9H, CH₃). ^{13}C NMR (CDCl_3 , 126 MHz): δ 167.9, 164.5 (d, $J_{\text{C-F}} = 256$ Hz), 163.8 (d, $J_{\text{C-F}} = 251$ Hz), 135.7 (dd, $J_{\text{C-F}} = 14$ Hz, $J_{\text{C-P}} = 8$ Hz), 133.3 (dd, $J_{\text{C-F}} = 8$ Hz, $J_{\text{C-P}} = 8$ Hz), 129.6 (dd, $J_{\text{C-P}} = 40$ Hz, $J_{\text{C-F}} = 4$ Hz), 128.5, 127.5 (dd, $J_{\text{C-P}} = 44$ Hz, $J_{\text{C-F}} = 4$ Hz), 126.1, 118.4, 116.3 (dd, $J_{\text{C-P}} = 21$ Hz, $J_{\text{C-F}} = 12$ Hz), 116.0 (dd, $J_{\text{C-P}} = 21$ Hz, $J_{\text{C-F}} = 12$ Hz), 105.4, 75.1 (d, $J_{\text{C-P}} = 12$ Hz), 71.2, 67.7, 60.1, 31.6, 30.4, 22.0, 21.8, 12.4, 3.7 (d, $J_{\text{C-P}} = 6$ Hz). ^{31}P NMR (CDCl_3 , 202 MHz): δ 31.6, –143.8 (sept, $J_{\text{P-F}} = 712$ Hz). Anal Calcd for $\text{C}_{29}\text{H}_{32}\text{F}_8\text{N}_2\text{O}_2\text{P}_2\text{Ru}$: C, 46.1; H, 4.27; N, 3.71. Found; C, 46.33; H, 4.54; N, 3.97. $[\alpha]_{\text{D}}^{25} = -77.6$ (c 0.08, CHCl_3).

(S)-[$\{\eta^5\text{-C}_5\text{H}_2(\text{Me})(\text{tBu})\text{CO}_2(\text{CH}_2)_2\text{P}(3,5\text{-}^i\text{Pr}_2\text{C}_6\text{H}_3)_2\}\text{Ru}(\text{CH}_3\text{CN})_2\}\text{[PF}_6\text{]} \text{ (Ig)}$

The title compound was obtained in 36% yield (step 2), whereas

2-{bis(3,5-diisopropylphenyl)phosphino}ethanol was prepared by method B in 23% yield (step 1). ¹H NMR (CDCl₃, 500 MHz): δ 7.20–7.17 (m, 3H, Ar), 7.12 (s, 1H, Ar), 6.85 (dd, 2H, *J* = 10.2, 1.4 Hz, Ar), 5.22–5.21 (m, 1H, Cp'H), 5.75–4.68 (m, 1H, CH₂), 4.41–4.40 (m, 1H, Cp'H), 4.09–4.01 (m, 1H, CH₂), 2.90 (hept, *J* = 6.6 Hz, CH), 2.83 (hept, *J* = 6.6 Hz, 1H), 2.64–2.57 (m, 1H, CH₂), 2.53–2.47 (m, 1H, CH₂), 2.20 (s, 3H, CH₃), 2.11 (s, 3H, CH₃), 2.03 (s, 3H, CH₃), 1.24–1.09 (m, 33H, CH₃). ¹³C NMR (CDCl₃, 126 MHz): δ 168.9, 149.5 (d, *J*_{C-P} = 10 Hz), 148.9 (d, *J*_{C-P} = 10 Hz), 132.8, 132.7, 132.5, 132.3, 128.4 (d, *J*_{C-P} = 11 Hz), 128.0 (d, *J*_{C-P} = 10 Hz), 127.8, 126.6, 126.2, 125.7, 119.1, 103.8, 75.6 (d, *J*_{C-P} = 12 Hz), 71.1, 66.3, 61.3, 34.2 (d, *J*_{C-P} = 10 Hz), 31.3, 30.3, 25.3, 25.0, 24.2, 24.0, 23.9, 23.8, 12.3, 3.7, 3.3. ³¹P NMR (CDCl₃, 202 MHz): δ 33.4, –143.9 (sept, *J*_{P-F} = 712 Hz). Anal Calcd for C₄₁H₅₈F₆N₂O₂P₂Ru: C, 55.46; H, 6.58; N, 3.15. Found; C, 55.64; H, 6.36; N, 3.19. [α]_D²⁵ = –54.6 (c 0.3, CHCl₃).

Synthesis of (*E*)-3-(4-Formylphenyl)allyl Chloride (2f)

(*E*)-ethyl 3-(4'-cyanophenyl)acrylate.

To a DMF solution (20 mL) of 4-bromobenzonitrile (2.73 g, 15 mmol), NaOAc (1.85g, 22.5mmol), NBu₄Br (48.3 mg, 1.5 mmol) and Herrman's catalyst (140 mg, 1 mol%) was added a DMF solution (10 mL) of methyl acrylate (2.25 g, 22.5 mmol), and the reaction mixture was stirred at 140 °C. After 12 h, the reaction mixture was cooled to room temperature, and filtered through Celite. The filtrate was extracted with diethyl ether, and combined organic layer was washed with brine. After dried over Na₂SO₄, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 9/1) to give yellow oil (2.69 g, 89%). NMR (CDCl₃, 400 MHz): δ 7.68–7.58 (m, 5H, Ar and CH=), 6.50 (d, 1H, *J* = 15.9 Hz, CH=), 4.28 (q, 2H, *J* = 7.1 Hz, CH₂), 1.35 (t, 3H, *J* = 7.1 Hz, CH₃).

3-(4'-formylphenyl)-2-propen-1-ol.

To a toluene solution (15 mL) of (*E*)-ethyl 3-(4-cyanophenyl)acrylate (2.00 g, 9.95 mmol) was added dropwise a 1.0 M *n*-hexane solution of DIBAL-H (33 mL, 33 mmol) at 0 °C, and the mixture was stirred for 2 h. The reaction was quenched by addition of MeOH and 3 N HCl. After evaporation of the solvent, the residue was extracted with diethyl ether. Combined organic layer was dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 2/1) to give yellow oil (1.05 g, 65%). ¹H NMR (CDCl₃, 400 MHz): δ 9.97 (s, 1H, CHO), 7.83 (d, 2H, *J* = 8.3 Hz, Ar), 7.51 (d, 2H, *J* = 8.3 Hz, Ar), 6.70 (d, 1H, *J* = 15.7 Hz, CH=), 6.52 (dt, 1H, *J* = 15.7, 5.1 Hz, CH=), 4.38 (d, 2H, *J* = 5.1 Hz, CH₂), 1.69 (br, 1H, OH).

(*E*)-3-(4'-formylphenyl)allyl chloride (2f)

A dichloromethane solution (20 mL) of *N*-chlorosuccinimide (1.03 g, 10.4 mmol) was charged with dimethyl sulfide (643 mg, 10.4 mmol) at 0 °C, and the resulting white suspension was stirred for 10 min. After cooling to –20 °C, a dichloromethane solution (10 mL) of 3-(4-formylphenyl)-2-propen-1-ol (800 mg, 4.9 mmol) was added, and the mixture was warmed to 0 °C and stirred for 2 h. The reaction mixture was diluted with water, and extracted with diethyl ether. Combined organic layer was washed with brine and dried over Na₂SO₄. After removal of the solvent, the residue was purified by silica gel column

chromatography (*n*-hexane/ethyl acetate = 9/1) to give white solid (790 mg, 90%). ¹H NMR (CDCl₃, 400 MHz): δ 9.95 (s, 1H, CHO), 7.83 (d, 2H, *J* = 8.4 Hz, Ar), 7.53 (d, 2H, *J* = 8.4 Hz, Ar), 6.71 (d, 1H, *J* = 15.7 Hz, CH=), 6.46 (dt, 1H, *J* = 15.7, 6.6 Hz, CH=), 4.26 (dd, 2H, *J* = 6.6, 1.0 Hz, CH₂), 2.69 (br, 1H, OH). ¹³C NMR (CDCl₃, 100 MHz): δ 191.9, 149.3, 139.4, 135.5, 129.9, 126.7, 116.0, 74.8. Anal Calcd for C₁₀H₁₀ClO: C, 66.49; H, 5.02. Found; C, 66.37; H, 4.97.

Synthesis of (*E,E*)-Methyl 6-Chlorohexa-2,4-dienoate (8)

(*E,E*)-methyl 6-hydroxyhexa-2,4-dienoate^{23,24}

A solution of methyl sorbate (7) (5.04 g, 40.0 mmol), *N*-bromosuccinimide (NBS, 7.84 g, 44.0 mmol) and AIBN (328 mg, 2.080 mmol) in chlorobenzene (40 mL) was stirred overnight at 100 °C. The solvent was removed under reduce pressure, and diethyl ether was added to the residual solid. The insoluble parts were filtered off, and the filtrate was washed with NaHCO₃ aq. and brine. After dried over Na₂SO₄, the solvent was evaporated, and the residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 10/1) to give a mixture of methyl sorbate and (*E,E*)-methyl 6-bromohexa-2,4-dienoate. The mixture of methyl sorbate and (*E,E*)-methyl 6-bromohexa-2,4-dienoate was suspended in acetone (60 mL) and NaHCO₃ aq. (40 mL), and the reaction mixture was refluxed for 3 h. After neutralization with 5% HCl, acetone was removed under reduce pressure. The aqueous solution was extracted with ethyl acetate, and the organic solution was washed with NaHCO₃ aq. and brine. After dried over Na₂SO₄, the solvent was evaporated and the residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 10/1 to 10/3) to give pale yellow oil (2.72 g, 19.2 mmol, 48%). NMR (CDCl₃, 400 MHz): δ 7.29 (dd, 1H, *J* = 15.4, 11.0 Hz, CH=), 6.42 (dd, 1H, *J* = 15.4, 11.0 Hz, CH=), 6.22 (dt, 1H, *J* = 15.4, 5.1 Hz, CH=), 5.87 (d, 1H, *J* = 15.4 Hz, CH=), 4.29 (d, 2H, *J* = 5.1 Hz, CH₂), 3.74 (s, 3H, CH₃).

(*E,E*)-methyl 6-chlorohexa-2,4-dienoate (8)²⁴

A solution of *N*-chlorosuccinimide (1.5 g, 10.6 mmol) in dichloromethane (20 mL) was charged with dimethyl sulfide (930 mg, 15.0 mmol) at 0 °C, and the resulting white suspension was stirred for 10 min. After cooling to -20 °C, a dichloromethane solution (10 mL) of (*E,E*)-methyl 6-hydroxyhexa-2,4-dienoate (1.5 g, 10.6 mmol) was added, and the mixture was allowed to warmed to room temperature. After stirring for 2 h, the reaction mixture was diluted with water, and extracted with diethyl ether. Combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was evaporated, and the residue was purified by silica gel chromatography (*n*-hexane/ethyl acetate = 10/1) to give pale yellow oil (790 mg, 90%). NMR (CDCl₃, 300 MHz): δ 7.27 (dd, 1H, *J* = 15.0, 10.9 Hz, CH=), 6.42 (dd, 1H, *J* = 15.0, 10.9 Hz, CH=), 6.18 (dt, 1H, *J* = 15.0, 6.7 Hz, CH=), 5.94 (d, 1H, *J* = 15.0 Hz, CH=), 4.14 (d, 2H, *J* = 6.7 Hz, CH₂), 3.76 (s, 3H, CH₃).

Standard Method of Catalytic Reaction

To a solution of allylic chloride (1.0 mmol) in THF (4.0 mL) and water (0.5 mL) were added sodium hydrogen carbonate (101 mg, 1.2 mmol) and Cp*Ru catalyst (10 μmol, 1 mol%), and the reaction mixture was stirred for 4 h at 25 °C. After dilution with diethyl ether, the insoluble parts were filtered off through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel

column chromatography using a mixture of *n*-hexane/ethyl acetate=10/1 as the eluent to give colorless oil.

Characterization of Allylic Alcohols

(*R*)-1-phenyl-2-propen-1-ol (3a).⁷

¹H NMR (CDCl₃, 400 MHz): δ 7.42–7.24 (m, 5H, Ar), 6.04 (ddd, 1H, *J* = 17.1, 10.4, 5.7 Hz, CH=), 5.34 (ddd, 1H, *J* = 17.1, 1.8, 1.8 Hz, CH=), 5.19–5.17 (m, 2H, CH and CH=), 1.99 (br, 1H, OH). ¹³C NMR (CDCl₃, 126 MHz): δ 142.6, 140.2, 128.5, 127.7, 126.3, 115.1, 75.3. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL/min, 220 nm; minor enantiomer (*S*): *t* = 32.1 min, major enantiomer (*R*): *t* = 36.1 min, 90% ee.

(*R*)-1-*p*-tolyl-2-propen-1-ol (3b)²⁶

¹H NMR (CDCl₃, 400 MHz): δ 7.24 (d, 2H, *J* = 8.0 Hz, Ar), 7.15 (d, 2H, *J* = 8.0 Hz, Ar), 6.03 (ddd, 1H, *J* = 17.0, 10.4, 5.8 Hz, CH=), 5.32 (ddd, 1H, *J* = 17.0, 1.2, 1.2 Hz, CH=), 5.18–5.15 (m, 2H, CH and CH=), 2.33 (s, 3H, CH₃), 1.97 (br, 1H, OH). ¹³C NMR (CDCl₃, 126 MHz): δ 140.3, 139.6, 137.4, 129.1, 126.2, 114.8, 75.2, 21.2. HPLC analysis: Chiralcel OB-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL/min, 220 nm; major enantiomer (*R*): *t* = 12.9 min, minor enantiomer (*S*): *t* = 14.1 min, 90% ee. [α]_D²⁵ = –5.2 (c 0.3, CHCl₃).

(*R*)-1-(4'-methoxyphenyl)-2-propen-1-ol (3c)⁷

¹H NMR (CDCl₃, 400 MHz): δ 7.30–7.26 (m, 2H, Ar), 6.90–6.86 (m, 2H, Ar), 6.04 (ddd, 1H, *J* = 17.1, 10.3, 5.9 Hz, CH=), 5.32 (ddd, 1H, *J* = 17.1, 1.5, 1.5 Hz, CH=), 5.18 (ddd, 1H, *J* = 10.3, 1.5, 1.5 Hz, CH=), 5.15 (br, 1H, CH), 3.80 (s, 3H, CH₃), 1.86 (br, 1H, OH). ¹³C NMR (CDCl₃, 76 MHz): δ 159.2, 140.4, 134.9, 127.6, 114.7, 113.9, 74.8, 55.2. HPLC analysis: Chiralcel OB-H column, *n*-hexane/*i*-PrOH = 99/1 (v/v), 1.0 mL/min, 220 nm; major enantiomer (*R*): *t* = 44.7 min, minor enantiomer (*S*): *t* = 49.1 min, 76% ee. [α]_D²⁵ = +2.1 (c 0.2, CHCl₃).

(*R*)-1-(4'-trifluoromethylphenyl)-2-propen-1-ol (3d)⁷

¹H NMR (CDCl₃, 400 MHz): δ 7.61 (d, 2H, *J* = 8.0 Hz, Ar), 7.49 (d, 2H, *J* = 8.0 Hz, Ar), 6.01 (ddd, 1H, *J* = 17.0, 10.5, 6.2 Hz, CH=), 5.37 (ddd, 1H, *J* = 17.0, 1.2, 1.2 Hz, CH=), 5.27–5.22 (m, 2H, CH and CH=), 2.02 (br, 1H, OH). ¹³C NMR (CDCl₃, 100 MHz): δ 146.3, 139.6, 129.8 (q, *J* = 35 Hz), 128.1, 126.5, 125.4 (q, *J* = 3 Hz), 116.1, 74.8. HPLC analysis: Chiralcel OB-H column, *n*-hexane/*i*-PrOH = 500/1 (v/v), 0.5 mL/min, 220 nm; major enantiomer (*R*): *t* = 19.8 min, minor enantiomer (*S*): *t* = 22.6 min, 94% ee. [α]_D²⁵ = –12.9 (c 0.3, CHCl₃).

(*R*)-1-(4'-methoxycarbonylphenyl)-2-propen-1-ol (3e)¹⁹

¹H NMR (CDCl₃, 400 MHz): δ 8.02 (d, 2H, *J* = 8.3 Hz, Ar), 7.43 (d, 2H, *J* = 8.3 Hz, Ar), 6.02 (ddd, 1H, *J* = 17.0, 10.3, 6.2 Hz, CH=), 5.36 (ddd, 1H, *J* = 17.0, 1.2, 1.2 Hz, CH=), 5.26 (d, 1H, *J* = 6.2 Hz, CH), 5.22 (ddd, 1H, *J* = 10.3, 1.2, 1.2 Hz, CH=), 3.91 (s, 3H, CH₃), 2.06 (br, 1H, OH). ¹³C NMR (CDCl₃, 126 MHz): δ 166.8, 147.5, 139.6, 129.7, 129.2, 126.0, 115.8, 76.7, 52.1. [α]_D²⁶ = –17.5 (c = 0.14, CHCl₃) for 93% ee. HPLC analysis: Chiralcel OB-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL/min, 254 nm;

minor enantiomer (*S*): *t* = 49.4 min, major enantiomer (*R*): *t* = 52.9 min, 93% ee. $[\alpha]_{\text{D}}^{25} = -17.5$ (*c* 0.2, CHCl_3).

(*R*)-1-(4'-formylphenyl)-2-propen-1-ol (3f)

^1H NMR (CDCl_3 , 400 MHz): δ 9.96 (s, 1H, CHO), 7.83 (d, 2H, *J* = 7.5 Hz, Ar), 7.53 (d, 2H, *J* = 7.5 Hz, Ar), 6.00 (ddd, 1H, *J* = 16.7, 10.6, 6.6 Hz, CH=), 5.36 (dq, 1H, *J* = 16.7, 1.2 Hz, CH=), 5.26 (br, 1H, *J* = 6.6 Hz, CH), 5.23 (ddd, 1H, *J* = 10.6, 1.2, Hz, CH=), 2.69 (br, 1H, OH). ^{13}C NMR (CDCl_3 , 100 MHz): δ 191.9, 149.3, 139.4, 135.5, 129.9, 126.7, 116.0, 74.8. $[\alpha]_{\text{D}}^{23} = -36.6$ (*c* = 0.40, CHCl_3) for 93% ee. Anal Calcd for $\text{C}_{10}\text{H}_{10}\text{O}_2$: C, 74.06; H, 6.21. Found; C, 73.72; H, 6.15. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH = 90/10 (v/v), 1.0 mL/min, 220 nm; minor enantiomer (*S*): *t* = 22.5 min, major enantiomer (*R*): *t* = 27.1 min, 93% ee. $[\alpha]_{\text{D}}^{25} = -36.6$ (*c* 0.4, CHCl_3).

(*R*)-1-(1'-naphthyl)-2-propen-1-ol (3g)²⁷

^1H NMR (CDCl_3 , 400 MHz): δ 8.18 (d, 2H, *J* = 8.3 Hz, Ar), 7.86 (d, 2H, *J* = 9.5 Hz, Ar), 7.79 (d, 2H, *J* = 8.3 Hz, Ar), 7.61 (d, 1H, *J* = 7.1 Hz, Ar), 6.25 (ddd, 1H, *J* = 17.1, 10.5, 6.4 Hz, CH=), 5.94 (br, 1H, CH), 5.44 (ddd, 1H, *J* = 17.1, 1.5, 1.5 Hz, CH=), 5.28 (ddd, 1H, *J* = 10.5, 1.5, 1.5 Hz, CH=), 2.04 (br, 1H, OH). ^{13}C NMR (CDCl_3 , 126 MHz): δ 139.6, 138.0, 133.9, 130.6, 128.7, 128.5, 126.0, 125.6, 125.3, 123.9, 123.7, 115.6, 72.3. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL/min, 220 nm; minor enantiomer (*S*): *t* = 15.9 min, major enantiomer (*R*): *t* = 22.3 min, 90% ee. $[\alpha]_{\text{D}}^{25} = +36.9$ (*c* 0.4, CHCl_3).

(*R*)-1-(2'-naphthyl)-2-propen-1-ol (3h)²⁸

^1H NMR (CDCl_3 , 400 MHz): δ 7.84–7.80 (m, 4H, Ar), 7.49–7.44 (m, 3H, Ar), 6.13 (ddd, 1H, *J* = 17.0, 10.3, 6.1 Hz, CH=), 5.41 (ddd, 1H, *J* = 17.0, 1.3, 1.3 Hz, CH=), 5.37 (br, 1H, CH), 5.24 (ddd, 1H, *J* = 10.3, 1.3, 1.3 Hz, CH=), 2.00 (br, 1H, OH). ^{13}C NMR (CDCl_3 , 126 MHz): δ 140.0, 139.9, 132.9, 128.2, 127.9, 127.6, 126.0, 125.9, 124.8, 124.4, 115.3, 75.4. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH = 90/10 (v/v), 1.0/min, 220 nm; minor enantiomer (*S*): *t* = 19.6 min, major enantiomer (*R*): *t* = 23.9 min, 89% ee. $[\alpha]_{\text{D}}^{25} = -3.0$ (*c* 0.3, CHCl_3).

(*R*)-(E)-1-phenyl-1,4-penta-dien-3-ol (3i)⁷

^1H NMR (CDCl_3 , 400 MHz): δ 7.39–7.37 (m, 2H, Ar), 7.32–7.29 (m, 2H, Ar), 7.25–7.21 (m, 1H, Ar), 6.61 (dd, 1H, *J* = 15.9, 1.2 Hz, CH=), 6.23 (dd, 1H, *J* = 15.9, 6.5 Hz, CH=), 5.98 (ddd, 1H, *J* = 17.2, 10.3, 6.5 Hz, CH=), 5.36 (ddd, 1H, *J* = 17.2, 1.2, 1.2 Hz, CH=), 5.19 (ddd, 1H, *J* = 10.3, 1.2, 1.2 Hz, CH=), 4.81 (dddd, 1H, *J* = 6.5, 6.5, 1.2, 1.2 Hz, CH). ^{13}C NMR (CDCl_3 , 126 MHz): δ 139.4, 136.5, 130.8, 130.3, 128.5, 127.7, 126.5, 115.3, 73.7. HPLC analysis: Chiralcel OB-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL/min, 254 nm; major enantiomer (*R*): *t* = 26.2 min, minor enantiomer (*S*): *t* = 30.0 min, 96% ee. $[\alpha]_{\text{D}}^{25} = -3.0$ (*c* 0.1, CHCl_3).

(*S*)-5-phenyl-1-penten-3-ol (3j)²⁸

^1H NMR (CDCl_3 , 400 MHz): δ 7.28–7.24 (m, 2H, Ar), 7.19–7.14 (m, 3H, Ar), 5.88 (ddd, 1H, *J* =

17.3, 10.5, 6.1 Hz, CH=), 5.23 (ddd, 1H, J = 17.3, 1.5, 1.5 Hz, CH=), 5.12 (ddd, 1H, J = 10.5, 1.5, 1.5 Hz, CH=), 5.12 (m, 1H, CH), 2.77–2.63 (m, 2H, CH₂), 1.90–1.78 (m, 2H, CH₂). ¹³C NMR (CDCl₃, 100 MHz): δ 141.7, 140.9, 128.3, 128.3, 125.7, 114.8, 72.4, 38.5, 31.6. HPLC analysis: Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v) 0.5 mL/min, 220 nm; minor enantiomer (S): t = 24.4 min, major enantiomer (R): t = 25.9 min, 85% ee. $[\alpha]_D^{25}$ = –3.6 (c 0.4, CHCl₃).

(S)-1-octen-3-ol (3k)²⁹

¹H NMR (CDCl₃, 400 MHz): δ 5.87 (ddd, 1H, J = 17.2, 10.6, 6.5 Hz, CH=), 5.25 (ddd, 1H, J = 17.2, 1.5, 1.5 Hz, CH=), 5.10 (ddd, 1H, J = 10.6, 1.5, 1.5 Hz, CH=), 4.10 (dt, 1H, J = 6.5, 6.2 Hz, CH=), 1.59–1.30 (m, 8H, CH₂), 0.89 (t, 3H, J = 6.5 Hz, CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 141.3, 114.4, 73.3, 37.1, 31.8, 25.1, 22.7, 14.1. $[\alpha]_D^{25}$ = +9.0 (c 0.4, CHCl₃).

(S)-1-octen-3-yl 4'-nitrobenzoate

¹H NMR (CDCl₃, 300 MHz): δ 8.30–8.28 (m, 2H, Ar), 8.24–8.21 (m, 2H, Ar), 5.90 (ddd, 1H, J = 17.1, 10.5, 6.6 Hz, CH=), 5.51 (q, 1H, J = 6.6 Hz, CH), 5.34 (ddd, 1H, J = 17.1, 1.2, 1.2 Hz, CH=), 5.25 (ddd, 1H, J = 10.5, 1.2, 1.2 Hz, CH=), 1.87–1.69 (m, 2H, CH₂), 1.45–1.28 (m, 6H, CH₂), 0.89 (t, 3H, J = 7.0 Hz, CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 163.8, 150.3, 135.8, 135.8, 130.5, 123.4, 117.3, 34.1, 31.5, 24.7, 22.5, 14.0. $[\alpha]_D^{20}$ = 23.4 (c = 0.59, CHCl₃) for 83% ee. Anal Calcd for C₁₅H₁₉NO₄: C, 64.97; H, 6.91; N, 5.05. Found; C, 65.12; H, 6.87; N, 4.98. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL/min, 254 nm; minor enantiomer (S): t = 6.5 min, major enantiomer (R): t = 7.6 min, 83% ee. $[\alpha]_D^{25}$ = +23.4 (c 0.6, CHCl₃).

(R)-1-cyclohexyl-2-propen-1-ol (3l)³⁰

¹H NMR (CDCl₃, 400 MHz): δ 5.78 (ddd, 1H, J = 17.1, 10.4, 6.6 Hz, CH=), 5.12 (m, 1H, CH=), 5.06 (m, 1H, CH=), 3.77 (t, 1H, J = 6.6 Hz, CH and CH=), 1.79–1.56 (m, 5H, CH₂), 1.37–1.28 (m, 1H, CH), 1.21–0.87 (m, 5H, CH₂). ¹³C NMR (CDCl₃, 100 MHz): δ 139.7, 115.3, 43.5, 28.8, 28.4, 26.6, 26.2, 26.1. $[\alpha]_D^{25}$ = +19.1 (c 0.4, CHCl₃).

(R)-1-cyclohexyl-2-propenyl 4'-nitrobenzoate

¹H NMR (CDCl₃, 300 MHz): δ 8.31–8.27 (m, 2H, Ar), 8.24–8.20 (m, 2H, Ar), 5.98 (ddd, 1H, J = 17.2, 10.5, 6.8 Hz, CH=), 5.35–5.25 (m, 3H, CH), 1.86–1.67 (m, 6H, CH₂), 1.34–1.03 (m, 5H, CH₂ and CH). ¹³C NMR (CDCl₃, 75 MHz): δ 163.9, 150.5, 136.1, 134.5, 130.7, 123.5, 118.3, 80.7, 41.7, 28.7, 28.4, 26.3, 25.9. $[\alpha]_D^{25}$ = –19.6 (c = 0.28, CHCl₃) for 97% ee. Anal Calcd for C₁₆H₁₉NO₄: C, 66.42; H, 6.62; N, 4.84. Found; C, 66.45; H, 6.53; N, 4.84. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL/min, 254 nm; minor enantiomer (S): t = 6.9 min, major enantiomer (R): t = 7.8 min, 97% ee. $[\alpha]_D^{25}$ = –19.6 (c 0.28, CHCl₃).

(R)-4-(tert-butyldiphenylsilyloxy)-1-buten-3-ol (3m)³¹

¹H NMR (CDCl₃, 300 MHz): δ 7.65–7.55 (m, 4H, Ar), 7.37–7.21 (m, 6H, Ar), 5.71 (ddd, 1H, J = 17.3, 10.6, 5.6 Hz, CH=), 5.23 (ddd, 1H, J = 17.3, 1.5, 1.5 Hz, CH=), 5.07 (ddd, 1H, J = 10.6, 1.5, 1.5 Hz,

CH=), 4.16–4.10 (m, 1H, CH), 3.62 (dd, 1H, $J = 10.3, 3.8$ Hz, CH₂), 3.47 (dd, 1H, $J = 10.3, 7.3$ Hz, CH₂), 2.52 (br, 1H, OH), 0.99 (s, 9H, ^tBu). ¹³C NMR (CDCl₃, 75 MHz): δ 136.6, 135.5, 135.5, 133.1, 133.1, 129.9, 127.8, 127.8, 127.7, 127.6, 116.4, 67.7, 26.8, 19.3. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL/min, 254 nm; minor enantiomer: $t = 9.0$ min, major enantiomer: $t = 10.9$ min, 90% ee. $[\alpha]_D^{25} = +4.2$ (c 0.4, CHCl₃).

1,1'-(1,3-phenylene)bis(2-propen-1-ol) (6)

¹H NMR (CDCl₃, 500 MHz): δ 7.39–7.25 (m, 4H, Ar), 6.01 (ddd, 2H, $J = 17.0, 10.5, 6.0$ Hz, CH=), 5.32 (ddd, 2H, $J = 17.0, 1.3, 1.3$ Hz, CH=), 5.19–5.16 (m, 4H, CH and CH=), 2.29 (br, 2H, OH). ¹³C NMR (CDCl₃, 126 MHz): δ 143.0, 140.2, 128.8, 125.8, 124.4, 115.3, 75.3. HR-MS (ESI): Calcd for C₁₂H₁₄O₂Na [M+Na⁺]: 213.0892, Found: $m/z = 213.0894$. $[\alpha]_D^{25} = -4.8$ ($c = 0.10$, CHCl₃) for 99% ee. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 90/10 (v/v), 1.0 mL/min, 220 nm; major enantiomer: $t = 18.4$ min, minor enantiomer: $t = 20.1$, minor diastereomer: $t = 21.3$ min, 99% ee, 82% de. $[\alpha]_D^{25} = -4.8$ (c 0.1, CHCl₃).

(S)-(E)-1-carbomethoxy-1,4-penta-dien-3-ol (9) ¹¹

¹H NMR (CDCl₃, 300 MHz): δ 6.86 (dd, 1H, $J = 15.7, 4.7$ Hz, CH=), 5.98 (dd, 1H, $J = 15.7, 1.8$ Hz, CH=), 5.78 (ddd, 1H, $J = 17.0, 10.5, 6.2$ Hz, CH=), 5.24 (ddd, 1H, $J = 17.0, 1.2, 1.2$ Hz, CH=), 5.13 (ddd, 1H, $J = 10.5, 1.2, 1.2$ Hz, CH=), 3.67 (s, 3H, CH₃), 3.03 (br, 1H, OH). ¹³C NMR (CDCl₃, 75 MHz): δ 166.7, 148.3, 137.4, 120.0, 116.4, 72.0, 51.6. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL/min, 220 nm; minor enantiomer: $t = 33.4$ min, major enantiomer: $t = 38.1$ min, 90% ee. $[\alpha]_D^{25} = +59.9$ (c 0.3, CHCl₃).

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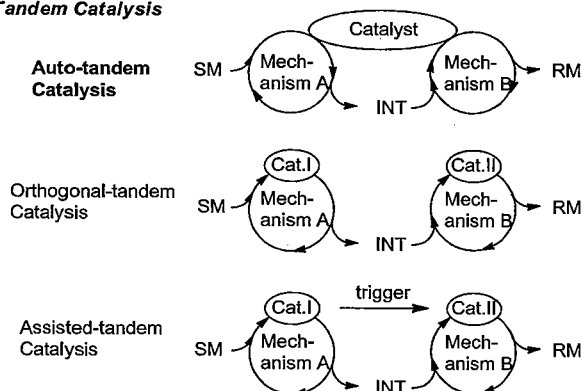
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Chapter 4: Asymmetric Auto-Tandem Catalysis with Planar-Chiral Cyclopentadienyl-Ruthenium Complex: Sequential Asymmetric Allylic Amidation and Atom Transfer Radical Cyclization

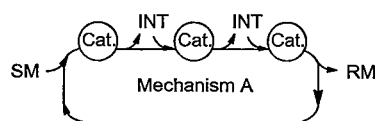
4-1 Introduction

The efficient synthesis of complex molecules with multi stereogenic centers is a daunting task in synthetic organic chemistry including natural product synthesis and pharmaceutical synthesis. In this field, one pot process involving the sequence of consecutive asymmetric transformation has received considerable attention because it can do away with time-consuming workup and the formidable job of isolating intermediary products.¹ One of such processes is tandem catalysis, which *involves two or more mechanistically distinct reactions* without workup and isolation of reaction intermediates.² This concept can be classified into three types^{2a}: orthogonal-,³ auto-,⁴ and assisted-tandem catalysis⁵ (Scheme 4-1). Auto-tandem catalysis, promoted by a single catalyst, can realize more efficient synthesis. However, there are limited numbers of reports on auto-tandem reactions because this system can be difficult to optimize reaction conditions, though there are numerous examples of domino reactions, in which a catalyst conducts two or more mechanistically similar reactions.^{1,2a} In 2001, Evans reported auto-tandem catalysis of a Rh complex for allylic substitution and Pauson-Khand reaction (Scheme 4-2(a)), which involved two mechanistically distinct reactions.^{4a} In contrast, Enders reported in 2006 that a three-component reaction proceeds by way of a catalyzed Michael reaction and aldol condensation sequence affording optically active products with good to moderate yields.⁶ The latter belongs to a domino

Tandem Catalysis



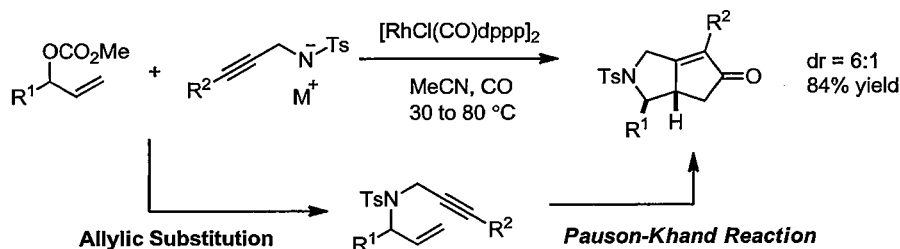
Domino (Cascade) Catalysis



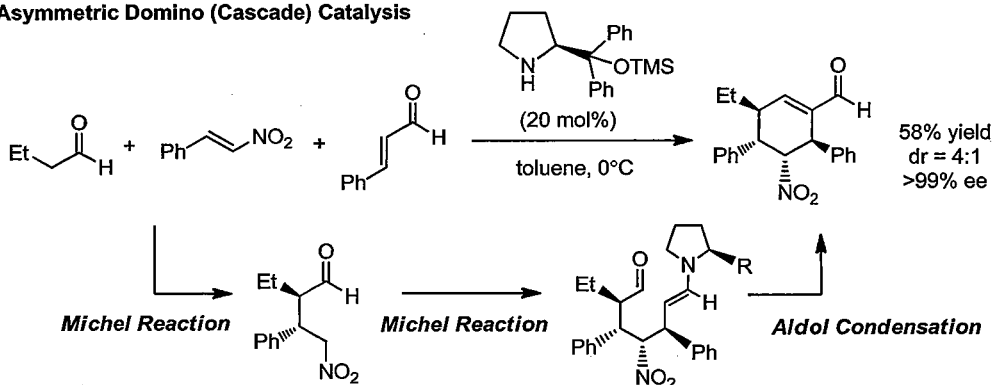
SM: Starting Material
INT: Intermediate
RM: Run Material

Scheme 4-1. Schematic Illustration of Tandem and Domino Catalysis

(a) **Auto-tandem Catalysis**

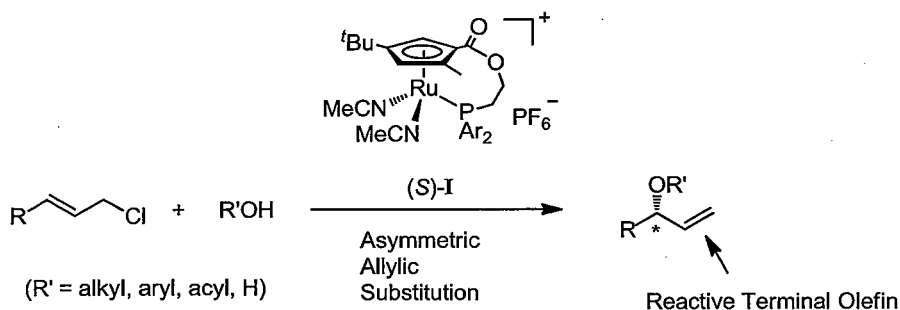


(b) **Asymmetric Domino (Cascade) Catalysis**



Scheme 4-2. Example of (a) Auto-tandem Catalysis and (b) Asymmetric Domino catalysis

reaction because the catalyst conducts two or more mechanistically similar reactions (Scheme 4-2(b)). To our best knowledge, there are no reports on asymmetric auto-tandem catalysis. We have successfully applied our planar-chiral ruthenium complex as a catalyst to the first example of asymmetric auto-tandem catalysis, which consist of allylic substitution and atom-transfer radical cyclization.



Scheme 4-3. Asymmetric Allylic Substitutions

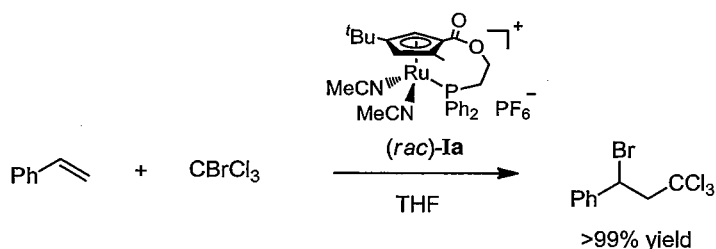
We have already shown in Chapters 2 and 3 that planar-chiral cyclopentadienyl-ruthenium (Cp^*Ru) complex (I) is a proficient catalyst for region- and

enantioselective allylic substitutions of monosubstituted allylic halides with oxygen nucleophiles.⁷ As these products possess a highly reactive terminal olefin, and in addition the catalytic activity of **I** is preserved even at the end of the reaction,^{7b} we have conceived an extension of our system to asymmetric auto-tandem catalysis (Scheme 4-3).

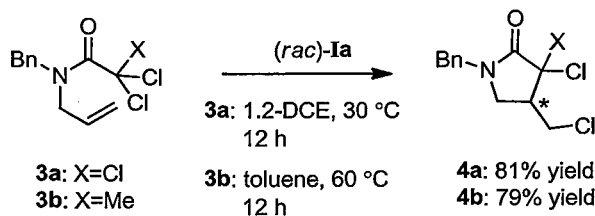
As a candidate for the transformation of the terminal olefin moiety on allylic compounds, we focused on an atom-transfer radical cyclization (ATRC) reaction because half-sandwiched Ru complexes analogous to **I** are known to promote an ATRC reaction.⁸ ATRC should be an efficient method from the view of atom economical manner because it proceeds generally under mild conditions and exhibits broad functional group tolerance. It may be hypothesized that complex **I** can realize such asymmetric auto-tandem catalysis consisting of allylic substitution and ATRC reaction.

4-2 Atom-transfer Radical Cyclization Catalyzed by (*S*)-**Ia**

We have already reported that complex **I** acts as a good catalyst for atom transfer radical addition (ATRA) to olefin (Scheme 4-4).⁹ Based on this study, we then investigated the catalytic activity of **I** for ATRC to realize the asymmetric auto-tandem catalysis starting from allylic substrates. Treatment of *N*-allyl-*N*-benzyl-2,2,2-trichloroacetamide **3a** in the presence of 3 mol% of **I** in 1,2-dichloroethane at 30 °C for 12 h resulted in the formation of a cyclic compound **4a** in 81% yield. As *N*-allyl-*N*-benzyl-2,2-dichloropropanamide **3b** was less reactive than **3a**, the reaction was performed in toluene at higher temperature of 60 °C to give **4b** in 79% yield with a low diastereoselectivity (1.8:1) (Scheme 4-5).



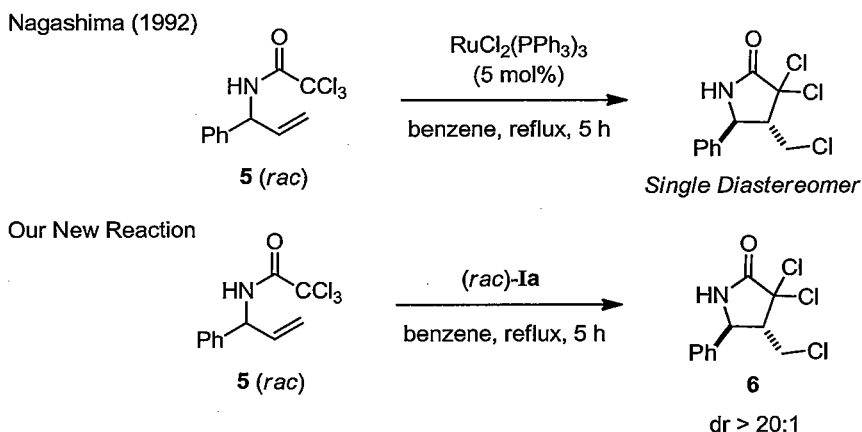
Scheme 4-4. Atom-transfer Radical Addition with Cp'**Ru** Complex (**I**)



Scheme 4-5. Atom-transfer Radical Cyclization with Cp^{*}Ru Complex (I)

An asymmetric version of ATRA promoted by a chiral Ru complex having chiral phosphine ligands has been already reported, but the enantioselectivity was less than 40% ee.¹⁰ Thus, we tried to develop a highly enantioselective ATRC using planar-chiral ruthenium complex I as a catalyst. However, in all the reactions tested here an improved enantioselectivity was not observed in comparison with the chiral Ru-phosphine complex catalyst.

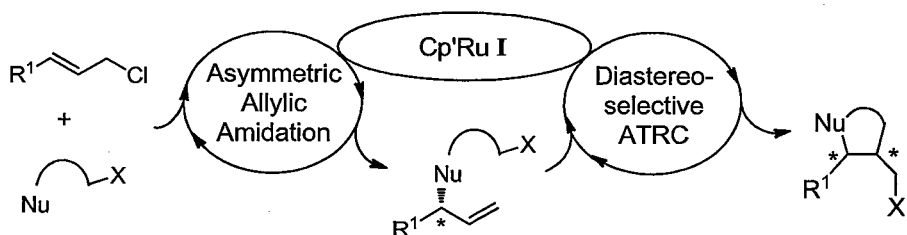
On the other hand, Nagashima reported diastereoselective ATRC reaction using a Ru catalyst and suggested that stereochemistry at the new stereogenic carbon would be controlled by the substituent on substrates.¹¹ We have applied his suggestion to our catalytic system. Thus, the reaction of *N*-1-phenylallyl-2,2,2-trichloroacetamide, which has no protecting groups on the amide nitrogen atom, in dioxane at 110 °C smoothly proceeded in a highly diastereoselective manner to give **6** in a high yield (Scheme 4-6).



Scheme 4-6. Diastereoselective Atom-transfer Radical Cyclization

Based on these experimental results, we have successfully designed an asymmetric auto-tandem reaction system. In the initial step, chiral allylic compounds would be given by

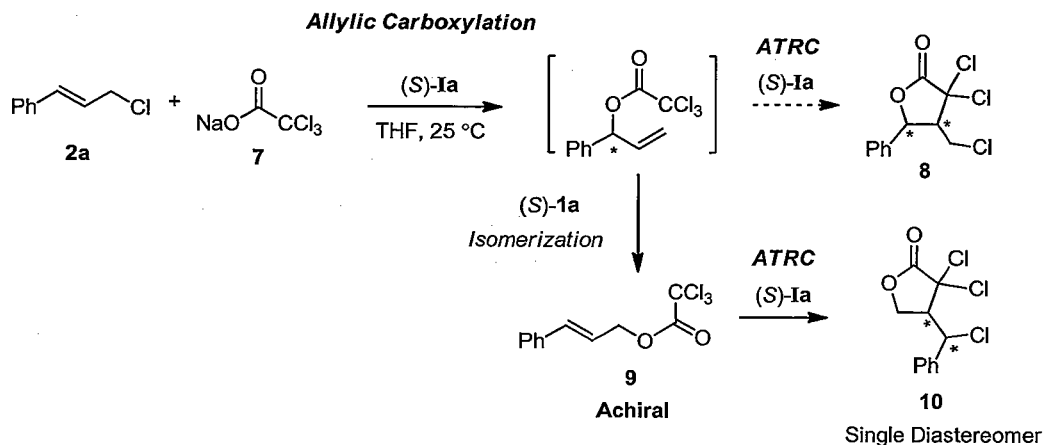
asymmetric catalysis with planar-chiral Cp*Ru complex (*S*)-I. Diastereoselective ATRC reaction would proceed in the second step to give enantiomerically enriched cyclic compounds with multi stereogenic centers, which should present the first example of asymmetric auto-tandem catalysis.



Scheme 4-7. Asymmetric Auto-tandem Catalysis by Cp*Ru Complex I

4-3 Tandem Catalysis Involving Allylic Carboxylation/ATRC

First, we tried the auto-tandem reaction combined together allylic carboxylation and ATRC reactions, in which the former was already described in Chapter 2 to give allylic esters from the reaction of allylic halides with metal carboxylates by the use of Cp*Ru complexes.^{7b} According to the results obtained from the allylic carboxylation, we treated cinnamyl chloride (**2a**) with trichloroacetic acid (**7**) in the presence of (*S*)-Ia under basic conditions, however, the reaction did not give a target cyclic compound (**8**), instead its isomer was obtained as a racemic mixture of a single diastereomers (**10**) (Scheme 4-8). This result suggested that branched allylic esters isomerized to a linear allylic ester (**9**) before being followed by ATRC, and the achiral linear allylic ester was converted to a racemic mixture of cyclic compound

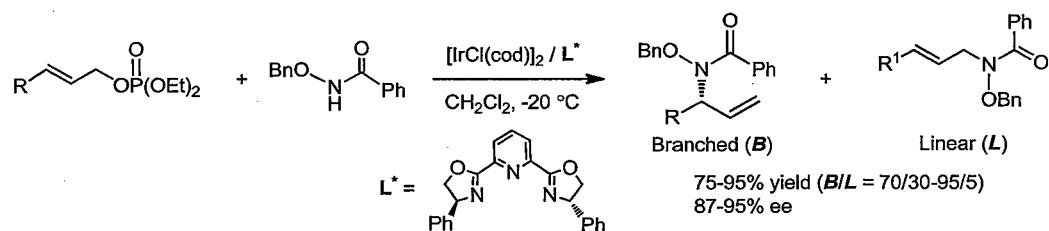


Scheme 4-8. Tandem Catalysis Involving Allylic Carboxylation/ATRC

(10) via ATRC. Therefore, control of the isomerization from the chiral branched product to the achiral linear one is essential to realize the expected asymmetric auto-tandem catalysis.

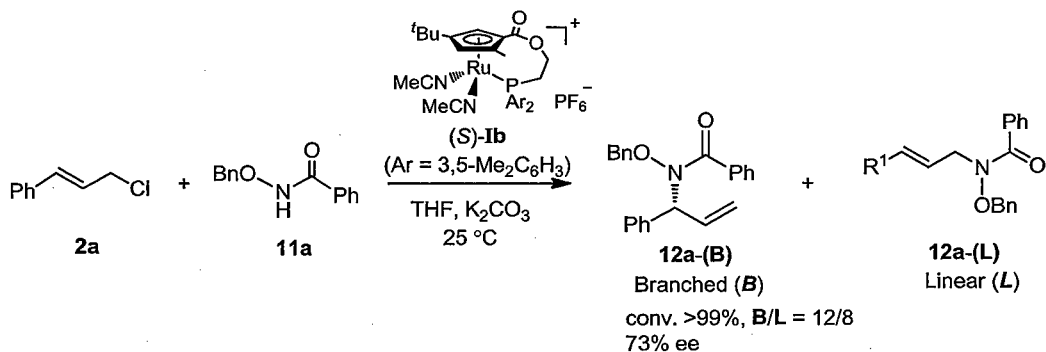
4-4 Asymmetric Allylic Amidation

Amides as a nucleophile are, in general, less reactive than carboxylic acid in allylic substitution reaction,¹²⁻¹⁴ and the resulting amides would be also less reactive than the allylic esters toward the bond-cleavage reaction caused by Cp^{*}Ru catalyst **I** which leads to the isomerization from branched to linear allylic structure.^{7b} The relatively low reactivity of amides suggested us that it would be possible to prevent isomerization of allylic derivatives by use of amides as a nucleophile reagent. Thus, we tried to extend our method to asymmetric allylic amidation. Until now, there were several reports about the asymmetric allylic amidations.¹²⁻¹⁴ Takemoto disclosed an iridium-catalyzed asymmetric allylic amidation of allylic phosphates with *N*-benzyloxyamide (Scheme 4-9).^{12a} We have also investigated the reaction of allylic amidation of allylic halides using our planar-chiral ruthenium complexes.



Scheme 4-9. Example of Asymmetric Allylic Amidation

In order to achieve an enantioselective amidation of allylic halides, we conducted a reaction of cinnamyl chloride (**2a**) with *N*-benzyloxybenzamide (**11a**) using 1 mol% of (*S*)-**1b** ($\text{Ar} = 3,5\text{-Me}_2\text{C}_6\text{H}_3$) as a catalyst in the presence of K_2CO_3 at 25°C in THF. The reaction



Scheme 4-10. Asymmetric Allylic Amidation Catalyzed by Cp^{*}Ru catalyst

proceeded with almost quantitative conversion after 12 h to produce branched and linear allylic amides in 12/8 ratio with 73% ee (Scheme 4-10). Since we confirmed the catalytic activity of the planar-chiral Ru complex for the asymmetric amidation of allylic halides, we then conducted optimization of reaction conditions in order to accomplish the enantioselective allylic amidation.

4-4-1 Optimization of Reaction Conditions

The optimization of reaction conditions for the present allylic amidation was carried out in terms of reaction temperature, reaction time, the kind of solvents, and the effect of additives. As the allylic amidation catalyzed by our Ru complexes proceeded with almost no side-reactions, the effects were evaluated on the basis of the conversion of starting substrate **2a**.

Reaction Temperature

Initially we investigated the effect of temperature for the reaction between **2a** and **11a** with the (*S*)-**Ib** catalyst in the presence of K₂CO₃ in THF for a reaction time of 12 h. Results obtained from the optimization of reaction conditions are summarized in Table 4-1. All reactions quantitatively proceeded. When the reactions were carried out at lower and higher temperatures than 25 °C (entries 2-4), the enantioselectivity was reduced in comparison with that at 25 °C. Thus, the best reaction temperature has been determined to be 25 °C.

Table 4-1. Effect of Temperature^a

entry	temp. (°C)	conv.(%) of 2a ^b	yield (%) of 12a ^e	12a-(B)/12a-(L) ^c	ee (%) of 12a ^d
1	25	>99	99	12/8	73 (<i>R</i>)
2	20	>99	99	14/6	66 (<i>R</i>)
3	15	>99	99	8/12	25 (<i>R</i>)
4	30	>99	99	15/5	72 (<i>R</i>)

^a (*S*)-**Ib** (0.003 mmol), **2a** (0.25 mmol), **11a** (0.275 mmol), K₂CO₃ (0.30 mmol) in 1.0 ml, stirred for 12 h. ^b Determined by ¹H NMR analysis. ^c Determined by ¹H NMR analysis. ^d The enantiomeric excess of the branched allylic amide. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses. ^e Isolated yield.

Effect of Base

Our previous studies have showed that the bases employed as an additive in the asymmetric allylic substitution using Cp^{*}Ru catalysts are crucial for achieving high selectivity of the product. Therefore, to improve the regio- and enantioselectivity, the effect of base was examined in the reaction between **2a** and **11a** with the (*S*)-**1b** catalyst in THF at 25 °C for a reaction time of 12 h (Table 4-2). It should be interesting to note that the selectivity was dependent on the kind of bases in the present reaction system. Changing the base from K₂CO₃ to Na₂CO₃ increased the regioselectivity (>20/1). Further screening by use of different types of bases showed KHCO₃ to be optimal. Although the reaction in the presence of KHCO₃ proceeded with quantitative conversion after 12 h to give the branched allylic amide in high regio- and enantioselectivities (>20/1, 95% ee), the products contained the branched allylic alcohol. Changing the base to NaHCO₃ caused a drastic reduction of the product yield (5%). When the bicarbonate was used as a base in the amidation reaction, branched allylic alcohol was formed as a by-product. In this case, the water, which might derive from the bicarbonate, worked as a nucleophile instead of amide to give the branched allylic alcohol.^{7c} Although use of the bicarbonates gave the hydroxylation product as a by-product, KHCO₃ may be of choice among bases tested here, because the bicarbonate accelerates the allylic amidation over the allylic hydroxylation and gave the target product (**12a**) in both high yield and high

Table 4-2. Effect of Base^a

entry	base	conv.(%) of 2a ^b	yield (%) of 12a ^c	12a-(B)/12a-(L) ^c	ee (%) of 12a ^d	yield (%) of 13a ^f
1	K ₂ CO ₃	>99	99	12/8	78 (<i>R</i>)	0
2	Na ₂ CO ₃	>99	98	>20/1	94 (<i>R</i>)	2
3	KHCO ₃	>99	75	>20/1	95 (<i>R</i>)	23
4	NaHCO ₃	5	-	>20/1	-	-

^a (*S*)-**1b** (0.003 mmol), **2a** (0.25 mmol), **11a** (0.275 mmol), KHCO₃ (0.30 mmol) in 1.0 ml, stirred at 25 °C for 12 h. ^b

Determined by ¹H NMR analysis. ^c Isolated yield. ^d Determined by ¹H NMR analysis. ^e The enantiomeric excess of the branched allylic amide. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses. ^f Isolated yield.

selectivity.

However, as described bellow, detailed experiments have revealed that the water can be completely removed from the reaction system by the use of molecular sieves as a desiccant agent (*vide infra*).

Effect of Solvent

To know the effect of solvents, we examined the reaction between **2a** and **11a** in a variety of solvents with (*S*)-**Ib** catalyst at 25 °C for a reaction time of 12 h. Hydrocarbons such as *n*-hexane and toluene are not suitable solvents for the reaction because the ruthenium catalyst showed a low solubility in hydrocarbons. The results obtained from the reactions in good solvents for the catalyst are summarized in Table 4-3. The reaction in THF gave the best result with 95% ee with 75% isolated yield of target product **12a**. Dichloromethane also gave a good result with only 5% yield of by-product **13a**, although the use of dimethylformamide resulted in a low conversion of less than 5% yield of **2a**. Thus, recommended solvent should be THF and dichloromethane.

Table 4-3. Effect of Solvent^a

entry	solvent	conv.(%) of 2a ^b	yield (%) of 12a ^c	12a-(B)/12a-(L) ^c	ee (%) of 12a ^d	yield (%) of 13a ^e
1	THF	>99	75	>20/1	95 (<i>R</i>)	23
2	CH ₂ Cl ₂	>99	90	>20/1	93 (<i>R</i>)	5
3	DMF	5>	-	-	-	-

^a (*S*)-**Ib** (0.003 mmol), **2a** (0.25 mmol), **11a** (0.275 mmol), KHCO₃ (0.30 mmol) in solvent (1.0 ml), stirred at 25 °C for 12 h. ^b Determined by ¹H NMR analysis. ^c Isolated yield. ^d Determined by ¹H NMR analysis. ^e The enantiomeric excess of the branched allylic amide. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses. ^f Isolated Yield.

Reaction Time

To investigate the effect of reaction time, the reaction between **2a** and **11a** with (*S*)-**Ib** catalyst in THF at 25 °C was conducted. The results are summarized in Table 4-4, suggesting that the reaction time gave no influence on the regio- and enantioselectivity. The reaction for 12 h completely converted the allylic chloride to the products (entry 3), and decrease in regio- and enantioselectivities was not observed at all when the reaction time was prolonged to 15 h (entry 4). The fact clearly indicates that isomerization of the product does not occur after

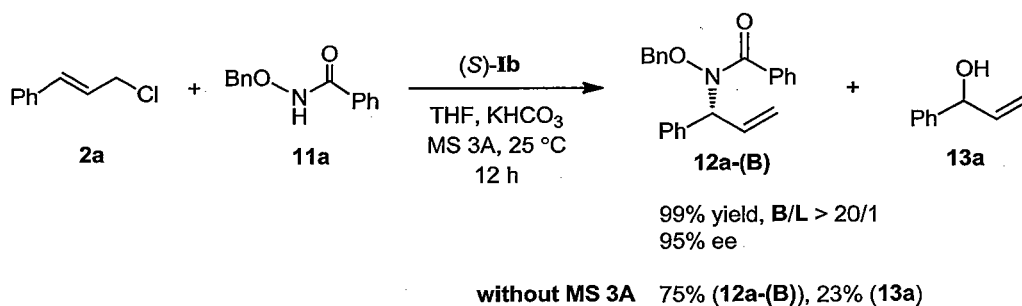
complete allylic amidation, though in the case of the allylic carboxylation an isomerization from branched allylic ester to linear one was observed (see Chapter 2).

Table 4-4. Effect of Reaction Time ^a

entry	reaction time (h)	conv. (%) of 2a ^b	yield (%) of 12a ^c	12a-(B)/12a-(L) ^d	ee (%) of 12a ^e	yield (%) of 13a ^f
1	3	30		>20/1	95 (<i>R</i>)	0
2	8	50		>20/1	93 (<i>R</i>)	0
3	12	>99	75	>20/1	95 (<i>R</i>)	23
4	15	>99	75	>20/1	95 (<i>R</i>)	23

^a (*S*)-**Ib** (0.003 mmol), **2a** (0.25 mmol), **11a** (0.275 mmol), KHCO₃ (0.30 mmol) in THF (1.0 ml), stirred at 25 °C. ^b Determined by ¹H NMR analysis. ^c Isolated yield. ^d Determined by ¹H NMR analysis. ^e The enantiomeric excess of the branched allylic amide. Determined by HPLC analysis using chiral stationary phase. Absolute configurations are indicated in parentheses. ^f Isolated Yield.

Effect of Molecular Sieves



Scheme 4-11. Asymmetric Allylic Amidation Catalyzed by (*S*)-**I** with MS 3A

Although the reaction proceeded with an almost quantitative conversion after 12 h in THF, the products include a branched allylic alcohol (**13a**). As mentioned above, KHCO₃ was used as a base in this reaction, water would be formed as a by-product, and the water should work as a nucleophile in this catalytic system to produce branched allylic alcohol **13a**. Removal of the water is, therefore, prerequisite to prevent the side reaction leading to the formation of allylic alcohols. Among of several trials the use of molecular sieves 3A (MS 3A) as a desiccant agent resulted in complete exclusion of the formation of the allylic alcohol and a quantitative formation of the branched allylic amide. Therefore, all of reactions described below have been conducted in the presence of MS 3A as desiccant agent.

From the experimental results described above, the optimal reaction conditions of the present allylic amidation have been determined as follows:

Reaction temperature, 25 °C;

Reaction time, 12 h;

Solvent, THF or dichloromethane;

Cp^{*}Ru complex catalyst, 1 mol% to a starting substrate;

Additives, KHCO₃ and MS 3A.

4-4-2. Screening of Substrates

Table 4-5 (1). Reaction of Allylic Chlorides **2** with Amides **11**

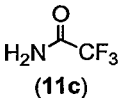
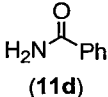
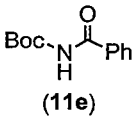
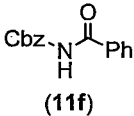
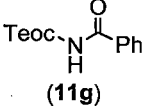
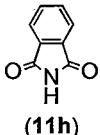
entry	R ¹	11	yield (%) of 12^b	12-(B)/12-(L) ^c	ee (%) of 12-(B) ^{d,e}
1	Ph (2a)	 (11a)	99 (12a)	>20/1	95 (<i>R</i>)
2	 (2b)	(11a)	98 (12b)	>20/1	97
3	 (2c)	(11a)	99 (12c)	>20/1	97
4	 (2d)	(11a)	85 (12d)	>20/1	93 (<i>R</i>)
5	Ph (2a)	 (11b)	85 (12e)	>20/1	97

^a Reaction conditions: (*S*)-**Ib** (0.005 mmol), **2** (0.50 mmol), **5** (0.55 mmol), KHCO₃ (0.60 mmol), THF (2.0 ml), 25 °C, 15 h. ^b Isolated yield. ^c Determined from the ¹H-NMR spectrum. ^d Determined by HPLC analysis. ^e Absolute configurations are indicated in parentheses.

Under the optimized conditions determined above, reactions of several other cinnamyl chloride derivatives **2b-d** with substituted *N*-benzyloxyamides (**11a** and **11b**) were carried out

in the presence of catalyst (*S*)-**1b**. The results are showed in Table 4-5(1), which reveals the selective formation of branched allylic amides **12b-e** with good yields and high enantioselectivities (Table 4-5(1), entries 2-5).

Table 4-5 (2). Reaction of Allylic Chlorides **2 with Amides **11****

$ \begin{array}{c} \text{R}^1\text{-CH=CH-CH}_2\text{-Cl} + \text{R}^3\text{-NH-C(=O)-R}^2 \xrightarrow[\text{MS 3A, 25 }^\circ\text{C, 12 h}]{\text{(S)-1b, THF, K}_2\text{CO}_3} \text{R}^3\text{-N(CH(R}^1\text{)-CH=CH}_2\text{)-C(=O)-R}^2 \\ \text{2a} \qquad \qquad \qquad \text{11} \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \qquad \text{12 (B)} \end{array} $					
entry	R ¹	11	yield (%) of 12 ^b	12 -(B)/ 12 -(L) ^c	ee (%) of 12 -(B) ^{d,e}
6	Ph (2a)	 (11c)	80 (12f)	>20/1	98
7	Ph (2a)	 (11d)	0 (12g)	-	-
8	Ph (2a)	 (11e)	99 (12h)	>20/1	97
9	Ph (2a)	 (11f)	90 (12i)	>20/1	97
10	Ph (2a)	 (11g)	99 (12j)	>20/1	97
11	Ph (2a)	 (11h)	99 (12k)	>20/1	96 (<i>R</i>)

^a Reaction conditions: (*S*)-**1b** (0.005 mmol), **2** (0.50 mmol), **5** (0.55 mmol), K₂CO₃ (0.60 mmol), THF (2.0 ml), 25 °C, 15 h. ^b Isolated yield. ^c Determined from the ¹H-NMR spectrum. ^d Determined by HPLC analysis. ^e Absolute configurations are indicated in parentheses.

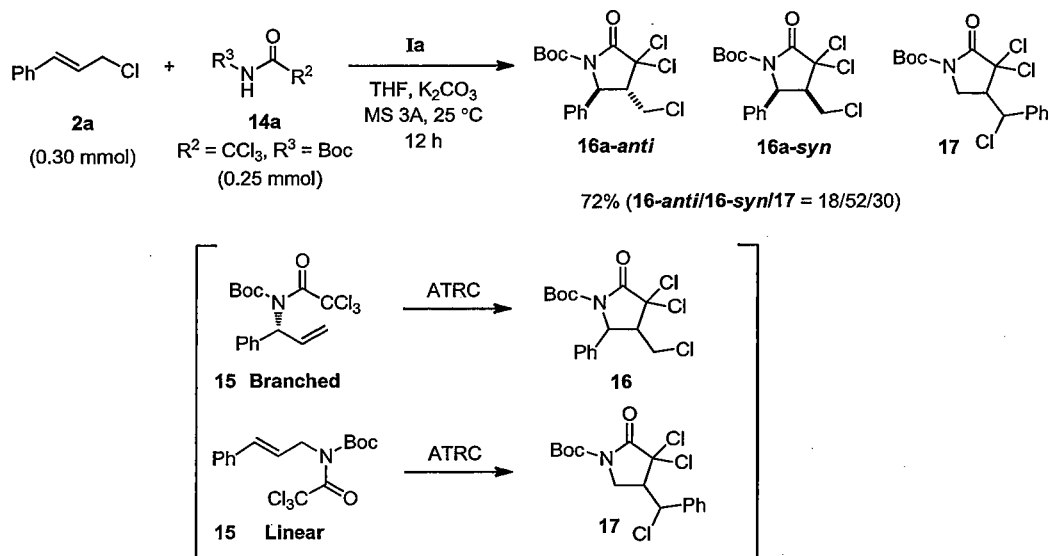
On the other hand, the reaction of **2a** with trifluoroacetamide (**11c**) did not proceed effectively under the optimal reaction conditions. When K₂CO₃ was used instead of KHCO₃ as a base, we observed the formation of desired branched allylic amide **12f** with high regio- and enantioselectivities; that is, the reaction between of **2a** and **11c** with 1 mol % of (*S*)-**1b** in

the presence of K_2CO_3 and MS 3A at 25 °C in THF afforded **12f** in 80% yield with 98% ee (Table 4-5(2), entry 6). However, benzamide (**11d**) did not react at all under the identical conditions (entry 7). These observations implied the crucial role of the acidity of amide NH in this catalysis. The pKa of benzamide **11d** is 23,¹⁵ whereas those of *N*-alkoxybenzamides lie in the range of 14.¹⁶ Amides **11e-g** protected with *tert*-butoxycarbonyl (Boc), carbobenzoxy (Cbz), or 2-(trimethylsilyl)ethoxycarbonyl (Teoc) group, whose acidity are also between 14 and 15,¹⁷ could be used as a nucleophile, producing the corresponding optically active allylic amides **12h-j** with high regio- and enantioselectivities (entries 8-10 in Table 4-5(2)). Moreover, the reaction of **2a** with phthalimide (**11h**, pKa = 14.7),¹⁸ which is known as an ammonia equivalent, also proceeded smoothly to give **12k** quantitatively (entry 11).

On the basis of these experimental results, importance of appropriate combination between the amide and base would be recognized for the allylic amidation. The combination of amides having pKa of around 14 with $KHCO_3$ as well as that of more acidic amides with K_2CO_3 seem to realize an effective and stereoselective amidation reaction, although the reason for the appropriate combination has not yet been clear.

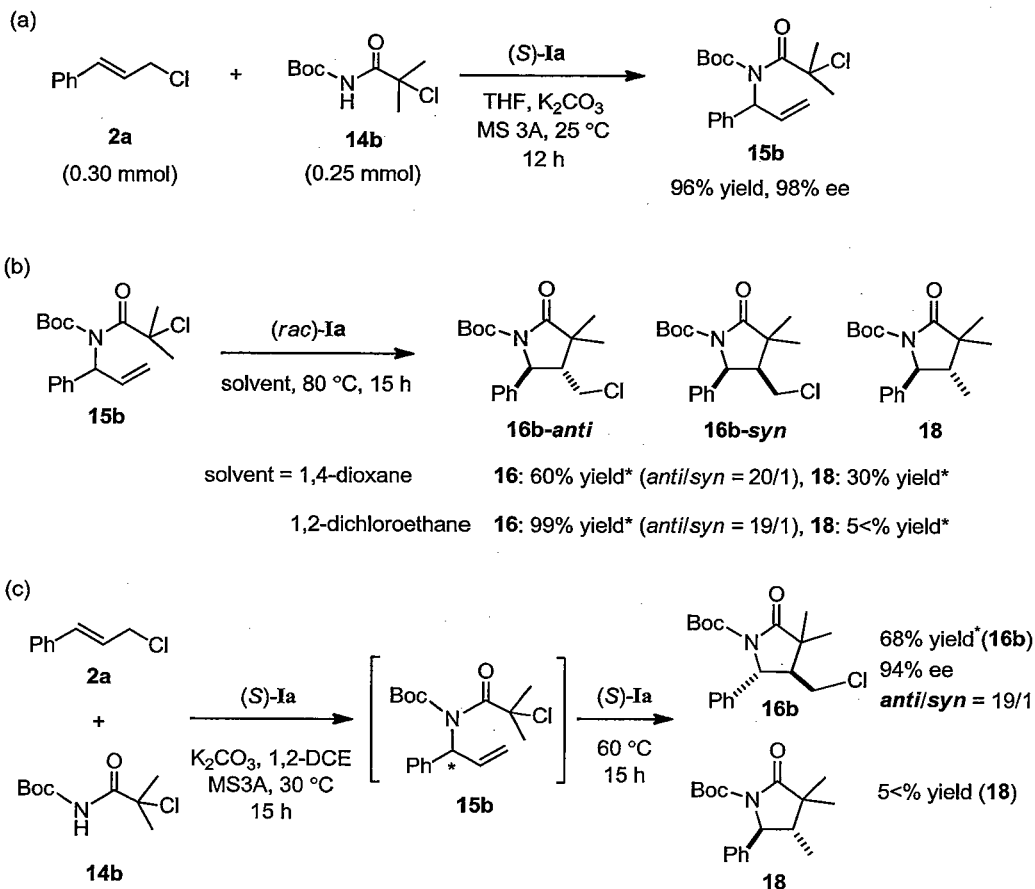
4-5 Auto Tandem Catalysis

Our Cp'Ru complex **I** turned out to be an effective catalyst for both the allylic amidation and ATRC, which suggests us that it may be possible to apply the catalyst to an auto-tandem asymmetric reaction as a catalyst. To realize asymmetric auto-tandem catalysis, we investigated a tandem reaction by use of α -trichloroamide **14a** ($R^2 = CCl_3$, $R^3 = Boc$) bearing both of amino and halo groups in a molecule as a nucleophile. As a test reaction, cinnamyl chloride **2a** was treated with **14a** in the presence of 1 mol% of (*S*)-**Ia** catalyst and K_2CO_3 in THF at 25 °C. The reaction proceeded smoothly and after 12 h gave a mixture of three kinds of γ -lactams in 72% yield (Scheme 4-12). The γ -lactams of **16a-anti** and **16a-syn** were formed with 52% yield with a rather low diastereoselectivity (*anti/syn* = 15/5). Another isomer **17** which was derived from linear allylic amide **15-(L)** was also formed with 20% yield. As γ -lactams **16a-anti** and **16a-syn** were formed by the ATRC of **15-(B)**, the reaction between **2a** and **14a** should proceed through an auto-tandem reaction consisting of allylic amidation and ATRC as expected, although the regioselectivity in the allylic amidation seems to be unsatisfied. In order to improve the regioselectivity, a less acidic amide (**14b**, $R^2 = CMe_2Cl$, $R^3 = Boc$) bearing a monochloromethyl group was used as a nucleophile (see, Section 4-4).



Scheme 4-12. Reaction of Cynamyl Chloride **2a** with Amide **14a**

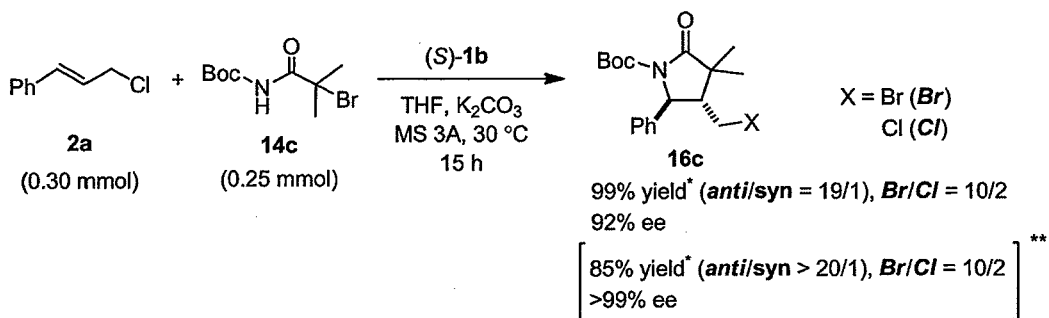
Thus, the reaction of **2a** with **14b** was carried out under the same reaction conditions as that in the case of nucleophile **14a**. The amidation reaction proceeded to give branched allylic amide **15b** in 96% yield with 98% ee (Scheme 4-13(a)), but the ATRC of **15b** was not observed probably due to a low reactivity of monochloromethyl group in **15b** toward the atom-transfer radical reaction. Indeed racemic **15b** was subjected to heating at 80 °C in 1,4-dioxane in the presence of 3 mol % of (*rac*)-**Ia** for 15 h, ATRC took place to give γ -lactam **16b** in 60% yield with high diastereoselectivity (*anti/syn* = 19/1) (Scheme 4-13(b)), but dehalogenated γ -lactam **18** was also formed in 30% yield. Changing the solvent from 1,4-dioxane to 1,2-dichloroethane suppressed the dehalogenation, and gave **16b** in a quantitative yield with a high diastereoselectivity. Thus, 1,2-dichloroethane (1,2-DCE) was used as a solvent to investigate auto-tandem catalysis. When the reaction between **2a** and **14b** with (*S*)-**Ia** catalyst in 1,2-dichloroethane was conducted at 30 °C, **15b** was formed in 96% yield with 94% ee. To achieve auto-tandem catalysis, after the allylic amidation of **2a** with **14b** the reaction mixture was warmed to 60 °C, giving target γ -lactam **16b** in 68% yield with *anti/syn* = 19/1 and 94% ee for the *anti* isomer (Scheme 4-13(c)).



*Determined by NMR analysis using 1,4-dimethoxybenzene as standard.

Scheme 4-13. Asymmetric Auto Tandem Catalysis

On the basis of the above observation, we tried to simplify the experimental procedure and employed a more reactive substrate, α -bromoamide **14c**, for the ATRC reaction. Subsequently, the auto-tandem reaction of **2a** with α -bromoamide **14c** was found to take place smoothly at 30 $^\circ\text{C}$, leading to the diastereo- and enantioselective formation of γ -lactam **16c** (*anti/syn* = 19/1, and 92% ee for the *anti* isomer) along with chloride analog **16c-Cl** (**16b**) in a combined yield of 99% with the ratio of 1/5 (Scheme 4-14). Chloride analog **16c-Cl** was confirmed by ^1H -NMR and mass spectrometry analyses (Figure 4-1). Upon recrystallization, the diastereo- and enantio-purities of product **16c** were improved to be >20/1 dr and >99% ee, respectively. Unfortunately, **16c-Cl** could not be separated from **16c-Br** even by recrystallization.



*Determined by NMR analysis using 1,4-dimethoxybenzene as standard.

** Purified by recrystallization.

Scheme 4-14. Asymmetric Auto Tandem Catalysis Using α -Bromoamide **14c**

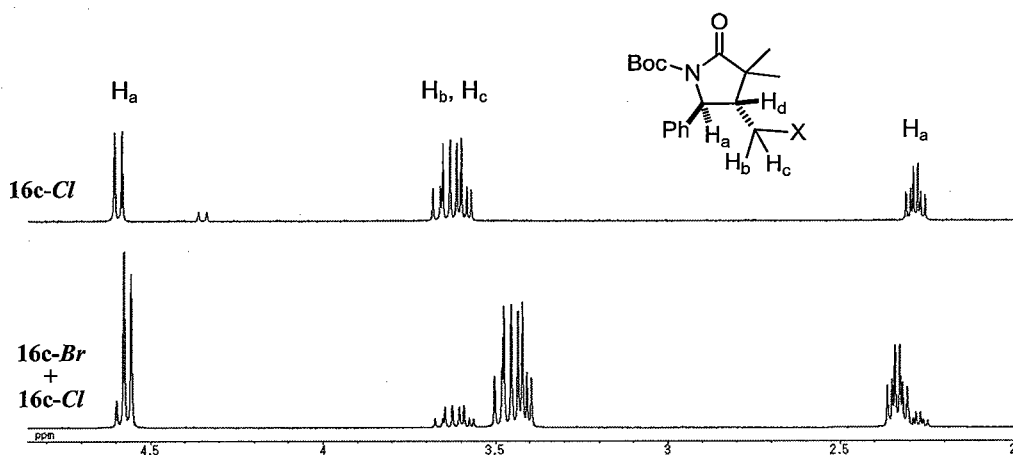






Figure 4-1. ¹H NMR Spectra

The scope of substrates for the present auto-tandem reaction is summarized in Table 4-6. In each case, the desired γ -lactam was obtained quantitatively as an inseparable mixture of the bromide and the chloride with high diastereo- and enantioselectivities. α -Bromoamide **14d** having a Cbz protecting group afforded optically active γ -lactam **16d**, whose absolute configuration was unequivocally determined to be (*R,R*) by X-ray crystallographic analysis for an enantiomerically pure sample.¹⁹ Various allylic chlorides were applicable to the auto-tandem catalysis: not only aryl-substituted γ -lactams **16e-g** but also alkyl-substituted **16h** were obtained with high diastereo- and enantioselectivities (entries 3-6).

Table 4-6. Reaction of Allylic Chlorides **2** with Amides **14**^a

entry	R ¹	R ²	yield (%) ^b	<i>anti/syn</i> ^c	<i>Br/Cl</i> ^{d,e}	ee (%) ^{f,g}
1	Ph (2a)	Boc (14c)	99 (16c) (85)	19/1 (>20/1)	5/1	92 (>99)
2	Ph (2a)	Cbz (14d)	99 (16d) (93)	19/1 (>20/1)	10/1	93 (>99) (<i>R,R</i>) ^h
3	 (2b)	Boc (14c)	99 (16e) (75)	20/1 (>20/1)	5/1	92 (96)
4	 (2c)	Boc (14c)	94 (16f) (68)	20/1 (>20/1)	10/1	94 (96)
5	 (2e)	Boc (14c)	99 (16g) (67)	11/1 (>20/1)	10/1	89 (>99)
6	 (2f)	Cbz (14d)	99 (16h) (67) ⁱ	10/1 (>20/1)	>20/1	90

^a Reaction conditions: (*S*)-**Ib** (5 μ mol), **2** (0.60 mmol), **14** (0.50 mmol), K₂CO₃ (0.50 mmol), CH₂Cl₂ (2.0 mL), 30 °C, 15 h. ^b Determined by ¹H NMR measurement, the combined isolated yield of *Br* and *Cl* in parentheses. ^c Determined from ¹H NMR spectrum of the crude product (isolated product in parentheses). ^d *Br*: X = Br, *Cl*: X = Cl. ^e Determined using a chiral stationary phase (isolated product in parentheses). ^f Absolute configuration is given in parentheses. ^g Absolute configuration determined by X-ray crystallographic analysis. ⁱ Isolated by column chromatography.

In the auto-tandem reactions, the major product, γ -lactam (**16-Br**), was always accompanied with a small amount of the chloride analog which was derived from replacement of bromine atom on **16-Br** by chlorine one coming from allylic chloride during the reaction involving the radical process of ATRC. To prevent the formation of the chloride analog, cinnamyl bromide was used instead of cinnamyl chloride, producing the selective formation of desired bromide product **16c-Br** without accompany by the chloride analog, but the enantioselectivity of product **16c** was reduced to 17% ee.

Although a small amount of the chloride analog accompanied the major product in this reaction, the mixture was easily transformed into a sole product (**19**) through a reductive

dehalogenation reaction.^{12a,b} Treatment of optically pure γ -lactam **16**, where either Br or Cl

Table 4-7. Reductive Dehalogenation of **16**^a

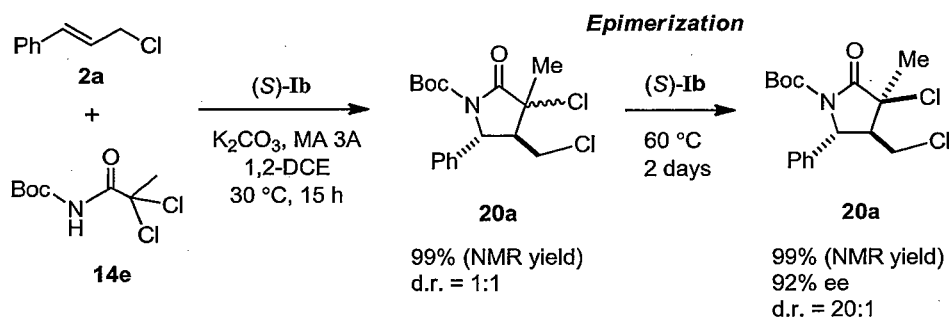
X = Br and Cl

entry	R ¹	yield (%) ^b	<i>anti/syn</i> ^c	ee (%) ^{d, e}
1	Ph (2a)	88	>20/1	>99 (<i>R,R</i>)
2	(2b)	94	>20/1	99
3	(2c)	89	>20/1	99
4	(2e)	89	>20/1	>99

^a Reaction conditions: AIBN (5 μ mol), **16** (0.50 mmol), ⁿBu₃SnH (1.50 mmol), Toluene (2.0 mL), 110 °C, 12 h. ^b Isolated yield. ^c Determined from the ¹H NMR spectrum (Crude products). ^d Determined from ¹H NMR spectrum. ^e Determined by HPLC analysis using a chiral atatory phase. Absolute configuration are indicated in parentheses.

atoms were found on the side chain, with ⁿBu₃SnH and a catalytic amount of 2,2'-azobis(isobutyronitrile) (AIBN) in toluene at 110 °C resulted in the formation of **19** in 88% yield without racemization (Table 4-7)

Finally, we examined the reactivity of α -dichloroamide **14e** in this asymmetric auto-tandem catalysis, which would produce γ -lactam with three consecutive stereogenic centers. When the reaction of **14e** with **2a** was carried out under conditions similar to those in Table 2, desired γ -lactam **20a** was obtained quantitatively (Scheme 4-15). The diastereomeric

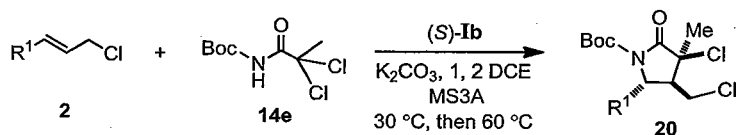


Scheme 4-15. Control of Three Stereogenic Centers in Tandem Catalysis

ratio at the carbon atom adjacent to the carbonyl group, however, was as low as 1:1. But we

have noticed that epimerization of **20a** occurs at a slightly higher temperature in the presence of **1b** to afford the thermodynamically stable diastereomer. The similar epimerization leading to the improvement of stereochemistry of reaction products has already reported in the system using a copper catalyst.²⁰ Thus, heating the reaction mixture at 60 °C for 2 days after the auto-tandem reaction resulted in increasing the diastereomeric ratio to 20:1. An X-ray crystallographic analysis of the enantio- and diastereopure sample of **20c** has established its relative and absolute configurations.¹⁹ In order to demonstrate the scope of the present auto-tandem catalysis, we conducted the reaction of several cinnamyl chloride derivatives with **14e** under the favorable conditions for the production of γ -lactam **20**, and the results obtained are listed in Table 4-8. Although the Table shows that the diastereoselectivity of thus formed γ -lactams **20** except **20a** is not so high even after the epimerization, fortunately recrystallization of the products furnished γ -lactams **20b-d** with excellent diastereo- and enantiopurities. Eventually the asymmetric auto-tandem reactions catalyzed by planar-chiral ruthenium complex **I** provides the first method for the synthesis of γ -lactams with well-controlled three consecutive stereogenic centers from allylic halides and

Table 4-8. Reaction of Allylic Chlorides **2** with Amides **1**^a



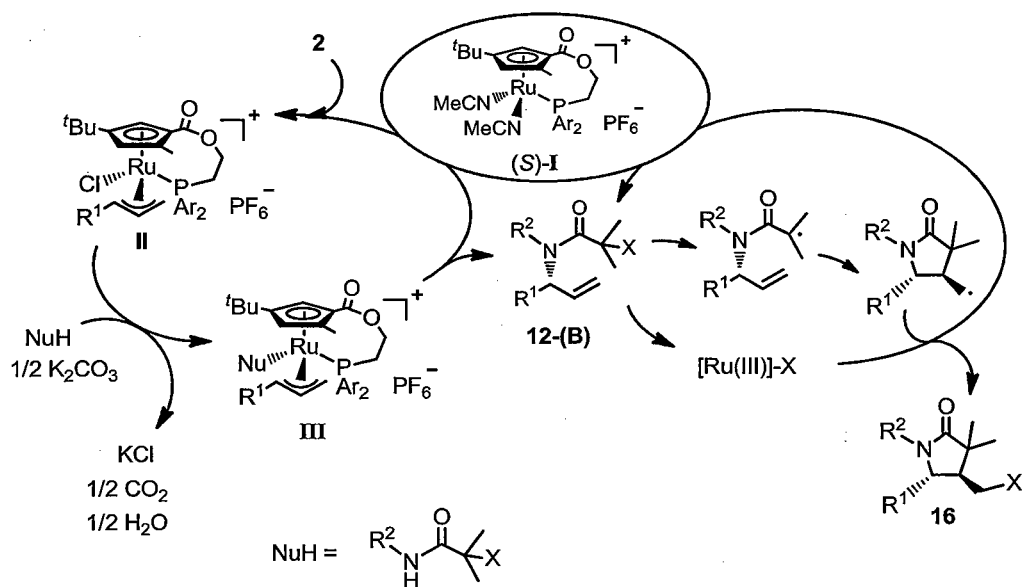
entry	R ¹	yield (%) ^b	dr ^c	ee (%) ^d
1	Ph (2a)	99 (20a) (68)	20/1 (>20/1)	92 (99)
2	Me-C ₆ H ₄ (2b)	99 (20b) (54)	6/1 (>20/1)	- ^e (92)
3	F ₃ C-C ₆ H ₄ (2c)	94 (20c) (53)	6/1 (>20/1)	92 (>99) (R,R) ^f
4	1-naphthyl (2d)	99 (20d) (66)	4/1 (>20/1)	91 (>99)

^a Reaction conditions: (S)-**Ib** (5 μ mol), **2** (0.60 mmol), **14** (0.50 mmol), K₂CO₃ (0.60 mmol), 1,2-dichloroethane (2.0 mL), 30 °C, 15 h. ^b Determined by ¹H NMR measurement, isolation yield in parentheses. ^c Diastereomeric ratio at 3-position determined from ¹H NMR spectrum of the crude product (isolated product in parentheses). ^d Determined by HPLC analysis using a chiral stationary phase (isolated product in parentheses). ^e Not determined. ^f Absolute configuration determined by X-ray crystallographic analysis.

haloacetamides.

4-6 Reaction Mechanism

A plausible reaction mechanism for the asymmetric auto-tandem catalysis is illustrated in Scheme 4-16. Oxidative addition of **2** to (*S*)-**I** forming key π -allyl intermediate **II** triggers this auto-tandem reaction. A subsequent inside attack of the amidate via Ru amidate complex **III** gives the initial product, branched allyl amide **12-(B)**.⁷ The high enantioselectivity as well as the absolute configuration of the final product would be determined at the allylic amidation stage. Thus formed allyl a C-C double bond in an intramolecular fashion. Finally, the X atom on Ru(III) complex recombines with the resulting primary radical to yield γ -lactam **16**. **12-(B)** enters into the ATRC cycle. Then, the atom transfer reaction between (*S*)-**I** and **12** furnishes Ru(III)-X intermediate and a tertiary radical species, the latter of which is reacted



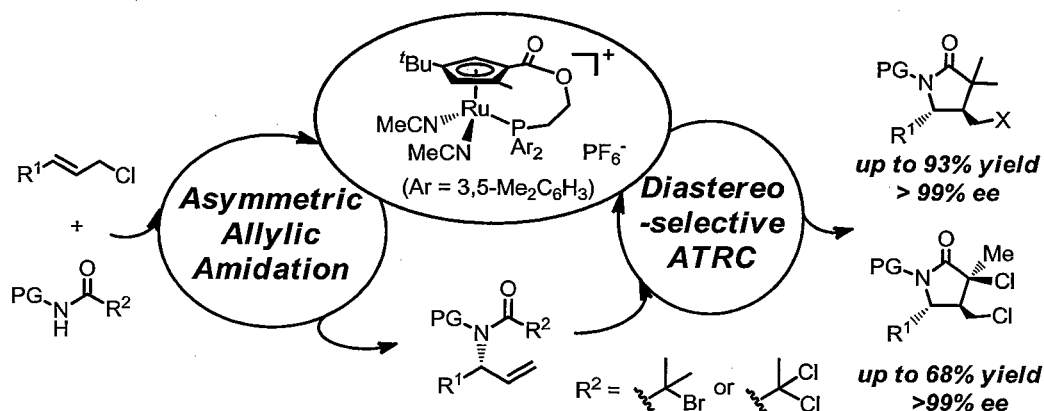
Scheme 4-16. Plausible Reaction Mechanism

4-7 Conclusions

We have developed an asymmetric auto-tandem allylic amidation/ATRC reaction catalyzed by sole planar-chiral Cp*Ru complex **I**, which proceeds in a highly regio-, diastereo-, and enantioselective manner. Optically active γ -lactams are constructed from readily available substrates in one-pot. The results exemplify that the asymmetric auto-tandem

catalysis is an efficient and environmentally benign synthetic method for useful chiral γ -lactams with well-controlled three consecutive stereogenic centers. To our best knowledge, this is the first example of asymmetric auto-tandem catalysis involving completely different reaction mechanisms.

The First Asymmetric Auto-Tandem Catalysis



4-8 Experimental Procedure

General.

All reactions were carried out under Ar atmosphere using Schlenk technique, and the workup was performed in air. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury 300, JEOL ECS400, or JEOL ECA500 spectrometers. Enantiomeric excess was obtained by HPLC analysis using Hitachi L-2130 or L-2455 equipped with DAICEL Chiralcel OJ-H, OD-H, Chiralpak AS-H, or AD-H columns. Optical rotation was measured on JASCO DIP-1000. HRMS measurements were carried out on Thermo Fisher Scientific LTQ-Orbitrap XL.

Materials.

All solvents used for reactions were passed through purification columns just before use. Planar-chiral Cp^*Ru complex **I** was prepared as reported previously.^{21,22} Cinnamyl chloride **2a** was purchased from TCI. Allylic chlorides were prepared by chlorination of the corresponding allylic alcohols with NCS/DMS.²³ All allylic chlorides were purified by distillation (**2b** and **2c**) or recrystallization from diethyl ether (**2d**) prior to use. *N*-(Benzyloxy)-benzamide (**3f**) was prepared according to the literature procedure.²⁴

tert-Butyl benzoylcarbamate (**11e**)¹⁷

The title compound was obtained in 80% yield as colorless crystals. ^1H NMR (CDCl_3 , 400 MHz): δ 7.84 (s, 1H, NH), 7.82 (d, 2H, $J = 7.1$ Hz, Ar), 7.58–7.54 (m, 1H, Ar), 7.46 (d, 2H, $J = 7.1$ Hz, Ar), 1.53 (s, 9H, CH_3). ^{13}C NMR (CDCl_3 , 101 MHz): δ 165.3, 149.7, 133.3, 132.7, 128.7, 127.5, 82.7, 27.9.

Benzyl benzoylcarbamate (11f)¹⁷

The title compound was obtained in 91% yield as colorless crystals. ¹H NMR (CDCl₃, 400 MHz): δ 8.33 (s, 1H, NH), 7.81 (d, 2H, *J* = 9.62 Hz, Ar), 7.59–7.31 (m, 8H, Ar), 5.29 (s, 2H). ¹³C NMR (CDCl₃, 101 MHz): δ 164.9, 150.9, 134.9, 132.9, 132.8, 128.7, 128.6, 127.6, 67.9. Two carbon peaks were missing due to overlapping.

2-(Trimethylsilyl)ethyl benzoylcarbamate (11g)

The title compound was obtained in 82 % yield as colorless crystals. Mp 121 °C. ¹H NMR (CDCl₃, 400 MHz): δ 8.15 (s, 1H, NH), 7.83 (d, 2H, *J* = 7.3 Hz, Ar), 7.58 (t, 1H, *J* = 7.6 Hz), 7.48 (d, 2H, *J* = 7.3 Hz, Ar), 4.35–4.31 (m, 2H, CH₂), 1.09–1.06 (m, 2H, CH₂), 0.06 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 101 MHz): δ 164.9, 151.3, 133.1, 132.9, 128.8, 127.6, 64.9, 17.5, -1.6. Anal. Calcd for C₁₃H₁₉NO₃Si: C, 58.84; H, 7.22; N, 5.28. Found: C, 58.84; H, 7.07; N, 5.36.

Synthesis of *tert*-butyl 2-chloro-2-methylpropanoylcarbamate (14b)

2-Chloro-2-methylpropanoyl chloride

To 2-hydroxy-2-methylpropanoic acid (8.0 g, 76.9 mmol) was added SOCl₂ (22.8 g, 190 mmol) and DMF (3.0 mL) at 0 °C, which was allowed to warm to 60 °C and stirred for 2 h. The reaction mixture was purified by distillation (60 torr, 45 °C) to give the titled compound as yellow oil (9.0 g, 64.3 mmol, 83%).

2-Chloro-2-methylpropanamide²⁵

To an aqueous solution of NH₃ (8.0 mL, 14 N) was added dropwise 2-chloro-2-methylpropanoyl chloride (9.0 g, 64.3 mmol) at -3 °C, which was stirred for 1 h. After addition of water, the mixture was allowed to warm to room temperature and extracted with dichloromethane. Combined organic layer was washed with aq. NaHCO₃ and dried over Na₂SO₄. Evaporation of the solvent gave the titled compound as a white crystalline solid (2.95 g, 24.4 mmol, 38%).

***tert*-Butyl-2-chloro-2-methylcarbamate (14b)**²⁶

To a solution of 2-chloro-2-methylpropanamide (1.21 g, 10.0 mmol) in 1,2-dichloroethane (20.0 mL) was added oxalyl chloride (1.36 mL, 15.0 mmol) at 0 °C, which was refluxed for 2 h. Then, a solution of *tert*-butyl alcohol (2.16 g, 20.0 mmol) in 1,2-dichloroethane (5.0 mL) was added to the reaction mixture cooled at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. After the addition of water, the reaction mixture was extracted with dichloromethane. Combined organic layer was washed with aq. NaHCO₃ and dried over Na₂SO₄. The volatiles were removed by evaporation and the residue was purified by column chromatography on silica gel (eluent: toluene to dichloromethane) to give the titled compound as a white powder. Analytically pure product was obtained by recrystallization from *n*-hexane as colorless crystals (1.43 g, 6.5 mmol, 65%). Mp 75 °C. ¹H NMR (CDCl₃, 400 MHz): 8.52 (s, 1H, NH), 1.81 (s, 6H, CH₃), 1.53 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 101 MHz): δ 169.9, 148.9, 83.1, 68.8, 30.5, 27.9. Anal. Calcd for C₉H₁₆ClNO₃: C, 48.76; H, 7.27; N, 6.32. Found: C, 48.73; H, 7.19; N, 6.30.

tert-Butyl 2-bromo-2-methylpropanovylcarbamate (14c)²⁶

According to the synthetic procedure of **3h**, the titled compound was obtained from 2-bromo-2-methylpropanamide (10.0 mmol), oxalyl chloride (15.0 mmol), and *tert*-butyl alcohol (20.0 mmol) in 65% yield as colorless crystals. Mp 108 °C. ¹H NMR (CDCl₃, 400 MHz): 8.36 (s, 1H, NH), 1.97 (s, 6H, CH₃), 1.53 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 101 MHz): δ 169.3, 149.0, 83.1, 60.8, 31.7, 27.9. Anal. Calcd for C₉H₁₆BrNO₃: C, 40.62; H, 6.06; N, 5.26. Found: C, 40.40; H, 5.86; N, 5.34.

Benzyl 2-bromo-2-methylpropanovylcarbamate (14d)²⁶

According to the synthetic procedure of **3h**, the titled compound was obtained from 2-bromo-2-methylpropanamide (10.0 mmol), oxalyl chloride (15.0 mmol), and benzyl alcohol (20.0 mmol) in 72% yield as colorless crystals. Mp 67 °C. ¹H NMR (CDCl₃, 400 MHz): 8.53 (s, 1H, NH), 7.42–7.26 (m, 5H, Ar), 5.23 (s, 2H, CH₂), 1.99 (s, 6H, CH₃). ¹³C NMR (CDCl₃, 101 MHz): δ 169.2, 150.3, 134.7, 128.8, 128.7, 128.7, 68.1, 60.4, 31.6. Anal. Calcd for C₁₂H₁₄BrNO₃: C, 48.02; H, 4.70; N, 4.67. Found: C, 48.32; H, 4.64; N, 4.59.

tert-Butyl (2,2-dichloropropanovyl)carbamate (14e)^{25,26}

According to the synthetic procedure of **3h**, the titled compound was obtained from 2,2-dichloropropanamide (7.1 mmol), oxalyl chloride (10.7 mmol), and *tert*-butyl alcohol (3.0 mL) in 94% yield as colorless crystals. Mp 75 °C. ¹H NMR (CDCl₃, 400 MHz): 8.30 (s, 1H, NH), 2.30 (s, 3H, CH₃), 1.54 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 101 MHz): δ 163.0, 148.6, 83.8, 81.4, 32.8, 27.9. Anal. Calcd for C₈H₁₃Cl₂NO₃: C, 39.69; H, 5.41; N, 5.79. Found: C, 39.66; H, 5.33; N, 5.75.

Standard Procedure for Asymmetric Allylic Amidation

To a mixture of K₂CO₃ (0.60 mmol), (*S*)-**I** (5 μmol, 1 mol%), amide (0.60 mmol), and molecular sieves 3A were added a solution of allylic chloride (0.50 mmol) in THF (2.0 mL), which was stirred for 15 h at 30 °C. After dilution with diethyl ether, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduce pressure. The residue was purified by silica gel column chromatography (eluent: *n*-hexane/diethyl ether = 10/1) to give a colorless oil.

(*R*)-*N*-(Benzyloxy)-*N*-(1-phenylallyl)benzamide (12a)²⁸

A white solid. ¹H NMR (CDCl₃, 500 MHz): δ 7.70 (d, 2H, *J* = 6.7 Hz, Ar), 7.52–7.46 (m, 3H, Ar), 7.43–7.32 (m, 5H, Ar), 7.27–7.19 (m, 3H, Ar), 6.84 (d, 2H, *J* = 7.2 Hz, Ar), 6.32 (ddd, 1H, *J* = 17.3, 10.3, 6.9 Hz, CHCH=CH₂), 6.14 (d, 1H, *J* = 6.9, CHCH=CH₂), 5.39 (d, 1H, *J* = 17.3 Hz, CHCH=CH₂), 5.38 (d, 1H, *J* = 10.3 Hz, CHCH=CH₂), 4.48 (d, 1H, *J* = 8.3 Hz, CH₂), 4.11 (d, 1H, *J* = 8.3 Hz, CH₂). ¹³C NMR (CDCl₃, 101 MHz): δ 170.3, 138.0, 134.9, 134.1, 134.0, 130.4, 129.3, 128.7, 128.5, 128.5, 128.1, 128.0, 128.0, 118.5, 78.5, 64.2. One carbon peaks were missing due to overlapping. Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL, 220 nm; minor enantiomer (*S*): *t* = 11.7 min, major enantiomer (*R*): *t* = 14.0 min, 95% ee. [α]_D²⁵ +42.7 (c 0.4, CHCl₃).

(R)-2,2,2-Trifluoro-N-(1-phenylallyl)acetamide (12f)²⁷

A colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 7.40–7.26 (m, 5H, Ar), 6.53 (br, 1H, NH), 6.03 (ddd, 1H, *J* = 17.1, 10.3, 5.5 Hz, CHCH=CH₂), 5.63 (br, 1H, CHCH=CH₂), 5.37 (ddd, 1H, *J* = 10.3, 1.7, 0.7 Hz, CHCH=CH₂), 5.29 (ddd, 1H, *J* = 17.1, 1.7, 0.7 Hz, CHCH=CH₂). ¹³C NMR (CDCl₃, 101 MHz): δ 156.3 (q, *J* = 38.4 Hz), 138.4, 135.2, 129.1, 124.5, 127.2, 117.3, 115.8 (q, *J* = 290 Hz), 55.7. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL, 220 nm; major enantiomer (*R*): *t* = 11.9 min, minor enantiomer (*S*): *t* = 13.5 min, 98% ee. [α]_D²⁵ +56.8 (c 0.4, CHCl₃).

tert-Butyl benzoyl(1-phenylallyl)carbamate (12h)

A colorless oil. ¹H NMR (CDCl₃, 300 MHz): δ 7.61–7.57 (m, 2H, Ar), 7.50–7.21 (m, 8H, Ar), 6.57 (ddd, 1H, *J* = 16.9, 10.3, 7.9 Hz, CHCH=CH₂), 6.21 (d, 1H, *J* = 7.9 Hz, CHCH=CH₂), 5.40 (dt, 1H, *J* = 16.9, 1.2 Hz, CHCH=CH₂), 5.39 (dt, 1H, *J* = 10.3, 1.2 Hz, CHCH=CH₂), 1.05 (s, 9H, 'Bu). ¹³C NMR (CDCl₃, 76 MHz): δ 172.8, 153.1, 139.7, 137.8, 135.4, 131.2, 128.2, 128.1, 127.6, 127.2, 127.1, 119.3, 83.1, 61.7, 27.3. HRMS (ESI): Calcd for C₂₁H₂₃NNaO₃ ([M+Na]⁺): *m/z* 360.1570, Found: *m/z* 360.1572. HPLC analysis: Chiralcel OJ-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL, 220 nm; minor enantiomer: *t* = 10.7 min, major enantiomer: *t* = 13.6 min, 96% ee. [α]_D²⁵ +48.5 (c 0.7, CHCl₃).

Benzyl benzoyl(1-phenylallyl)carbamate (12i)

A colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 7.57 (d, 2H, *J* = 8.4 Hz, Ar), 7.47–7.42 (m, 3H, Ar), 7.36–7.30 (m, 4H, Ar), 7.27–7.21 (m, 2H, Ar), 7.17 (t, 2H, *J* = 7.1 Hz, Ar), 6.75 (d, 2H, *J* = 7.1 Hz, Ar), 6.56 (ddd, 1H, *J* = 17.1, 10.3, 7.8 Hz, CHCH=CH₂), 6.20 (d, 1H, *J* = 7.8 Hz, CHCH=CH₂), 5.40 (dt, 1H, *J* = 17.1, 1.1 Hz, CHCH=CH₂), 5.38 (dt, 1H, *J* = 10.3, 1.1 Hz, CHCH=CH₂), 4.86 (d, 1H, *J* = 12.1, CH₂), 4.84 (d, 1H, *J* = 12.1 Hz, CH₂). ¹³C NMR (CDCl₃, 101 MHz): δ 172.4, 154.6, 139.2, 137.0, 135.1, 134.2, 131.7, 128.4, 128.3, 128.2, 127.7, 127.4, 127.2, 119.7, 68.6, 68.5, 62.4. One carbon peak was missing due to overlapping. HRMS (ESI): Calcd for C₂₄H₂₁NNa O₃ ([M+Na]⁺): *m/z* 394.1414, Found: *m/z* 394.1417. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL, 220 nm; major enantiomer: *t* = 10.3 min, minor enantiomer: *t* = 12.7 min, 96% ee. [α]_D²⁵ +42.7 (c 0.4, CHCl₃).

2-(Trimethylsilyl)ethyl benzoyl(1-phenylallyl)-carbamate (12j)

A colorless oil. ¹H NMR (CDCl₃, 400 MHz): δ 7.86–7.83 (m, 2H, Ar), 7.76–7.57 (m, 7H, Ar), 7.53–7.49 (m, 1H, Ar), 6.85 (ddd, 1H, *J* = 16.9, 10.3, 7.8 Hz, CHCH=CH₂), 6.47 (d, 1H, *J* = 7.8 Hz, CHCH=CH₂), 5.67 (dt, 1H, *J* = 16.9, 1.1 Hz, CHCH=CH₂), 5.66 (dt, 1H, *J* = 10.3, 1.1 Hz, CHCH=CH₂), 4.20–4.08 (m, 2H, CH₂), 0.70–0.64 (m, 2H, CH₂), 0.15 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 101 MHz): δ 172.5, 154.9, 139.4, 137.3, 135.2, 131.4, 128.3, 128.2, 127.5, 127.3, 127.2, 119.4, 65.3, 62.1, 62.0, 16.5. HRMS (ESI): Calcd for C₂₂H₂₇NNaO₃Si ([M+Na]⁺): *m/z* 404.1652, Found: *m/z* 404.1660. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL, 220 nm; major enantiomer: *t* = 4.9 min, minor enantiomer: *t* = 5.4 min, 96% ee. [α]_D²⁵ +40.4 (c 0.5, CHCl₃).

(R)-2-(1-Phenylallyl)isoindoline-1,3-dione (12k)²⁹

¹H NMR (CDCl₃, 400 MHz): δ 7.83 (dd, 2H, $J = 5.4, 3.2$ Hz, Ar), 7.70 (dd, 2H, $J = 5.4, 3.2$ Hz, Ar), 7.46–7.44 (m, 2H, Ar), 7.35–7.25 (m, 3H, Ar), 6.65 (ddd, 1H, $J = 17.2, 10.3, 6.9$ Hz, CHCH=CH₂), 5.96 (d, 1H, $J = 6.9$ Hz, CHCH=CH₂), 5.37 (dt, 1H, $J = 10.3, 1.1$ Hz, CHCH=CH₂), 5.35 (dt, 1H, $J = 17.2, 1.1$ Hz, CHCH=CH₂). ¹³C NMR (CDCl₃, 101 MHz): δ 167.7, 138.4, 134.1, 134.0, 131.9, 128.5, 127.7, 127.7, 123.3, 119.0, 56.8. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 95/5 (v/v), 1.0 mL, 220 nm; major enantiomer (*R*): $t = 8.6$ min, minor enantiomer (*S*): $t = 10.4$ min, 96% ee. $[\alpha]_D^{25} +36.0$ (*c* 1.2, CHCl₃).

tert-Butyl (2-chloro-2-methylpropanoyl)(1-phenylallyl)carbamate (15b)

A colorless oil. ¹H NMR (CDCl₃, 300 MHz): δ 7.37–7.21 (m, 5H, Ar), 6.36 (ddd, 1H, $J = 17.3, 10.0, 7.6$ Hz, CHCH=CH₂), 6.00 (d, 1H, $J = 7.6$ Hz, CHCH=CH₂), 5.37 (dt, 1H, $J = 17.3, 1.2$ Hz, CHCH=CH₂), 5.36 (dt, 1H, $J = 10.0, 1.2$ Hz, CHCH=CH₂), 1.93 (s, 3H, CH₃), 1.75 (s, 3H, CH₃), 1.29 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 101 MHz): δ 177.9, 152.8, 139.2, 134.9, 128.2, 127.4, 127.3, 119.1, 83.6, 70.2, 62.9, 32.9, 31.6, 27.5. HRMS (ESI): Calcd for C₁₈H₂₄ClNNaO₃ ([M+Na]⁺): m/z 360.1337, Found: m/z 360.1342. HPLC analysis: Chiralpak AD-H column, *n*-hexane/*i*-PrOH = 99.5/0.5 (v/v), 1.0 mL, 220 nm; major enantiomer: $t = 11.2$ min, minor enantiomer: $t = 12.7$ min, 98% ee. $[\alpha]_D^{25} +68.7$ (*c* 0.5, CHCl₃).

Standard Procedure for Auto Tandem Reaction

To a mixture of K₂CO₃ (0.60 mmol), (*S*)-1 (5 μ mol, 1 mol%), amide (0.60 mmol), and molecular sieves 3A was added a solution of allylic chloride (0.50 mmol) in THF (2.0 mL), which was stirred for 15 h at 30 °C. After dilution with diethyl ether, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduce pressure. The residue was purified by silica gel column chromatography (eluent: toluene to *n*-hexane/diethyl ether = 7/3) and recrystallization from *n*-hexane to give a colorless crystal.

tert-Butyl 4-(chloromethyl)-3,3-dimethyl-2-oxo-5-phenylpyrrolidine-1-carboxylate (16b)

Colorless crystals. Recrystallization from *n*-hexane. Mp 150 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.39–7.24 (m, 5H, Ar), 4.59 (d, 1H, $J = 8.5$ Hz, CH), 3.65 (dd, 1H, $J = 11.6, 8.6$ Hz, CH₂), 3.59 (dd, 1H, $J = 11.6, 5.1$ Hz, CH₂), 2.28 (ddd, 1H, $J = 8.6, 8.5, 5.1$ Hz, CH), 1.38 (s, 3H, CH₃), 1.26 (s, 3H, CH₃), 1.19 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 101 MHz): δ 178.5, 149.2, 141.0, 128.8, 128.0, 126.0, 83.3, 62.6, 53.8, 44.6, 41.2, 27.5, 25.6, 19.6. HRMS (ESI): Calcd for C₁₈H₂₄ClNNaO₃ ([M+Na]⁺): m/z 360.1337, Found: m/z 360.1344. HPLC analysis: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 95/5 (v/v), 1.0 mL, 220 nm; major enantiomer: $t = 9.7$ min, minor enantiomer: $t = 19.0$ min, >99% ee. $[\alpha]_D^{25} +30.8$ (*c* 1.2, CHCl₃).

tert-Butyl 4-(bromomethyl)-3,3-dimethyl-2-oxo-5-phenylpyrrolidine-1-carboxylate (16c)

Colorless crystals. Recrystallization from *n*-hexane. Mp 156 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.39–7.25 (m, 5H, Ar), 4.57 (d, $J = 8.5$ Hz, 1H, CH), 3.48 (dd, 1H, $J = 10.8, 8.7$ Hz, CH₂), 3.42 (dd, 1H, $J = 10.8, 5.3$ Hz, CH), 2.33 (ddd, 1H, $J = 8.7, 8.5, 5.3$ Hz, CH), 1.40 (s, 3H, CH₃), 1.26 (s, 3H, CH₃), 1.19 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 101 MHz): δ 178.5, 149.1, 140.9, 128.8, 128.0, 126.0, 83.2, 63.8, 53.5, 44.9, 28.5, 27.5, 25.6, 19.4.

HRMS (ESI): Calcd for $C_{18}H_{24}BrNNaO_3$ ($[M+Na]^+$): m/z 404.0832, Found: m/z 404.0839. HPLC analysis: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 95/5 (v/v), 0.5 mL, 220 nm; major enantiomer: $t = 13.9$ min, minor enantiomer: $t = 29.2$ min, >99% ee. $[\alpha]_D^{25} +19.6$ (c 0.1, $CHCl_3$).

(4*R*,5*R*)-Benzyl 4-(bromomethyl)-3,3-dimethyl-2-oxo-5-phenylpyrrolidine-1-carboxylate (16d)

A colorless crystal. Recrystallization from *n*-hexane. Mp 125 °C. 1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.26 (m, 8H, Ar), 7.08–7.06 (m, 2H, Ar), 5.09 (d, 1H, $J = 12.2$ Hz, CH_2), 5.06 (d, 1H, $J = 12.2$ Hz, CH_2), 4.70 (d, 1H, $J = 8.0$ Hz, CH), 3.48 (dd, 1H, $J = 10.8, 8.5$ Hz, CH_2), 3.40 (dd, 1H, $J = 10.8, 5.5$ Hz, CH_2), 2.38 (ddd, 1H, $J = 8.5, 8.0, 5.5$ Hz, CH), 1.39 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 178.2, 150.9, 140.1, 134.7, 129.0, 128.4, 128.2, 128.1, 128.0, 125.9, 68.3, 63.5, 53.5, 45.1, 28.8, 25.8, 19.5. HRMS (ESI): Calcd for $C_{21}H_{22}BrNNaO_3$ ($[M+Na]^+$): m/z 438.0675, Found: m/z 438.0681. HPLC analysis: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 95/5 (v/v), 1.0 mL, 220 nm; minor enantiomer: $t = 43.7$ min, major enantiomer: $t = 49.7$ min, >99% ee. $[\alpha]_D^{25} +11.4$ (c 0.3, $CHCl_3$).

(4*R*,5*R*)-Benzyl 4-(chloromethyl)-3,3-dimethyl-2-oxo-5-phenylpyrrolidine-1-carboxylate

1H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.26 (m, 8H, Ar), 7.08–7.06 (m, 2H, Ar), 5.09 (d, 1H, $J = 12.2$ Hz, CH_2), 5.06 (d, 1H, $J = 12.2$ Hz, CH_2), 4.71 (d, 1H, $J = 8.0$ Hz, CH), 3.64 (dd, 1H, $J = 11.5, 8.3$ Hz, CH_2), 3.56 (dd, 1H, $J = 11.5, 5.5$ Hz, CH_2), 2.31 (ddd, 1H, $J = 8.3, 8.0, 5.5$ Hz, CH), 1.39 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). HRMS (ESI): Calcd for $C_{21}H_{22}ClNNaO_3$ ($[M+Na]^+$): m/z 394.1180, Found: m/z 438.0681.

tert-Butyl 4-(bromomethyl)-3,3-dimethyl-2-oxo-5-(p-tolyl)pyrrolidine-1-carboxylate (16e)

Colorless crystals. Recrystallization from *n*-hexane. Mp 132 °C. 1H NMR ($CDCl_3$, 400 MHz): δ 7.18–7.12 (m, 4H, Ar), 4.53 (d, 1H, $J = 8.5$ Hz, CH_2), 3.46 (dd, 1H, $J = 10.8, 9.0$ Hz, CH_2), 3.40 (dd, 1H, $J = 10.8, 5.3$ Hz, CH_2), 2.36 (s, 3H, CH_3), 2.31 (ddd, 1H, $J = 9.0, 8.5, 5.3$ Hz, CH), 1.39 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.21 (s, 9H, CH_3). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 179.9, 149.6, 138.4, 137.2, 129.1, 125.9, 82.5, 66.1, 47.6, 44.5, 27.5, 23.0, 21.0, 19.1, 9.8. HRMS (ESI): Calcd for $C_{19}H_{26}BrNNaO_3$ ($[M+Na]^+$): m/z 418.0988, Found: m/z 418.0992. HPLC analysis: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 95/5 (v/v), 1.0 mL, 220 nm; major enantiomer: $t = 8.3$ min, minor enantiomer: $t = 14.3$ min, 96% ee. $[\alpha]_D^{25} +21.4$ (c 0.5, $CHCl_3$).

tert-Butyl 4-(chloromethyl)-3,3-dimethyl-2-oxo-5-(p-tolyl)pyrrolidine-1-carboxylate

1H NMR ($CDCl_3$, 400 MHz): δ 7.18–7.12 (m, 4H, Ar), 4.54 (d, 1H, $J = 7.8$ Hz, CH), 3.46 (dd, 1H, $J = 11.5, 8.7$ Hz, CH_2), 3.40 (dd, 1H, $J = 11.5, 5.3$ Hz, CH_2), 2.36 (s, 3H, CH_3), 2.25 (ddd, 1H, $J = 8.7, 7.8, 5.3$ Hz, CH), 1.38 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.21 (s, 9H, CH_3). HRMS (ESI): Calcd for $C_{19}H_{26}BrNNaO_3$ ($[M+Na]^+$): m/z 374.1493, Found: m/z 374.1497.

tert-Butyl 4-(bromomethyl)-3,3-dimethyl-2-oxo-5-(4-(trifluoromethyl)-phenyl)-pyrrolidine-1-carboxylate (16f)

Colorless crystals. Recrystallization from *n*-hexane. Mp 182 °C. 1H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, 2H, $J = 8.0$ Hz, Ar), 7.43 (d, 2H, $J = 8.0$ Hz, Ar), 4.73 (d, 1H, $J = 7.8$ Hz, CH_2), 3.50 (dd, 1H, $J = 10.8, 8.0$ Hz,

CH₂), 3.40 (dd, 1H, J = 10.8, 5.7 Hz, CH₂), 2.31 (ddd, 1H, J = 8.0, 7.8, 5.7 Hz, CH), 1.37 (s, 3H, CH₃), 1.25 (s, 3H, CH₃), 1.25 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 101 MHz): δ 178.0, 149.1, 145.2, 130.4 (q, J = 32.6 Hz), 126.4, 125.8, 123.9 (q, J = 272.2), 83.8, 62.3, 53.5, 45.2, 28.6, 27.6, 25.7, 19.7. HRMS (ESI): Calcd for C₁₉H₂₃Br₃FNNaO₃ ([M+Na]⁺): m/z 472.0706, Found: m/z 472.0713. HPLC analysis: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 95/5 (v/v), 1.0 mL, 220 nm; minor enantiomer: t = 7.2 min, minor enantiomer: t = 14.4 min, 96% ee. $[\alpha]_D^{25}$ +16.5 (c 0.3, CHCl₃).

tert-Butyl 4-(chloromethyl)-3,3-dimethyl-2-oxo-5-(4-(trifluoromethyl)phenyl)pyrrolidine-1-carboxylate

¹H NMR (CDCl₃, 400 MHz): δ 7.65 (d, 2H, J = 8.0 Hz, Ar), 7.43 (d, 2H, J = 8.0 Hz, Ar), 4.75 (d, 1H, J = 7.8 Hz, CH₂), 3.67 (dd, 1H, J = 11.0, 7.8 Hz, CH₂), 3.40 (dd, 1H, J = 11.0, 5.7 Hz, CH₂), 2.25 (ddd, 1H, J = 7.8, 7.8, 5.7 Hz, CH), 1.36 (s, 3H, CH₃), 1.26 (s, 3H, CH₃), 1.26 (s, 9H, CH₃). HRMS (ESI): Calcd for C₁₉H₂₃BrF₃NNaO₃ ([M+Na]⁺): m/z 428.1211, Found: m/z 428.1218.

tert-Butyl 4-(bromomethyl)-3,3-dimethyl-5-(naphthalen-2-yl)-2-oxopyrrolidine-1-carboxylate (16g)

Colorless crystals. Recrystallization from *n*-hexane. Mp 169 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.89–7.81 (m, 3H, Ar), 7.72 (s, 1H, Ar), 7.53–7.49 (m, 2H, Ar), 7.40 (dd, 1H, J = 8.5, 1.8 Hz, Ar), 4.77 (d, 1H, J = 8.5 Hz, CH), 3.52 (dd, 1H, J = 10.8, 8.4 Hz, CH₂), 3.45 (dd, 1H, J = 10.8, 5.3 Hz, CH₂), 2.43 (ddd, 1H, J = 8.5, 8.4, 5.3 Hz, CH), 1.42 (s, 3H, CH₃), 1.29 (s, 3H, CH₃), 1.14 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 101 MHz): 178.6, 149.2, 138.1, 133.1, 133.0, 129.0, 127.8, 127.7, 126.7, 126.3, 125.3, 123.4, 83.4, 63.9, 53.3, 45.1, 28.7, 27.5, 25.7, 19.5. HRMS (ESI): Calcd for C₂₂H₂₆BrNNaO₃ ([M+Na]⁺): m/z 454.0995, Found: m/z 454.0998. HPLC analysis: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 95/5 (v/v), 1.0 mL, 220 nm; major enantiomer: t = 11.9 min, minor enantiomer: t = 26.8 min, >99% ee. $[\alpha]_D^{25}$ +26.6 (c 0.5, CHCl₃).

tert-Butyl 4-(chloromethyl)-3,3-dimethyl-5-(naphthalen-2-yl)-2-oxopyrrolidine-1-carboxylate.

¹H NMR (CDCl₃, 400 MHz): δ 7.89–7.81 (m, 3H, Ar), 7.71 (s, 1H, Ar), 7.53–7.49 (m, 2H, Ar), 7.39 (dd, 1H, J = 8.5, 1.8 Hz, Ar), 4.79 (d, 1H, J = 8.7 Hz, CH), 3.70 (dd, 1H, J = 11.6, 8.3 Hz, CH₂), 3.62 (dd, 1H, J = 11.6, 5.3 Hz, CH₂), 2.37 (ddd, 1H, J = 8.7, 8.3, 5.3 Hz, CH), 1.40 (s, 3H, CH₃), 1.24 (s, 3H, CH₃), 1.14 (s, 9H, CH₃). HRMS (ESI): Calcd for C₂₂H₂₆BrNNaO₃ ([M+Na]⁺): m/z 410.1493, Found: m/z 410.1501.

Benzyl 4-(bromomethyl)-5-cyclohexyl-3,3-dimethyl-2-oxopyrrolidine-1-carboxylate (16h)

A pale yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 7.45–7.29 (m, 5H, Ar), 5.34 (d, 1H, J = 12.6 Hz, CH₂), 5.30 (d, 1H, J = 12.6 Hz, CH₂), 3.75 (dd, 1H, J = 5.6, 5.6 Hz, CH), 3.45 (dd, 1H, J = 10.6, 8.5 Hz, CH₂), 3.37 (dd, 1H, J = 10.6, 5.3 Hz, CH₂), 2.31 (ddd, 1H, J = 8.5, 5.6, 5.6 Hz, CH), 2.12–1.53 (m, 6H, CH₂), 1.36 (s, 3H, CH₃), 1.26 (s, 3H, CH₃), 1.26–1.04 (m, 5H, CH₂). ¹³C NMR (CDCl₃, 126 MHz): δ 178.4, 141.9, 135.2, 128.6, 128.3, 128.0, 68.3, 63.8, 45.0, 44.6, 41.1, 32.6, 29.3, 27.3, 27.2, 26.4, 26.2, 25.9, 21.0. HR-MS (ESI): Calcd for C₂₁H₂₈BrNNaO₃ ([M+Na]⁺): m/z 444.1145, Found: m/z 444.1151. HPLC analysis: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 95/5 (v/v), 1.0 mL, 220 nm; minor enantiomer: t = 16.3 min, major enantiomer: t = 20.9 min, 91% ee. $[\alpha]_D^{25}$ +11.4 (c 0.3, CHCl₃).

Procedure for Reductive Dehalogenation of 16^{30,31}

To a mixture of **16** (0.18 mmol) and molecular sieves 3A in toluene (1.0 mL) was added a solution of tributyltin hydride (0.60 mmol in toluene (0.5 mL)) and AIBN (9 μ mol, 5 mol %), which was stirred for 15 h at 110 °C. After dilution with diethyl ether, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was Purification by column chromatography (10% w/w anhydrous K₂CO₃-silica; eluent: 10% diethyl ether in petroleum ether) afforded a white crystalline solid (88%).

tert-Butyl 3,3,4-trimethyl-2-oxo-5-phenylpyrrolidine-1-carboxylate (19a).

A white solid. Mp 132 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.37–7.22 (m, 5H, Ar), 4.34 (d, 1H, J = 9.5 Hz, CH), 1.83 (dq, 1H, J = 9.5, 6.9 Hz, 1H), 1.21 (s, 3H, CH₃), 1.15 (s, 9H, CH₃), 1.10 (s, 3H, CH₃), 0.94 (d, 3H, J = 6.9 Hz, CH₃). ¹³C NMR (CDCl₃, 101 MHz): δ 179.9, 149.5, 141.5, 128.5, 127.5, 126.0, 82.6, 66.3, 47.5, 44.5, 27.5, 23.0, 19.1, 9.8. HRMS (ESI): Calcd for C₁₈H₂₅NNaO₃ ([M+Na]⁺): m/z 326.1727, Found: m/z 326.1731. HPLC analysis: Chiralpak AS-H column, *n*-hexane/*i*-PrOH = 95/5 (v/v), 1.0 mL, 220 nm; major enantiomer: t = 13.9 min, minor enantiomer: t = 29.2 min, >99% ee. [α]_D²⁵ +39.4 (*c* 0.3, CHCl₃).

Standard Procedure for Auto Tandem Reaction

To a mixture of K₂CO₃ (0.60 mmol), (*S*)-**I** (5 μ mol, 1 mol%), amide (0.60 mmol), and molecular sieves 3A was added a solution of allylic chloride (0.50 mmol) in THF (2.0 mL), which was stirred for 15 h at 30 °C. The reaction mixture was warmed to 60 °C and stirred at that temperature for 2 days. After dilution with diethyl ether, the reaction mixture was filtered through Celite and the filtrate was concentrated under reduce pressure. The residue was purified by silica gel column chromatography (eluent: toluene to *n*-hexane/diethyl ether = 7/3) and recrystallization from *n*-hexane to give the desired product.

tert-Butyl 3-chloro-4-(chloromethyl)-3-methyl-2-oxo-5-phenylpyrrolidine-1-carboxylate (20a)

Colorless crystals. Recrystallization from *n*-hexane. Mp 121 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.42–7.34 (m, 3H, Ar), 7.26–7.23 (m, 2H, Ar), 4.51 (d, 1H, J = 9.2 Hz, CH), 3.97 (dd, 1H, J = 11.6, 9.4 Hz, CH₂), 3.59 (dd, 1H, J = 11.6, 4.1 Hz, CH₂), 2.41 (ddd, 1H, J = 9.4, 9.2, 4.1 Hz, CH), 1.97 (s, 3H, CH₃), 1.17 (s, 9H, 'Bu). ¹³C NMR (CDCl₃, 101 MHz): δ 170.3, 148.6, 138.8, 129.1, 128.7, 126.4, 84.1, 69.1, 62.9, 55.6, 39.9, 27.4, 25.6. Anal. Calcd for C₁₇H₂₁Cl₂NO₃: C, 56.99; H, 5.91; N, 3.91. Found: C, 56.93; H, 5.67; N, 3.91. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL, 220 nm; major enantiomer: t = 15.1 min, minor enantiomer: t = 22.7 min, 99% ee. [α]_D²⁵ +20.5 (*c* 0.3, CHCl₃).

tert-Butyl 3-chloro-4-(chloromethyl)-3-methyl-2-oxo-5-(p-tolyl)pyrrolidine-1-carboxylate (20b)

A pale yellow solid. Mp 96 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.20 (d, 2H, J = 8.0 Hz, Ar), 7.13 (d, 2H, J = 8.0 Hz, Ar), 4.48 (d, 1H, J = 9.2 Hz, CH), 3.96 (dd, 1H, J = 11.6, 9.5 Hz, CH), 3.58 (dd, 1H, J = 11.6, 3.9 Hz, CH), 2.37 (ddd, 1H, J = 9.5, 9.2, 4.1 Hz, CH), 2.37 (s, 3H, CH₃), 1.97 (s, 3H, CH₃), 1.19 (s, 9H, CH₃). ¹³C NMR (CDCl₃, 126 MHz): δ 170.2, 128.6, 138.5, 135.6, 129.6, 126.2, 83.9, 69.2, 62.6, 55.6, 39.9, 27.5, 25.6, 21.1. HRMS (ESI): Calcd for C₁₈H₂₃Cl₂NNaO₃ ([M+Na]⁺): m/z 394.0947, Found: m/z 394.0954. HPLC analysis:

Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 95/5 (v/v), 1.0 mL, 220 nm; major enantiomer: *t* = 6.6 min, minor enantiomer: *t* = 8.1 min, 92% ee. $[\alpha]_D^{25} +13.6$ (*c* 0.2, CHCl₃).

tert-Butyl 3-chloro-4-(chloromethyl)-3-methyl-2-oxo-5-(4-(trifluoromethyl)phenyl)pyrrolidine-1-carboxylate (20c)

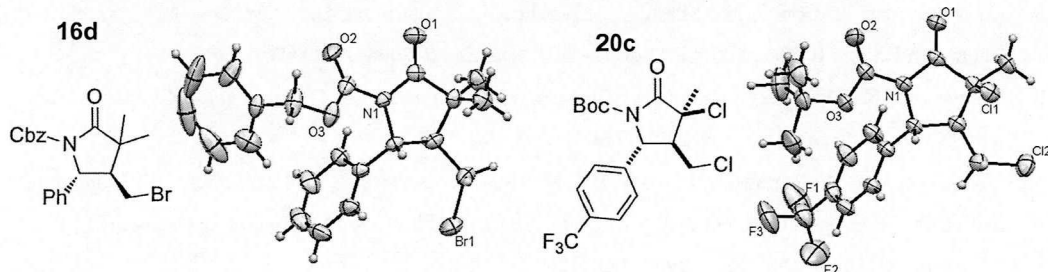
Colorless crystals. Recrystallization from methanol. Mp 163 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.68 (d, 2H, *J* = 8.2 Hz, Ar), 7.41 (d, 2H, *J* = 8.2 Hz, Ar), 4.64 (d, 1H, *J* = 9.1 Hz, CH), 3.97 (dd, 1H, *J* = 11.7, 8.8 Hz, CH₂), 3.58 (dd, 1H, *J* = 11.7, 4.4 Hz, CH₂), 2.40 (ddd, 1H, *J* = 9.1, 8.8, 4.4 Hz, CH), 1.96 (s, 3H, CH₃), 1.23 (s, 9H, 'Bu). ¹³C NMR (CDCl₃, 101 MHz): δ 169.8, 148.5, 143.1, 131.1 (q, *J* = 32 Hz), 126.8, 126.1, 123.7 (q, *J* = 275 Hz), 84.6, 68.8, 62.4, 55.2, 39.7, 27.5, 25.5. Anal. Calcd for C₁₈H₂₀Cl₂F₃NNaO₃: C, 50.72; H, 4.73; N, 3.29. Found: C, 50.61; H, 4.64; N, 3.26. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL, 220 nm; major enantiomer: *t* = 15.7 min, minor enantiomer: *t* = 23.1 min, >99% ee. $[\alpha]_D^{25} +29.3$ (*c* 0.3, CHCl₃).

tert-Butyl 3-chloro-4-(chloromethyl)-3-methyl-5-(naphthalen-2-yl)-2-oxopyrrolidine-1-carboxylate (20d)

A white solid. Recrystallization from *n*-hexane. Mp 190 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.92–7.82 (m, 3H, Ar), 7.72 (s, 1H, Ar), 7.56–7.50 (m, 2H, Ar), 7.34 (dd, 1H, *J* = 8.5, 1.8 Hz, Ar), 4.70 (d, 1H, *J* = 9.2 Hz, CH), 4.01 (dd, 1H, *J* = 11.5, 9.5 Hz, CH₂), 3.63 (dd, 1H, *J* = 11.5, 4.0 Hz, CH₂), 2.52 (ddd, 1H, *J* = 9.5, 9.2, 4.0 Hz, CH), 2.00 (s, 3H, CH₃), 1.11 (s, 9H, 'Bu). ¹³C NMR (CDCl₃, 101 MHz): δ 170.3, 148.6, 135.9, 133.2, 133.1, 129.2, 127.8, 127.7, 126.9, 126.6, 126.1, 123.1, 84.1, 69.1, 63.0, 55.3, 39.9, 27.4, 25.6. HRMS (ESI): Calcd for C₂₁H₂₂Cl₂NNaO₃ ([M+Na]⁺): *m/z* 430.0947, Found: *m/z* 430.0953. HPLC analysis: Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 98/2 (v/v), 1.0 mL, 220 nm; major enantiomer: *t* = 12.4 min, minor enantiomer: *t* = 15.2 min, >99% ee. $[\alpha]_D^{25} +38.0$ (*c* 0.5, CHCl₃).

Crystal Data for 16d: C₂₁H₂₁BrNO₃, *M_r* = 416.31, *P*2₁ (no. 4), *a* = 6.317(2), *b* = 27.873(6), *c* = 11.038(2) Å, β = 92.071(9), *V* = 1942.3(7) Å³, *Z* = 4, ρ_{calcd} = 1.427 gcm⁻³, Mo-Kα (λ = 0.711 Å), *T* = -73 °C, 2θ_{max} = 55.0°, 18900 measured reflections, *R* = 0.0556, *R_w* = 0.1176, Flack parameter = -0.001(7).

Crystal Data for 20c: C₁₈H₂₀Cl₂F₃NO₃, *M_r* = 426.26, *P*2₁ (no. 4), *a* = 7.4263(4), *b* = 9.5017(6), *c* = 14.553(1) Å, β = 100.472(7), *V* = 1008.4(1) Å³, *Z* = 2, ρ_{calcd} = 1.404 gcm⁻³, Mo-Kα (λ = 0.711 Å), *T* = -73 °C, 2θ_{max} = 55.0°, 9573 measured reflections, *R* = 0.0558, *R_w* = 0.0940, Flack parameter = -0.03(5).



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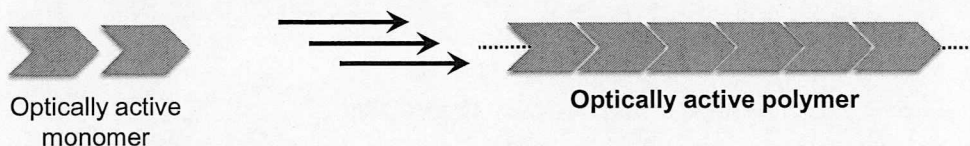
Chapter 5: Asymmetric Polymerization by Means of Asymmetric Allylic Substitution Catalyzed by Planar-Chiral Cyclopentadienyl-Ruthenium Complex

5-1 Introduction

The optically active polymers have received much attention, because the most of naturally-occurring polymers, such as polypeptide, polysaccharides, and nucleic acids are optically active ones and some of them show characteristic and individual functionalities based on their perfectly controlled stereostructures and higher-order structure as well as distinctively regular molecular sequence. In recent years, synthesis of optically active polymers has been reported,¹ and their interesting features such as molecular recognition ability have been studied by several researchers.² These artificial polymers have attracted attention, because they are expected to exhibit groundbreaking functions that are comparable to or better than those of natural optically active polymers in terms of new functional polymer materials. However, few of optically active artificial polymers have been successfully applied to practical use, therefore, extensive researches on the precise synthesis of a new type of optically active polymers and on their distinctive features would be eagerly desired.

Synthetic methods of optically active polymers can be classified into two types (Figure 5-1). One is *polymerization of optically active monomer*, in which is most general manner of optically active polymer synthesis, because optically active carbon is certainly introduced to the main chain unless racemization occurs during the polymerization. However, the method

(a) Polymerization of Optically Active Monomer



(b) Asymmetric Polymerization of Achiral Monomer

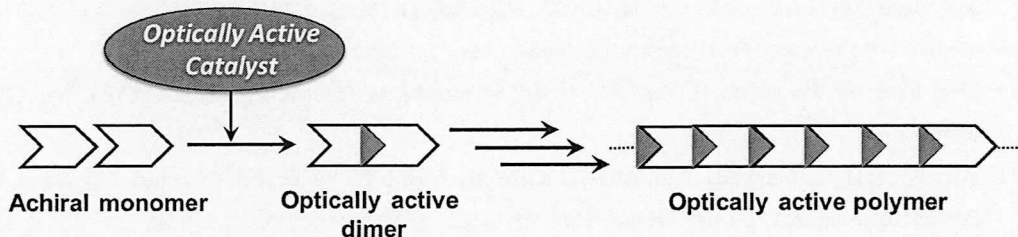


Figure 5-1. Synthesis of Optically Active Polymer

suffers from the limited availability and high expense of enantiomerically enriched monomers. The other method is *asymmetric polymerization of achiral monomers*, which optically active polymer can be obtained by using optically active catalyst.¹ Latter method is considerable attention, because use of achiral monomers extends the range of applicable monomer structure. However, precise synthesis of optically active polymer by means of asymmetric polymerization is generally very difficult, since highly enantioselective reaction has to be maintained throughout polymerization.

Asymmetric Polymerization of Achiral Monomer

In asymmetric polymerization, general vinyl monomers have often been used as achiral monomer, and the relation between optical activity of the resultant polymer and its main chain configuration has been discussed by several researchers.¹ However, when general vinyl monomers such as propene, styrene, and alkyl methacrylate are used, resultant iso- and syndiotactic polymers did not show optical activity even if a significant asymmetric induction occurred at stereogenic carbons in the main chain (Figure 5-2(a)).^{1,3-5} As these vinylpolymers possess a mirror plane if the end group (pseudo-chirality) and the secondary structure such as helicity² are ignored, they do not show optical activity.¹ Therefore, in order to obtain optically active polymer, some higher-order stereoregularities are necessary.^{1,6} The possibility of asymmetric polymerization of vinyl polymer was surveyed by Wulff and co-workers.^{6,7} For example, achiral syndiotactic vinyl polymer was converted to chiral polymer by introducing unsymmetrically comonomer units to remove the mirror symmetry in the direction

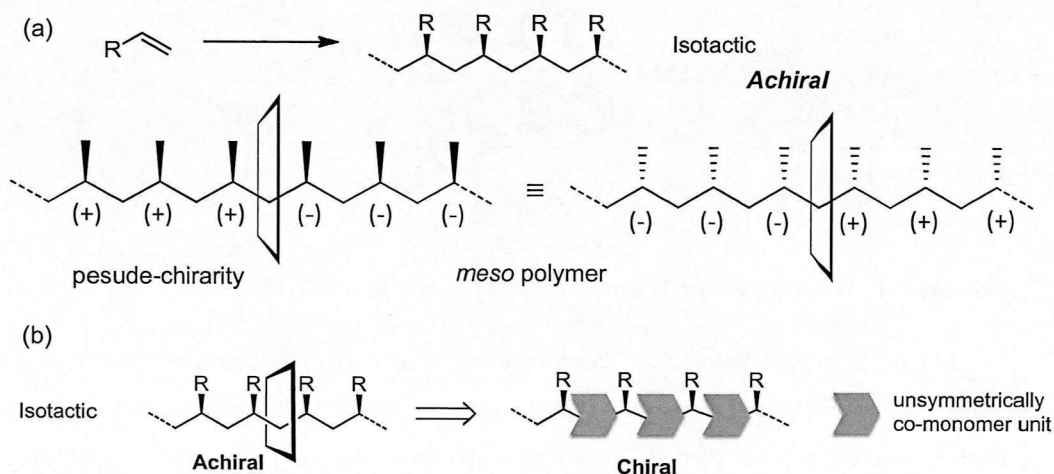
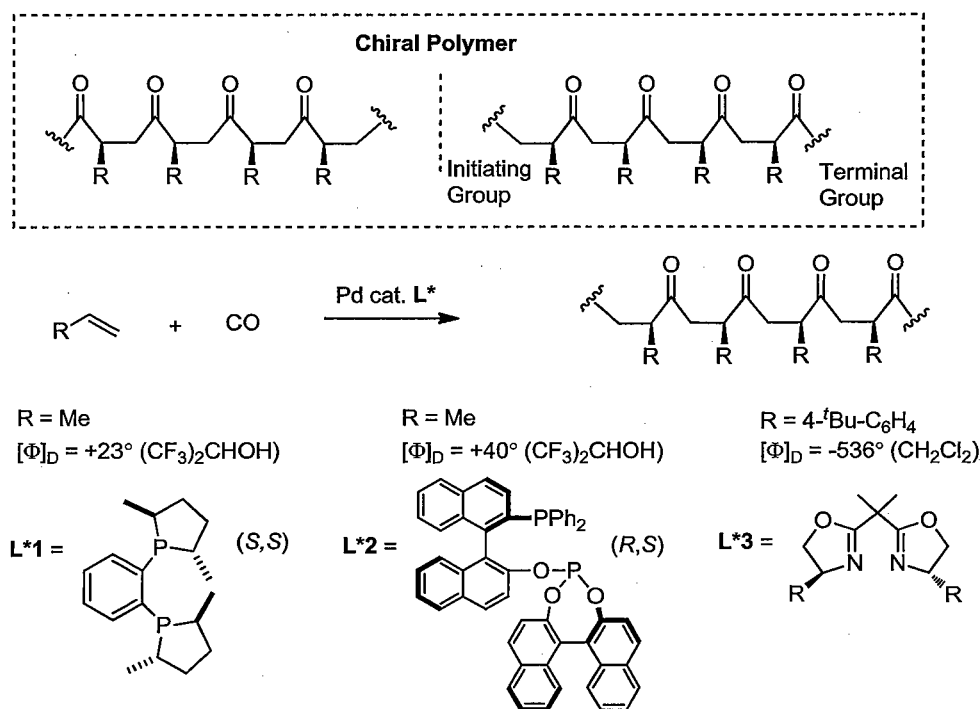


Figure 5-2. Asymmetric Polymerization of Achiral Vinyl Monomer

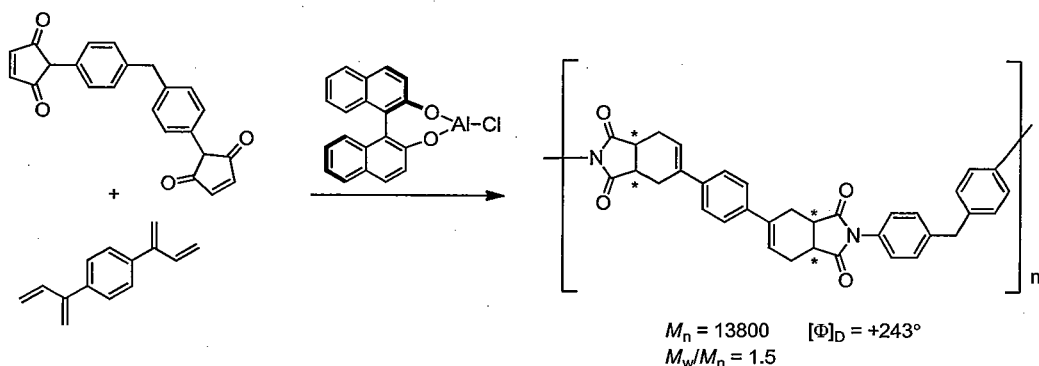
perpendicular to the translational axis (Figure 5-2(b)). In the case of asymmetric alternating polymerization of α -olefin with CO, the resulting polymer is chiral, in the polymer it exists a pair of enantiomers that have the opposite sign for the chirotopic centers in the main chain (Scheme 5-1).⁸ There have been considerable studies on the asymmetric alternating copolymerization of α -olefin with using chiral palladium catalysts which produces optically active polymer. In 1994 and 1995, successful examples of asymmetric copolymerization of α -olefin such as 1-alkene and vinylarenes with CO giving polymers with high regio- and stereoselectivity were reported from some research groups.^{9,10} They used a catalyst consisting of palladium and chiral phosphine-phospite or imine ligand (Scheme 5-1). Until now, several efficient systems for asymmetric polymerization of achiral vinyl monomers have also appeared in the literature.^{1a,11-13}



Scheme 5-1. The Asymmetric Polymerization of α -Olefin with CO

In past decades, a number of asymmetric reactions have been developed in the field of organic synthesis, in which highly enantioselective reaction proceeds with quantitative chemical conversion.¹⁴ If such the enantioselective reaction can be applied to asymmetric polymerization and repetitive asymmetric reaction is kept throughout polymerization, the synthesis of a new type of optically active polymers possessing various backbone and

functionality in the main chain would be allowed. Nevertheless, asymmetric polymerization involving this approach has not yet been studied extensively. In common polymerization system, highly enantioselective reaction can be hardly maintained from the beginning to the end of polymerization, since it should be difficult for asymmetric catalyst to recognize small reactive terminal moiety of the polymer. Itsuno and co-workers reported asymmetric polymerizations by use of asymmetric C-C bond forming reaction such as asymmetric Diels-Alder reaction, Hosomi-Sakurai reaction, and Mukaiyama aldol reaction, and prepared various asymmetric polymers having various backbone (Scheme 5-2).¹⁵

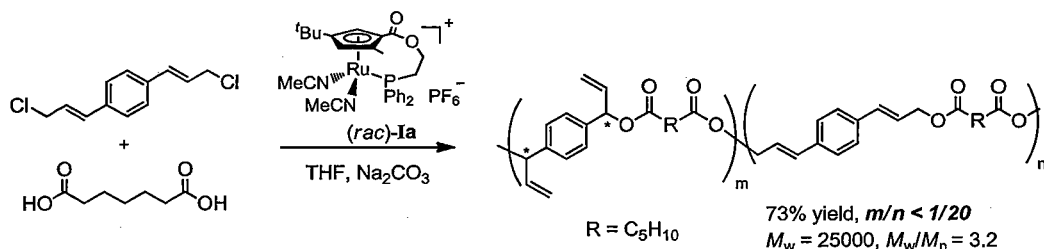


Scheme 5-2. The Asymmetric Polymerization via Asymmetric Diels Alder Reaction

We have already shown in Chapters 2 and 3 that planar-chiral cyclopentadienyl-ruthenium (Cp*Ru) complex (**1**) is a proficient catalyst for regio- and enantioselective allylic substitutions of monosubstituted allylic halides with heteroatom nucleophiles.¹⁶ As these reaction systems exhibit high reactivity and selectivity, we have conceived an extension of our system to asymmetric polymerization. Nomura and co-workers reported regioselective but not enantioselective polycondensation using allylic substitution catalyzed by an achiral Ir complex.¹⁷

Initially, in order to accomplish polymerization using a Cp*Ru (**1**)-catalyzed allylic substitution, we investigated a reaction of allylic carboxylation as a fundamental process of polymerization because the catalytic system of allylic carboxylation is highly reactivity (Chapter 2). Thus, we conducted the reaction between bifunctional allylic chloride and dicarboxylic acid with (*rac*)-**1a** (3 mol %) under the same basic conditions as those of allylic carboxylation using **1a** (scheme 5-3). The polymerization proceeded quantitatively and, after 12 h, yielded a polymer with broad molecular weight distribution ($M_w = 25000$, $M_w/M_n = 3.2$). The resulting polymer, however, was exclusively linear poly-(allylic ester) (**B/L** < 1/20). This

result suggests that the branched allylic ester moieties of the polymer isomerized to linear allylic esters. Therefore, prevention of the isomerization from the chiral branched product to the achiral linear one is essential to realize the expected asymmetric polymerization.



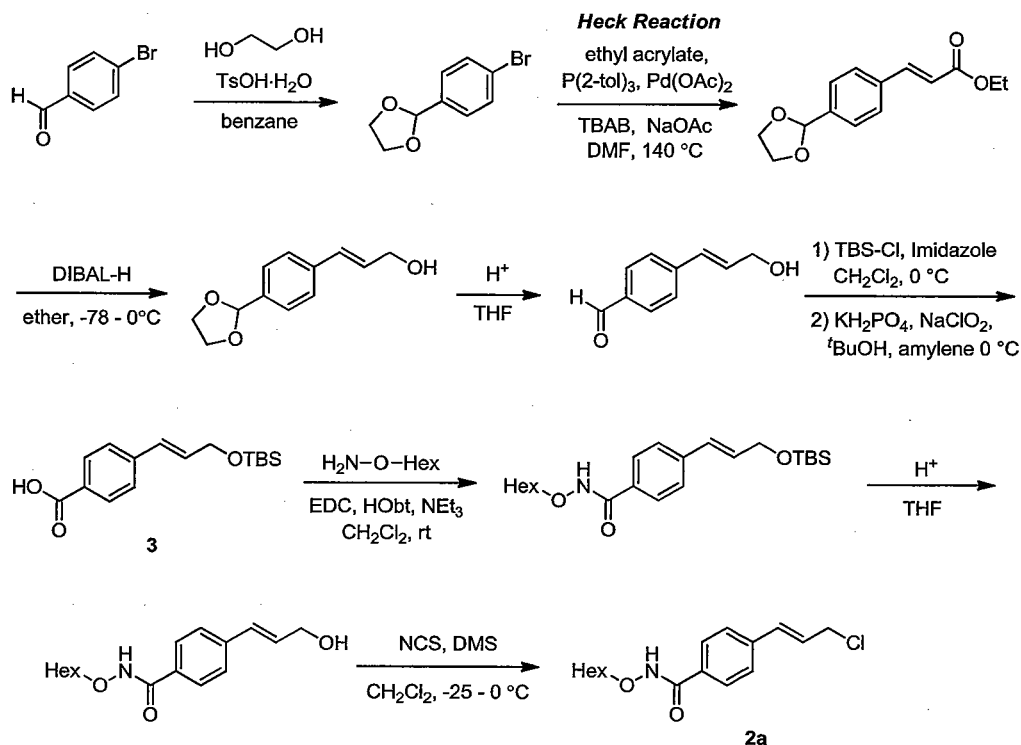
Scheme 5-3. The Polymerization Using Allylic Carboxylation Catalyzed by Cp'Ru I

5-2 Asymmetric Polymerization via Asymmetric Allylic Amidation

On the other hand, we have already succeeded in the development of regio- and enantioselective reactions of monosubstituted allylic halide with amide nucleophiles, which produce enantiomerically enriched branched allylic amides in quantitative yield (Chapter 4). As resulting allylic amide is less reactive than allylic ester, no loss of regioselectivity was observed when the reaction was conducted allylic chloride with an equimolar amount of amide as nucleophile. Then, we started our investigation for applying our allylic amidation to a new type of asymmetric polymerization.

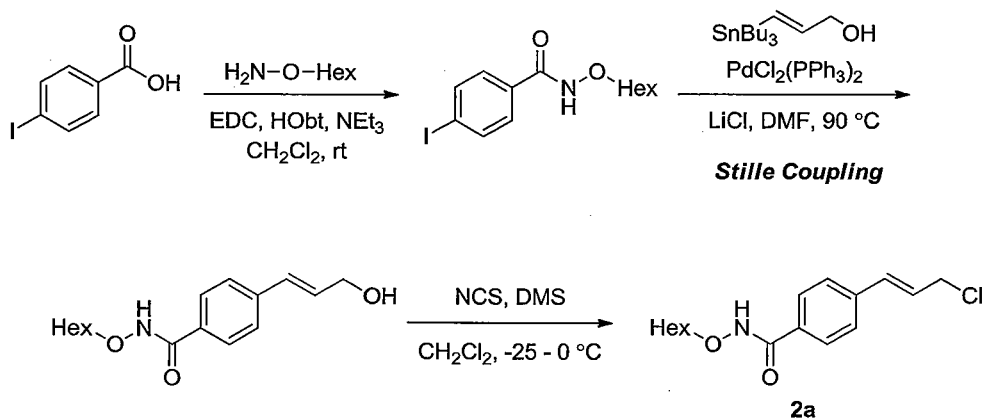
Synthesis of Monomer

For a monomer of asymmetric polymerization, we have designed AB type monomer **2a** which has both allylic chloride and *N*-hexyloxyamide moieties in a molecule. The synthetic route is shown in Scheme 5-4, in which intermediate **3** was synthesized according to the literature method.¹⁸ Thus, *p*-bromobenzaldehyde was converted to **3** via six steps. Amidation of **3** was carried out by condensation with *O*-hexylhydroxylamine using EDC *N*-[3-(dimethylamino)propyl]-*N*-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt), followed by deprotection, and then chlorination by Corey–Kim method to give monomer **2a**.



Scheme 5-4. Synthesis of Monomer **2a** (Method 1)

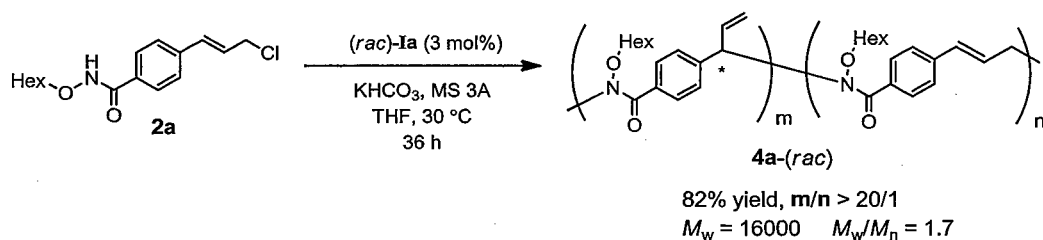
However, Method 1 required many synthetic steps, in addition, introduction of allylic moiety was not easy, and we reviewed other methods. The improved method (Method 2) is shown in Scheme 5-5. Introduction of allylic moiety to 4-iodobenzamide was achieved by Stille coupling using (*E*)-3-(tributylstannyl)prop-2-en-1-ol. By using Method 2 monomer **2a** was prepared via three synthetic steps.



Scheme 5-5. Synthesis of Monomer **2a** (Method 2)

Polymerization of Monomer 2a

The polymerization conditions referred to those for asymmetric allylic amidation (Chapter 4). Polymerization of monomer **2a** was conducted with 3 mol% of (*rac*)-**1a** in the presence of KHCO_3 and molecular sieves 3A (MS 3A) at 30 °C in THF (0.8 M) (Scheme 5-6). The polymerization proceeded with almost quantitative monomer conversion after 36 h, and usual work-up of the reaction mixture gave a crude polymer ($M_w = 12000$) with a broad molecular weight distribution (MWD, $M_w/M_n = 2.4$) along with oligomers. (Figure 5-3) The crude product was purified to remove the catalyst by silica-gel chromatography using dichloromethane and then ethyl acetate as an eluant. The polymer (**4a-(rac)**) was obtained in 82% yield from the first fraction eluted by dichloromethane, and the GPC analysis of **4a-(rac)** showed the molecular weight of $M_w = 16000$ and comparatively narrow MWD ($M_w/M_n = 1.7$) (Figure 5-3). The second fraction eluted by ethyl acetate gave residual oligomers, indicating that effective purification of the polymer can be performed by silica gel chromatography.



Scheme 5-6. Polymerization Using Asymmetric Allylic Amidation

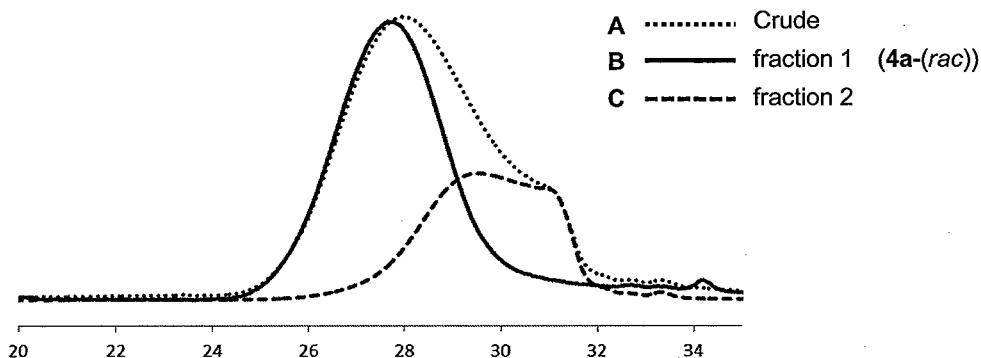
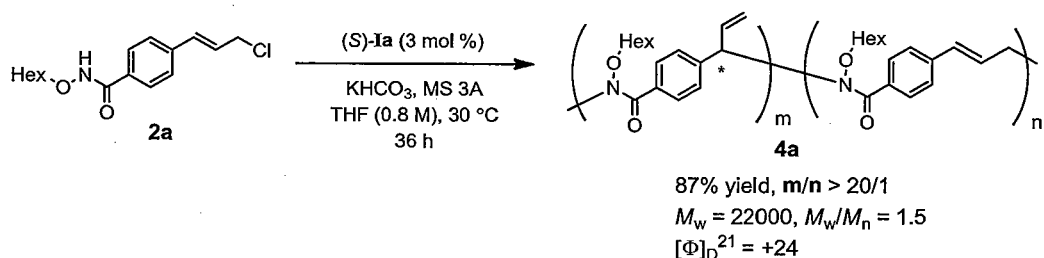


Figure 5-3. GPC analysis of resulting polymer before (A: Crude) and after purification by Silica-Gel chromatography (B: First fraction eluted with dichloromethane, C: Second fraction eluted with AcOEt).

Thus obtained polymer **4a**-(*rac*) is pale yellow solid and soluble in dichloromethane and THF, sparingly soluble in ethyl acetate, acetone, and benzene, but insoluble in *n*-hexane and acetonitrile. The polymer is stable in the air, and shows melting point at about 80 °C, and thermogravimetric analysis of the polymer exhibited an onset of weight loss at 230 °C under nitrogen.

Asymmetric Polymerization of Monomer **2a**

In order to investigate if asymmetric polymerization of monomer **2a** is realized via catalysis of planar-chiral ruthenium complex. To obtain an optically active polyamide, we conducted the reaction of monomer **2a** in the presence of 3 mol% of (*S*)-**1a** (Ar = Ph) at 25 °C for 36 h. The reaction smoothly proceeded with quantitative monomer conversion to produce polyamide **4a** in 87% yield ($M_w = 22000$, $M_w/M_n = 1.5$) after purification by silica-gel chromatography. Polymer **4a** showed optical rotation power of $[\Phi]_D^{21} = +24^\circ$, which may indicate that the main chain of the polymer should be optically active. Thermogravimetric analysis of the polymer exhibited an onset of weight loss at 200 °C under nitrogen



Scheme 5-7. Asymmetric Polymerization Using Asymmetric Allylic Amidation

5-3 Characterization of Polyamide **4a**

¹H NMR Spectrum

The NMR spectral analysis offers valuable information on the main chain structure of polymer. We also utilized an NMR spectral method for structure analyses of polymer **4a** by comparing with branched allylic compound (**5**) which was prepared by asymmetric amidation using (*S*)-**1a**. The ¹H NMR spectra of polymer **4a** and model compound **5** in CDCl₃ at 303 K are shown in Figure 5-4. In the spectrum of **4a** (Figure 5-4 (b)), there are multiplet peaks in the region of 5.34-5.55 ppm due to terminal olefinic protons assigned to a branched allylic structure, which is almost identical with the spectrum of the model branched allylic compound **5** (Figure 5-4(a)). Although very weak peaks (δ 6.65 (d, $\text{CH}=\text{CH}$, 1H), 6.45-6.38 (m, $=\text{CHCH}_2$, 1H), 4.53 (brs, $=\text{CHCH}_2$, 2H) ppm) assignable to the linear allylic compounds

were detected, they were negligible compared with peaks due to branched structure ($m/n > 20/1$) (Figure 5-4(c)). These results suggest that the polymerization catalyzed by Cp*Ru complex **1** proceeds in a high regioselectivity, thus the catalytic system using **1** can be applied to asymmetric polymerization, which may realize to introduce asymmetric carbons in the main chain of polymers.

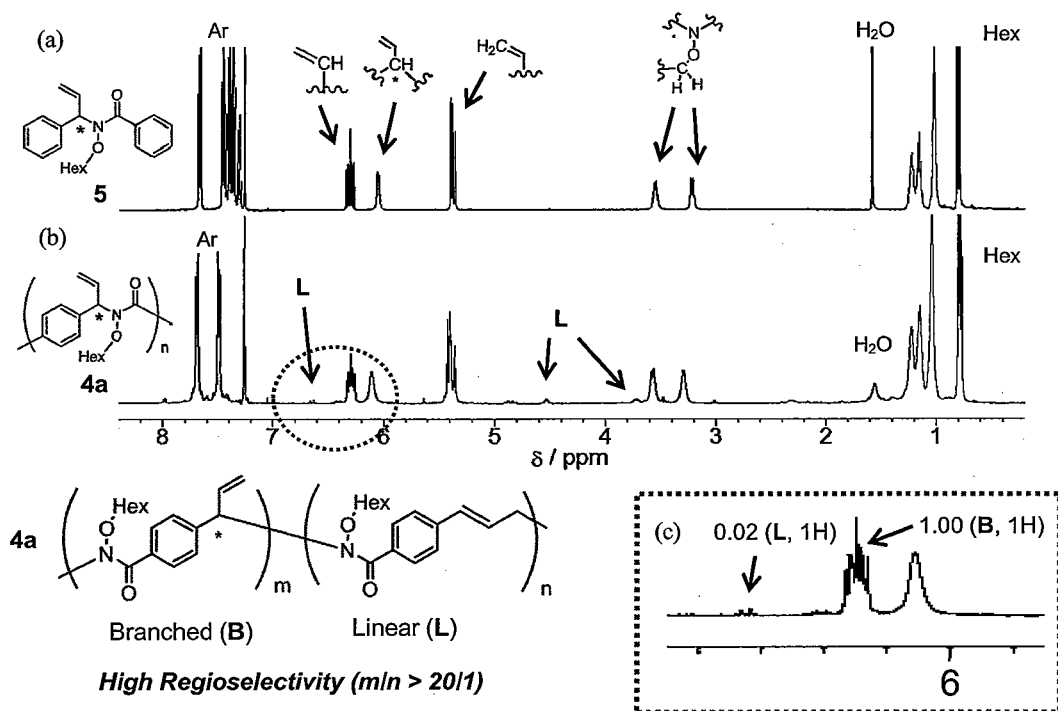


Figure 5-4. ^1H NMR Spectra of model branched allylic compound and polyamide **4**. (a) Model compound, (b) Polyamide **4a**, (c) Olefin region of polyamide **4** shown in higher magnification.

5-4 Screening of Reaction Conditions

In order to attain high enantioselectivity of the polymerization, we investigated to optimize the reaction conditions of the polymerization. In the optimization experiments, stereochemistry in the main chain structure was evaluated by the value of optical rotation power.

Effect of Concentration of the Monomer in the Reaction System

Initially, we investigated the influence of the concentration of monomer **2a** in the reaction system by using the (*S*)-**1a** catalyst in THF. The results are summarized in Table 5-1.

Lowering the concentration of monomer **2a** decreased the reactivity of the system and optical rotation power of the resultant polymer. When the reaction was conducted in a monomer concentration of 0.25 M, the monomer conversion was only 80% after the reaction of 12 h and unreacted monomer remained intact. Moreover, in 0.5 M a little amount of the monomers underwent the allylic hydroxylation and were transformed to the branched allylic alcohol (*ca.*10%), which was detected by ^1H NMR analysis. On the contrary, increasing the concentration up to 0.8 M led to improve the reactivity and optical rotation power. The results suggest the concentration to be crucial for the present polymerization, and we decided to conduct all the polymerization reaction described below in the monomer concentration of 0.8 M, which corresponds to the monomer to the catalyst ratio of *ca.* 83.

Table 5-1. Effect of Concentration of the monomer ^a

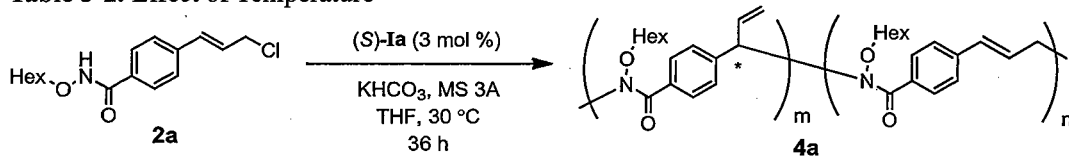
entry	concentration (M)	conversion ^b of 2a (%)	yield (%) ^c of 4a	m/n ^b	M_w ^d	M_w/M_n ^d	$[\Phi]_D$ ^e
1	0.25	80	- ^f	20/1	- ^f	- ^f	- ^g
2	0.50	>99	70	>20/1	21000	1.4	+22
3	0.8	>99	87	>20/1	22000	1.5	+24
4	1.0	>99	85	20/1	23000	1.5	+24
5	1.2	>99	73	20/1	21000	1.4	+22

^a (S)-**Ia** (0.008 mmol), **2a** (0.25 mmol), K_2CO_3 (0.275 mmol) in THF (0.3 mL), stirred at 30 °C for 36 h. ^b Determined by ^1H NMR analysis. ^c Isolated yield. ^d Estimated by GPC analysis using polystyrene standard. ^e Molar optical rotation analysis in CHCl_3 . ^f Not isolated. ^g Not detected.

Effect of Temperature

To investigate the effect of reaction temperature, the polymerization of monomer **2a** (0.8 M) with (S)-**Ia** catalyst in THF was carried out. As already described above, the reaction temperature also influences the enantioselectivity of products in allylic amidation. In the case of the polyoimerization, the enantioselectivity of the reaction at 40 °C was found to be same as at 30 °C, but lowering the reaction temperature to 25 °C resulted in higher optical rotation power. Thus, the best reaction temperature for the polymerization has been determined to be 25 °C.

Table 5-2. Effect of Temperature ^a

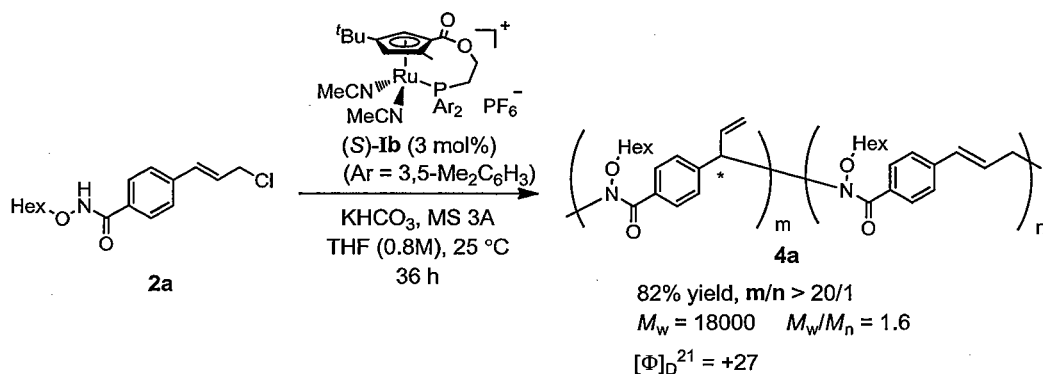


entry	temperature (°C)	conversion ^b of 2a (%)	yield (%) ^c of 4a	m/n ^b	<i>M</i> _w ^d	<i>M</i> _w / <i>M</i> _n ^d	[Φ] _D ^e
1	40	>99	67	20/1	7200	1.9	+24
2	30	>99	87	>20/1	22000	1.5	+24
3	25	>99	83	>20/1	14000	1.6	+25
4	20	>99	70	>20/1	4000	1.5	+23

^a (S)-Ia (0.008 mmol), **2a** (0.25 mmol), K₂CO₃ (0.275 mmol) in THF (0.3 mL), stirred for 36 h. ^b Determined by ¹H NMR analysis. ^c Isolated yield. ^d Estimated by GPC analysis using polystyrene standard. ^e Molar optical rotation analysis in CHCl₃.

Selection of Catalyst

We have already shown that the aryl groups on the phosphine ligand in the Cp*Ru complex plays an important role for the enantioselectivity of allylic substitution reactions. Thus, we conducted the reaction using (S)-Ib (Ar = 3,5-Me₂C₆H₃) as catalyst under the optimum conditions (Scheme 5-8). The resulting polymer showed an optical rotation power of [Φ]_D²¹ = +27°. Thus, all of reactions described below have been conducted in the presence of (S)-Ib as catalyst.



Scheme 5-8. Asymmetric Polymerization of Optically Active Monomer **2a**

From the experimental results described above, the optimal reaction conditions of the present allylic polymerization have been determined as follows:

Reaction temperature, 25 °C;

Solvent, THF (0.8 M);

Cp'Ru complex catalyst, 3 mol% of (*S*)-**Ib**;

Additives, KHCO₃ and MS 3A.

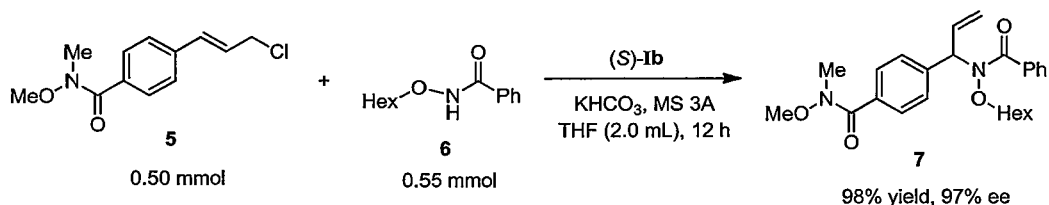
5-5 Evaluation of the Stereochemistry of the Main Chain

As described above, polymer **4a**, which was obtained from the allylic amidation polymerization of monomer **2a** by the catalysis of planar-chiral Ru complex **Ib**, exhibited an optical rotation power of $[\Phi]_D^{21} = +27$. The use of a racemic catalyst (a mixture of (*S*)- and (*R*)-**Ia**) afforded optically inactive polymer **4a-(rac)** with $[\Phi]_D^{21} = 0$. In addition, the use of planar-chiral Ru catalyst (*R*)-**Ia** possessing an opposite absolute configuration to (*S*)-**Ia** in the polymerization of **2a** resulted in the formation of an optically active polymer **4a** with an opposite sign of optical rotation power, $[\Phi]_D^{21} = -25^\circ$. These facts suggest that the polymerization of **2a** catalyzed by planar-chiral Ru complex **I** is featured as an asymmetric polymerization.

Generally, determining the optical purity of stereogenic carbons in the main chain should be very difficult problem. One of the most direct methods for the analysis of enantiomeric purity of the repeating unit in a chiral polymer is to degrade the polymer to the repeating unit and then to determine the enantioselectivity.^{19,20} However, it is difficult that to substantiate such a procedure, as it requires very efficient degradation of the polymer backbone and the protection of the stereogenic centers in the polymer from being racemized during the degradation process. In the case of our polyamide, degradation method would be inapplicable because we could not find a suitable procedure under mild reaction conditions for cleaving the C-N bonds in the polymer main chain.

On the other hand, the reaction of allylic chloride with an *N*-bezyloxyamide, classified here as a fundamental allylic amidation, proceeded selectively to give optically active allylic amides with a high regioselectivity of **B/L** > 20 and a high enantioselectivity of 95% ee (Chapter 4). Moreover, the reaction between allylic chloride **5** and *N*-hexyloxyamide **6**, which may be corresponding to the initial step of the polymerization of **2a**, was performed in the presence of (*S*)-**Ib** to give expected branched allylic amide **7** in 98% yield with 97% ee. Therefore, it is likely that allylic amidation catalyzed by Cp'Ru (**1**) complex proceeds in a

high regio- and enantioselective manner even in polymerization. Then, we have tried to know the stereochemistry of the polymer on the basis of spectral method as describes below.



CD and UV Investigation of Chiral Polyamide.

Enantioselectivity in the asymmetric polymerization of monomer **2a** has been evaluated by means of ultra-violet (UV) and circular dichroism (CD) spectroscopic methods.^{20,21} The UV and CD spectra of polymer **4a**, along with those of model dimer **7** measured in CHCl_3 at 298 K are shown in Figure 5-5. The CD spectrum of polymer **4a-((S)-Ib)** was normalized on the basis of the number of the model compound unit in the main chain of **4a**. As seen from the Figure 5-5 (a), model compound **7** (97% ee) exhibited a Cotton effect in the region of 240–260 nm in the CD spectrum, which is assignable to the absolute twist between the $\pi-\pi^*$ transition of each benzene chromophore.²² Polymer **4a-((S)-Ib)** also displayed a CD spectral pattern quite similar to that of model compound **7**. In polymer **4a-((S)-Ib)**, the UV absorption band

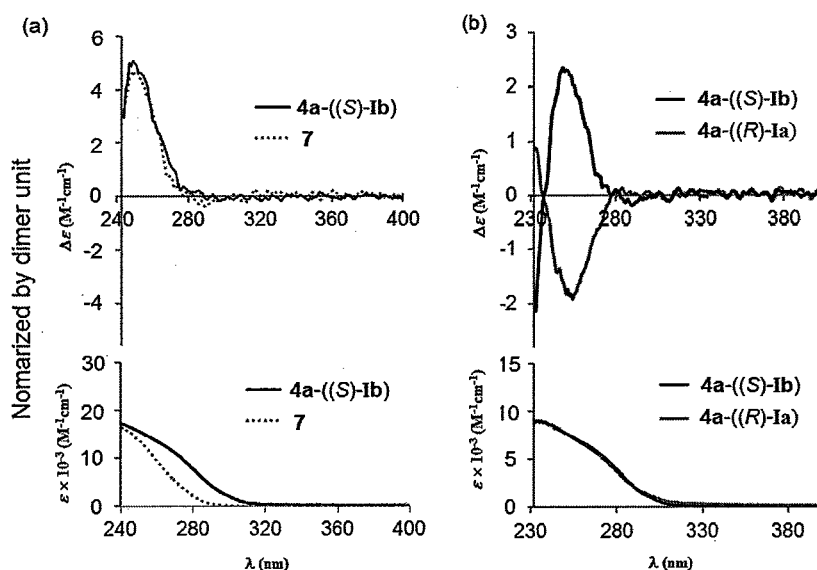
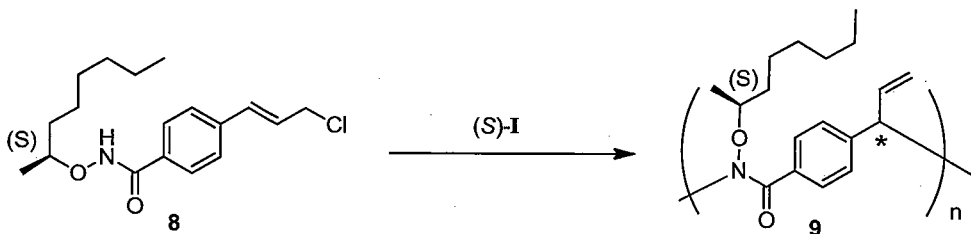


Figure 5-5. CD and UV spectra of (a) Polymer **4a-((S)-Ib)** and model compound **7** (b) Polymer **4a-((S)-Ib)** and **4a-((R)-Ia)**. Polymers, **4a-((S)-Ib)** and **4a-((R)-Ia)** were prepared from the polymerization of monomer **2a** by using catalyst **(S)-Ib** and **(R)-Ia** respectively.

appeared at around 280 nm. The absorption in the UV spectrum is probably attributed to intramolecular interaction among benzene rings in the polymer main chain, which have no relation to the chirality. In addition, polymer **4a**-((*R*)-**1a**), which was prepared by the polymerization of **2a** with (*R*)-**1a** exhibited a CD spectrum in mirror-image spectrum of polymer **4a**-((*S*)-**1b**) (Figure 5-5(b)). These facts indicate that enantioselectivity of the new stereogenic centers of polymer **4a** is determined by asymmetric allylic amidation using Cp*Ru (**1**) catalyst, and polymer **4a** may be formed with high stereoselectivity.

Determination of the Optical Purity of the Main Chain

To determine the optical purity of the main chain which was formed by the polymerization using (*S*)-**1b** catalyst, we conducted the NMR analysis of chiral polymer (**9**) prepared from optically active monomer (**8**) bearing (*S*)-2-octyloxyamine group (Scheme 5-9). If the asymmetric polymerization of **8** takes place by the catalysis of (*S*)-**1b**, the repeating unit of resulting polymer **9** should have two chiral carbons, whose configuration is either (*S,S*) or (*S,R*). Then, we have tried to determine the optical purity of the main chain by this diastereomer method using chiral monomer **8**.



Scheme 5-9. Asymmetric Polymerization of optically active monomer **8**

Initially, we carried out the model reaction between cinnamyl chloride and *N*-2-octyloxybenzamide **10** with (*rac*)-**1a** and analyzed the resulting product by an NMR spectroscopy (Figure 5-6). The reaction proceeded to give expected branched allylic amide (**11**((*rac*)-**1a**)) in a good yield (99%). ¹H NMR analysis of **11**((*rac*)-**1a**) made it possible to determine the enantiopurity, and diastereomeric methine protons on 2-octyloxy group were equivalently separated (3.75 and 3.50 ppm), indicating that kinetic resolution did not occur during the reaction (Figure 5-6 (b)). When (*S*)-**1b** was used as a catalyst, **11**-((*S*)-**1b**) was obtained with 95 % ee, which was determined by HPLC analysis using chiral stationary phase. ¹H NMR spectrum of **11**-((*S*)-**1b**) is shown in Figure 5-6 (a), mainly one peak (3.75 ppm) was

observed, indicating the degree of enantioselectivity of the present asymmetric allylic amidation reaction to be ca. 93% ee (the % ee value may be actually much higher, but unfortunately the resolving power of the NMR instrument used does not allow to determine it), which was almost same optical purity value as that by HPLC analysis.

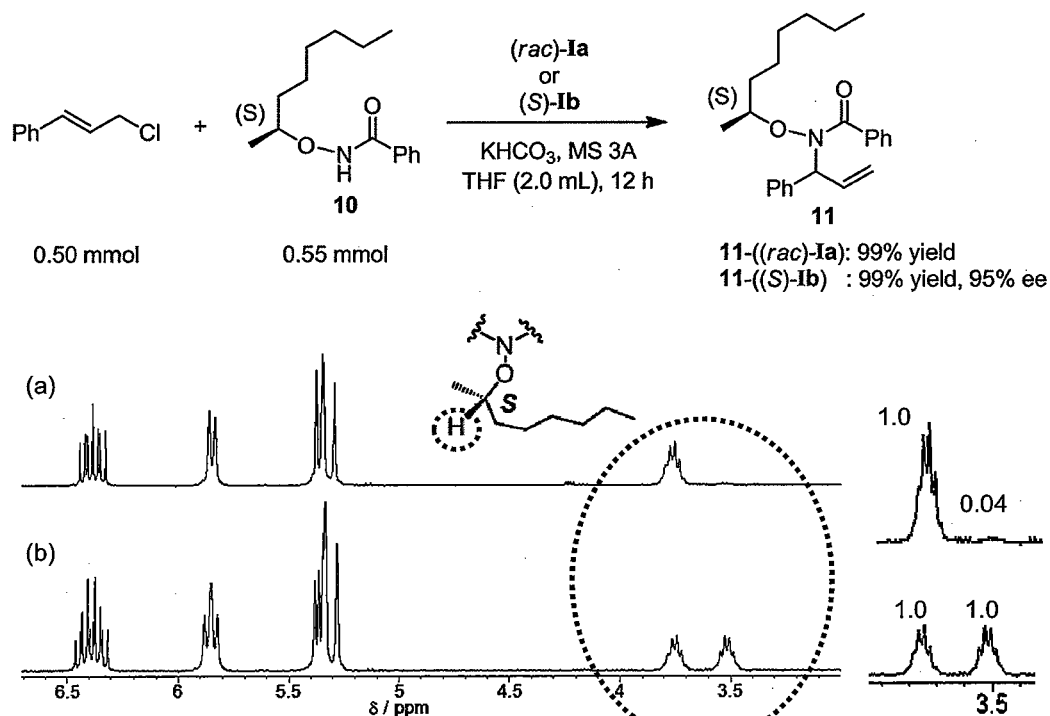


Figure 5-6. ^1H -NMR Spectra of **11** (303 K in CDCl_3). (a) Using (S)-**1b** as a catalyst. (b) Using (rac)-**1a** as a catalyst.

Then, we applied this method to determine the optical purity of the main chain of polymer **9**. The polymerization of **8** was conducted in the presence of (S)-**1b** catalyst under the optimized polymerization conditions (*vide supra*) to give **9**-(S)-**1b** with quantitative monomer conversion ($M_w = 5900$, $M_w/M_n = 1.5$). The ^1H NMR spectra of **9**-(S)-**1b** are shown in Figure 5-7, in which mainly one peak was observed in the region corresponding to methine hydrogen (3.76 ppm). In contrast, when (rac)-**1a** was used as a catalyst, two peaks due to methine hydrogens of each diastereomer were observed at 3.77 and 3.58 ppm with a ratio of 1:1. Additionally, changing the catalyst from (S)-**1b** to (R)-**1a**, single peak due to a methine proton in the opposite absolute configuration was observed. These facts clearly suggest that stereogenic centers of **9** to be highly controlled by the asymmetric allylic amidation using (S)-**1b** catalyst. The results reveal that the polymerization proceeds in highly stereoselective

manner to give optically active polymers.

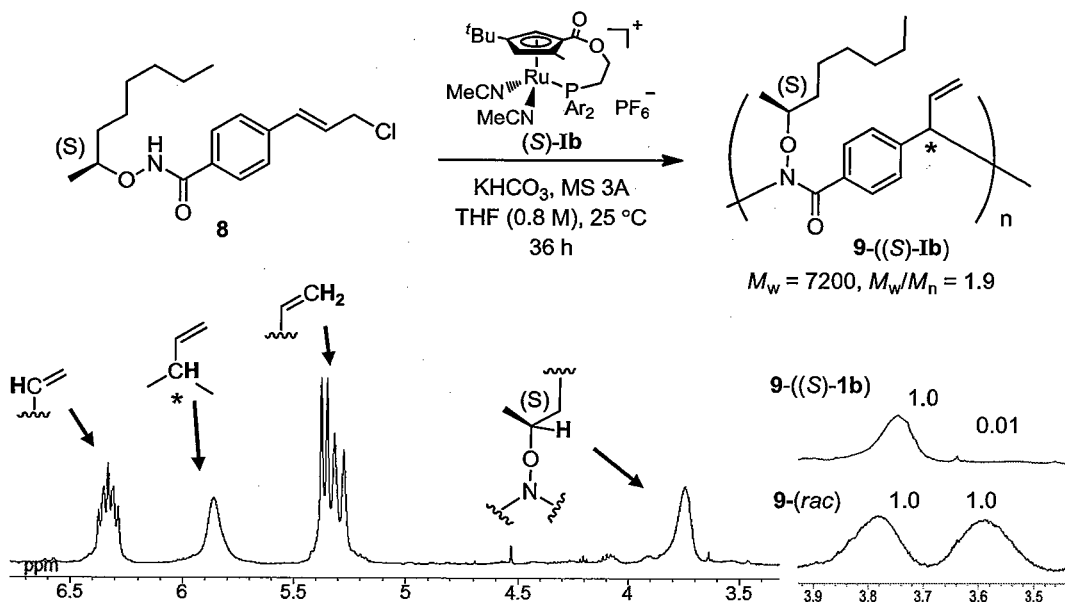


Figure 5-7. $^1\text{H-NMR}$ spectra of **9** (303 K in CDCl_3).

5-5 Screening of Substrate

Our polymerization method has potential to synthesize polymers the possessing a variety of backbones. Thus, under the optimized conditions, polymerization of several bifunctional monomers **2b-e** bearing allylic chloride and *N*-alkoxyamide moieties were carried out in the presence of catalyst **(S)-Ib**. The results are summarized in Table 5-3. Monomer **2b** possessing an alkynyl group, which builds a rigid backbone, also proceeded with quantitative conversion of monomer **2b** to produce polymer **4b** in good yield with high molecular weight and high regioselectivity. On the other hand, monomer **2c** bearing an ester group gave polymer **4c** with a relatively low molecular weight. Monomer **2d** having a 1,3-phenylene group in a molecule was also polymerized to give polymer **4d**, but showed a low reactivity. All of polymers obtained here showed optical activities, indicating that the planar-chiral Cp^*Ru complexes can catalyze an asymmetric polymerization of allylic chlorides having a variety of amido groups via allylic substitution reactions.

Table 5-3. Screening of Substrate^a

entry	R	conversion ^b of 2 (%)	yield (%) ^c of 4	m/n ^b	M _w ^d	M _w /M _n ^d
1		>99	90 (4b)	>20/1	31000	2.1
2		>99	90 (4c)	>20/1	14000	2.1
3		>99	59 (4d)	>20/1	7200	1.4

^a (S)-1a (0.008 mmol), 2a (0.25 mmol), KHCO₃ (0.275 mmol) in THF, stirred at 30 °C for 36 h. ^b Determined by ¹H NMR analysis. ^c Isolated yield. ^d Estimated by GPC analysis using polystyrene standard.

5-6 Reaction Mechanism of Asymmetric Polymerization

To investigate the reaction mechanism of asymmetric polymerization, we conducted a model reaction for the polymerization of 2a, thus the reaction between allylic chloride 5 and *N*-hexyloxyamide 6 was performed in the presence of (S)-1b to give expected branched allylic amide 7 in 98% yield with 97% ee. The CD spectrum of 7 exhibited a spectral pattern similar to that of polymer 4a which was synthesized by use of the same catalyst, (S)-1b. (Figure 5-6) Since the CD spectrum is thought to reflect a local conformation of polymer 4a, the result of spectral analyses indicates that stereogenic carbons in 4a are same absolute configuration as model compound 7. Consequently the present asymmetric polymerization proceeds according to the same reaction mechanism as the asymmetric allylic amidation using the Cp*Ru catalysts.

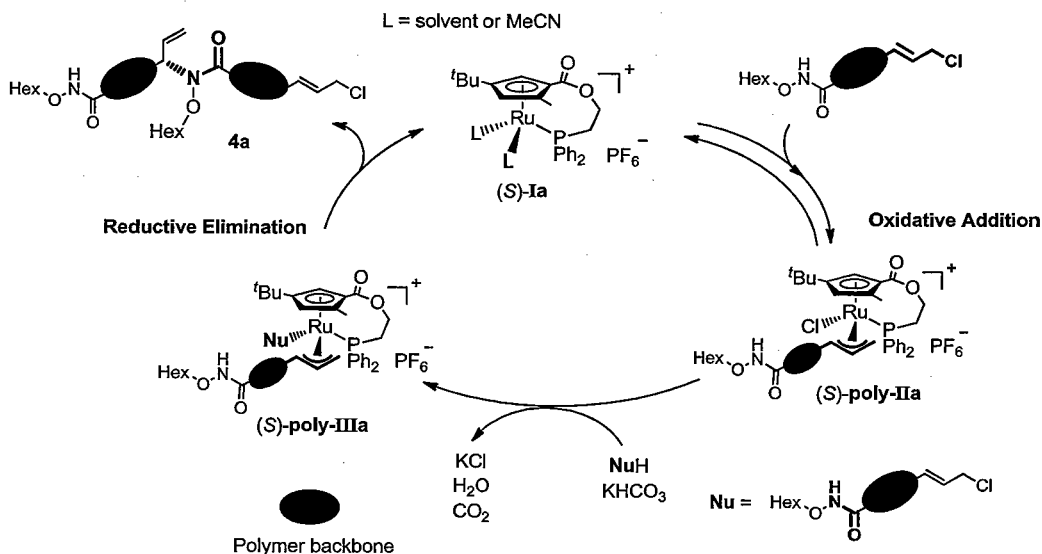
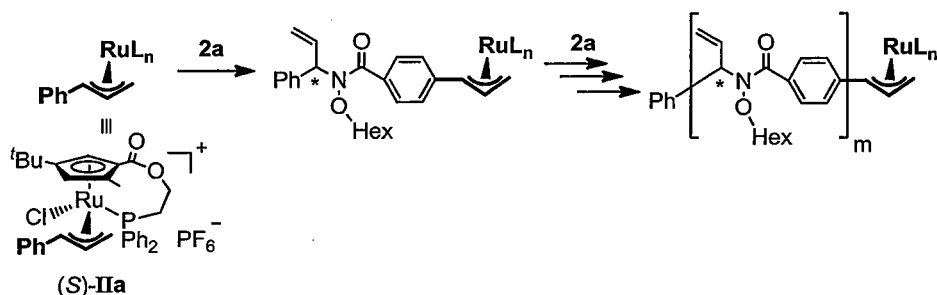


Figure 5-8. Plausible Reaction Mechanism of Asymmetric Polymerization

A plausible reaction mechanism based on the experimental results is illustrated in Figure 5-8. The asymmetric polymerization proceeds according to a reaction mechanism similar to the asymmetric allylic amidation described in Chapter 4, which involves oxidative addition of an allylic moiety to (S)-I affording the π -allyl intermediate (S)-poly-IIa with high diastereoselectivity. Subsequent inside attack of the amide nucleophile via Ru-amide complex (S)-poly-IIIa gives branched allylic amide polymers. The present polymerization can be classified as an asymmetric condensation polymerization by allylic amidation reaction.

Recently, Yokozawa and co-workers reported a condensation polymerization catalyzed by an organonickel complex and proposed a mechanism involving chain growth condensation polymerization, in which the catalytic active site exists on the polymer end and propagation reaction occurs at the polymer end, that is, a mechanism like a living polymerization mechanism.²³ The important point in such the polymerization is that one catalyst forms one polymer chain (Scheme 5-10). In our case, to obtain more detailed information on the polymerization mechanism, we examined the polymerization of **2a** in the presence of π -allyl complex (S)-poly-IIa (Ar=Ph) as catalyst instead of (S)-Ib. If chain growth polycondensation

Catalyst transfer mechanism

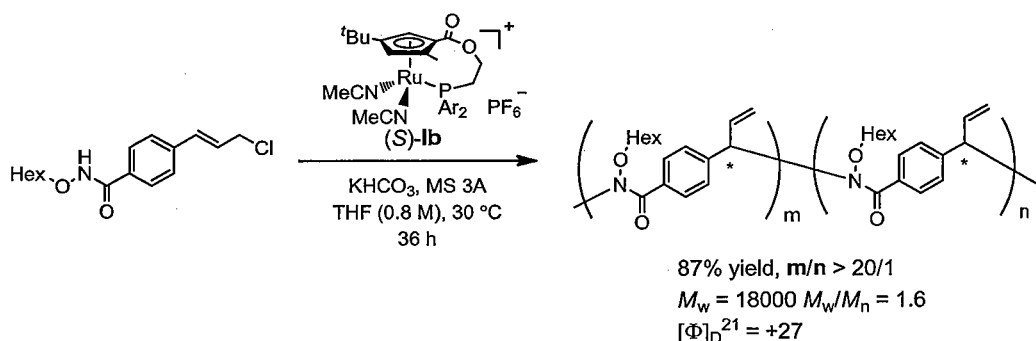


Scheme 5-10. Chain Growth Polymerization Mechanism

occurs in the system, a polymer with narrow molecular weight distribution (MWD) would be expected to form by the catalysis of (S)-IIa ($\text{Ar}=\text{Ph}$) as initiator. The reaction smoothly proceeded to give **4a** in good yield with high regioselectivities, but the polymer has rather wide MWD ($M_w = 11000$, $M_w/M_n = 2.2$ before purification) similar to that of **4a** prepared by (S)-Ib. The result implies that the present asymmetric polymerization does not proceed via chain growth condensation polymerization mechanism.

5-7. Conclusion

In this Chapter, we demonstrated the asymmetric polymerization by use of the repeating asymmetric allylic amidation catalyzed by planar-chiral Cp^*Ru complexes. The structure of resulting polymer was analyzed by ^1H NMR, UV, and CD spectroscopic methods, and it has been proved that the polymerization proceeds with high regio- and enantioselectivity. This is the first asymmetric polymerization using asymmetric allylic substitution. The result indicates that the planar-chiral Cp^*Ru catalysts work as a highly efficient catalyst for controlling the stereochemistry even in a polymerization reaction.



5-7 Experimental Procedure

General. All reactions were carried out under Ar atmosphere using Schlenk technique, whereas the workup was performed in air. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on Varian Mercury 300, JEOL ECA400 and JEOL ECA500 spectrometers. Enantiomeric excess was obtained by HPLC analysis using Shimadzu LC-10 and SPD-10AV equipped with DAICEL Chiralcel OD-H columns. Polymerization progress was checked by Gel permeation chromatography equipped with TOSHO α -M using Shimadzu LC-6AD and Shimadzu SPD-10A UV-VIS detector. Optical power rotation was measured on JASCO DIP-1000. CD spectra were measured by JASCO J-720WO. UV spectra were measured by Shimadzu UV 3100PC. Thermogravimetric analysis (TGA) was conducted under a nitrogen atmosphere, from 25 to 500 $^\circ\text{C}$ at a heating rate of 10 $^\circ\text{C}$ using Mettler-Toledo TGA/DSC 1 STAR $^\circ$ System.

Materials. All solvents used for reactions were passed through purification columns just before use. Planar-chiral Cp $^*\text{Ru}$ complex **Ia** and **Ib** was prepared as reported previously.^{24,25}

Standard method of the polymerization of **2a**

To a solution of (*E*)-4-(3-chloroprop-1-en-1-yl)-*N*-hexyloxy-benzamide (0.25 mmol, mol) and Cp $^*\text{Ru}$ catalyst (7 μmol , 3 mol%) in THF were added potassium bicarbonate (0.30 mmol), and the reaction mixture was stirred. After 36 h, MeOH (5 mL) was added and stirred for 10 min. The filtrate was extracted with dichloromethane, and combined organic layer was washed with brine. After dried over Na_2SO_4 , the solvent was removed under reduced pressure. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography with CH_2Cl_2 to give yellow-brown solid. **2a**: ^1H NMR (CDCl_3 , 500 MHz): δ 7.69 (d, 1H, J = 8.0 Hz, Ar), 7.49 (d, 1H, J = 8.0 Hz, Ar), 7.69 (ddd, 1H, J = 17.3, 10.2, 7.2 Hz, CH=), 6.11 (br, 1H, CH), 5.40 (d, 1H, J = 10.2 Hz, CH=), 5.37 (d, 1H, J = 17.3 Hz, CH=), 3.56 (br, 1H, CH), 3.28 (br, 1H, CH), 1.30-0.98 (m, 8H, CH_2), 0.79 (t, 3H, J = 7.2 Hz, CH_3). ^{13}C NMR (CDCl_3 , 126 MHz): δ 169.8, 141.1, 134.0, 133.8, 128.3, 127.9, 119.4, 77.2, 63.7, 31.4, 27.8, 25.4, 22.4, 13.9.

(*E*)-4-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-1-yl)benzoic acid (**3**)

(*E*)-ethyl 3-(4'-cyanophenyl)acrylate

To a DMF solution (45 mL) of 4-bromobenzonitrile (8.20 g, 45 mmol), NaOAc (6.70 g, 67.2 mmol), NBu_4Br (1.50 g, 45 mmol), $\text{Pd}(\text{OAc})_2$ (101 mg, 1 mol%) and tri-*o*-tolylphosphine (8.74 g, 43.5 mmol) was added methyl acrylate (6.70 g, 67.0 mmol), and the reaction mixture was stirred at 140 $^\circ\text{C}$. After 2 h, the reaction mixture was cooled to room temperature, and filtered through Celite. The filtrate was extracted with diethyl ether, and combined organic layer was washed with brine. After dried over Na_2SO_4 , the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 9/1) to give yellow oil (8.74 g, 97%).

3-(4'-formylphenyl)-2-propen-1-ol

To a ether solution (200 mL) of (*E*)-ethyl 3-(4-cyanophenyl) acrylate (4.00 g, 20.0 mmol) was added

dropwise a 1.5 M hexane solution of DIBAL-H (44 mL, 66 mmol) at 0 °C, and the mixture was stirred for 2 h. The reaction was quenched by addition of K₂CO₃. After 30-min stirring at r.t., the resulting solid was removed by filtration. Solid was dissolved in CH₂Cl₂ and added 1M HCl. The yellow suspension was stirred for 30 min at r.t.. The aq layer was further extracted by CH₂Cl₂. The combined organic layers were washed with H₂O, and dried over Na₂SO₄. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to give yellow oil (2.3g, 14.2 mmol, 71%).

(E)-4-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)benzaldehyde

The aldehyde allyl alcohol compound (2.3 g, 14.2 mmol) and CH₂Cl₂ (40 ml) were placed in two bottom flask. To this was added imidazole (1.23 g, 18.2 mmol). After cooling to 0 °C followed by addition of TBDMSCl (2.74 g, 18.3 mmol), the mixture was stirred at 0 °C for 15 min. The resulting precipitate was separated by filtration, and washed with CH₂Cl₂. Evaporation of the combined filtrates followed by silica gel chromatography (hexane/ethyl acetate = 10/1) to give yellow oil (3.5g, 12.6 mmol, 89%).

(E)-4-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)benzoic acid (3)

To a t-BuOH solution (30.0 mL) of the TBDMS-protected aldehyde allyl alcohol compound (3.5 g, 12.6 mmol) and amylene (30 mL) were cooled to 0 °C, and an aq. solution (35 mL) of NaH₂PO₄ (3.40 g, 25 mmol) and NaClO₂ (2.26 g, 25 mmol) was added. The resulting mixture was vigorously stirred at 0 °C for 8 h. After the two phase was separated, the aq layer was extracted by EtOAc. The organic layers were successively washed with 3 M aq KOH (100 mL) and H₂O. The combined aq layers were then carefully acidified by 1 M aq HCl so that pH of the solution became 6. The aq layers were washed with CH₂Cl₂ and dried over Na₂SO₄, and concentrated in vacuo to give (E)-2-(3-(tert-butyldimethylsilyloxy)prop-1-enyl)benzoic acid (4.17 g, 85% yield).

(E)-4-(3-chloroprop-1-en-1-yl)-N-hexyloxy-benzamide (2a)

(E)-4-(3-hydroxyprop-1-en-1-yl)-N-hexyloxy-benzamide

To a solution of THF solution (20 mL) of (E)-4-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)-N-hexyloxy-benzamide (1.92 g, 4.91 mmol) was added 1M HCl aq. and the mixture was stirred for 30 min. The reaction mixture was added EtOAc and H₂O, and extracted with EtOAc, and combined organic layer was washed with brine. After dried over Na₂SO₄, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/1) to give yellow oil (quant).

(E)-4-(3-chloroprop-1-en-1-yl)-N-hexyloxy-benzamide (2a)

A dichloromethane solution (30 mL) of N-chlorosuccinimide (1.03 g, 10.4 mmol) was charged with dimethyl sulfide (643 mg, 10.4 mmol) at 0 °C, and the resulting white suspension was stirred for 5 min. After cooling to -25 °C, a dichloromethane solution (10 mL) of (E)-4-(3-hydroxyprop-1-en-1-yl)-N-hexyloxy-benzamide (977 mg, 3.6 mmol) was added, and the mixture was warmed to 0 °C and stirred for 2 h. The reaction mixture was diluted with water, and extracted with CH₂Cl₂. Combined organic layer was washed with brine and dried over Na₂SO₄. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/ethyl

acetate = 7/3) to give white solid (1.0 g, 94%). ¹H NMR (CDCl₃, 400 MHz): δ 8.65 (br, 1H, NH), 7.70 (d, 2H, *J* = 8.2 Hz, Ar), 7.44 (d, 2H, *J* = 8.2 Hz, Ar), 6.68 (d, 1H, *J* = 15.6 Hz, CH=), 6.40 (d, 2H, *J* = 15.6, 7.1 Hz, CH), 4.24 (d, 2H, *J* = 7.1 Hz, CH₂), 4.02 (t, 2H, *J* = 6.6, CH₂), 1.71 (q, 2H, *J* = 6.6, CH₂), 1.49-1.29 (m, 6H, CH₂), 0.93-0.88 (m, 3H, CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 166.2, 139.5, 132.8, 131.5, 127.5, 127.3, 126.9, 77.2, 44.9, 31.6, 28.0, 25.5, 14.0.

Synthesis of (*E*)-4-((4-(3-chloroprop-1-en-1-yl)phenyl)ethynyl)-*N*-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzamide(2b)

***(E)*-tert-butyl((3-(4-ethynylphenyl)allyl)oxy)dimethylsilane**

To a triethylamine solution (15 mL) of (*E*)-((3-(4-bromophenyl)allyl)oxy)(tert-butyl)dimethylsilane²⁶ (2.4 g, 7.5 mmol), bis(triphenylphosphine)palladium dichloride (262 mg, 0.395 mmol, 5.0 mol%), ethynyltrimethylsilane (1.1 g, 11.3 mmol), was added CuI (71 mg, 0.375 mmol), and the reaction mixture was stirred at 60 °C. After 15 h, the reaction mixture was cooled to room temperature, and filtered through Celite. The filtrate was extracted with ethyl acetate, and combined organic layer was washed with brine. After dried over Na₂SO₄, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20/1) to give orange solid.

To a THF/MeOH solution (1:1, 50 mL) of resulting products was added NaOH aq. (2N, 0.5 mL). The reaction mixture was stirred for 1 h to give dark red solution, and quenched with NH₄Cl aq., and extracted with ethyl acetate. The combined organic layer was washed with brain, and dried over Na₂SO₄. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 9/1) to give brown solid (3.0g, 11.0 mmol, 97%).

4-iodo-*N*-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzamide

To a DMF solution (10 mL) of *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (EDC) (1.7 g, mol), HOBT (512 mg, 11.0 mol), triethylamine (1.8 g, 18.0 mmol) was slowly added an DMF solution (20 mL) of *O*-(2-(2-(2-methoxyethoxy)ethoxy)ethyl)hydroxylamine (1.2 g, 8.6 mmol), followed by 4-iodo benzoic acid (2.0 g, 8.0 mmol). The reaction mixture was allowed to warm to r.t. and stirred overnight. The reaction mixture was extracted with ethyl acetate. Combined organic layer was washed with brine and dried over Na₂SO₄. After removal of the solvent, the residue was purified by silica gel column chromatography (dichloromethane /ethyl acetate = 8/2 to 2/8) to give yellow oil (1.0 g, 40%).

***(E)*-4-((4-(3-chloroprop-1-en-1-yl)phenyl)ethynyl)-*N*-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzamide (2b)**

To a triethylamine solution (15 mL) of (*E*)-((3-(4-bromophenyl)allyl)oxy)(tert-butyl)dimethylsilane (1.4 g, 5.0 mmol), bis(triphenylphosphine)palladium dichloride (70 mg, 0.1 mmol), 4-iodo-*N*-(2-(2-(2-methoxyethoxy)ethoxy)ethoxy)benzamide (1.6 g, 4.6 mmol), PPh₃ (52.4 mg, 0.2 mmol) was added CuI (19 mg, 0.1 mmol), and the reaction mixture was stirred at room temperature. After 7 h, the reaction mixture was filtered through Celite. The filtrate was extracted with ethyl acetate, and combined organic layer

was washed with brine. After dried over Na₂SO₄, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane /ethyl acetate = 7/3 to ethyl acetate/methanol = 20/1) to give pale brown solid.

Resulting product was dissolved in THF (20 mL), HCl (1N, 30 mL). The reaction mixture was stirred for 30 min. The reaction mixture was extracted with ethyl acetate and washed with brine. Combined organic layer was washed with brine and dried over Na₂SO₄. After removal of the solvent, the residue was purified by silica gel column chromatography (dichloromethane /ethyl acetate = 8/2 to 2/8) to give yellow oil.

A dichloromethane solution (10 mL) of *N*-chlorosuccinimide (667 mg, 5.0 mmol) was charged with dimethyl sulfide (0.4 mL, 5.0 mmol) at -25 °C, and the resulting white suspension was stirred for 5 min. After cooling to -25 °C, a dichloromethane solution (20 mL) of resulting allylic alcohol was added, and the mixture was warmed to 0 °C and stirred for 2 h to give brown solution. The reaction mixture was diluted with water, and extracted with CH₂Cl₂. Combined organic layer was washed with brine and dried over Na₂SO₄. After removal of the solvent, the residue was purified by silica gel column chromatography (dichloromethane /ethyl acetate = 7/3 to ethyl acetate/methanol = 20/1) to give pale yellow solid (1.0 g, 44%). ¹H NMR (CDCl₃, 400 MHz): δ 10.3 (br, 1H, NH), 7.79 (d, 2H, *J* = 7.8 Hz, Ar), 7.55 (d, 2H, *J* = 7.8 Hz, Ar), 7.48 (d, 2H, *J* = 7.6 Hz, Ar), 7.37 (d, 2H, *J* = 7.6 Hz, Ar), 6.64 (d, 2H, *J* = 15.6 Hz, CH=), 6.34 (dt, 1H, *J* = 15.6, 7.1 Hz, CH=), 4.24 (d, 2H, *J* = 7.1 Hz, CH₂), 4.19 (br, 2H, CH₂), 3.80 (br, 2H, CH₂), 3.70-3.62 (br, 6H, CH₂), 3.47 (br, 2H, CH₂), 3.27 (s, 3H, CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 165.2, 136.2, 133.4, 132.2, 132.1, 131.7, 131.4, 127.4, 126.8, 126.2, 122.5, 91.7, 89.7, 75.1, 71.8, 70.4, 70.4, 70.3, 70.0, 59.9, 45.3.

Synthesis of (E)-4-((hexyloxy)carbamoyl)benzyl 4-(3-chloroprop-1-en-1-yl)benzoate (2c)

4-formyl-N-hexyloxybenzamide

To a dichloromethane solution (10 mL) of *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (EDC) (2.0 g, 10.4 mol), DMAP (1.3 g, 11.0 mol) was slowly added an dichloromethane solution (10 mL) of *N*-hydroxydimethylamine (1.2 g, 10.0 mmol), followed by 4-formylbenzoic acid (1.5 g, 10 mmol) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred overnight. The reaction mixture was extracted with dichloromethane. Combined organic layer was washed with brine and dried over Na₂SO₄. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 7/3) to give white solid (1.0 g, 40%).

4-(hydroxymethyl)-N-hexyloxybenzamide

To a ethanol (30 mL) solution of 4-formyl-N-hexyloxybenzamide (1.0 g, 4.0 mmol) was added NaBH₄ (152 mg, 4.0 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was quenched with water (1.0 mL) and extracted with ethyl acetate. Combined organic layer was washed with brine and dried over Na₂SO₄. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 7/3) to give white solid (0.99 g, 99%).

(E)-4-((hexyloxy)carbamoyl)benzyl 4-(3-hydroxyprop-1-en-1-yl)benzoate

To a dichloromethane solution (10 mL) of *N*-[3-(dimethylamino)propyl]-*N'*-ethylcarbodiimide hydrochloride (EDC) (800 mg, 4.2 mol), DMAP (512 mg, 11.0 mol) was slowly added an dichloromethane solution (20 mL) of 4-(hydroxymethyl)-*N*-hexyloxybenzamide (1.0 g, 3.9 mmol), followed by (E)-4-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)benzoic acid (1.2 g, 4.0 mmol) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred overnight. The reaction mixture was extracted with dichloromethane. Combined organic layer was washed with brine and dried over Na₂SO₄. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 7/3) to give white solid (1.0 g, 40%).

To a solution of THF solution (10 mL) of (E)-4-((hexyloxy)carbamoyl)benzyl 4-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-1-yl)benzoate was added 1M HCl aq. (10 mL) and the mixture was stirred for 30 min. The reaction mixture was added EtOAc and H₂O, and extracted with EtOAc, and combined organic layer was washed with brine. After dried over Na₂SO₄, the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 1/2) to give yellow solid (640 mg, 40%).

(E)-4-((hexyloxy)carbamoyl)benzyl 4-(3-chloroprop-1-en-1-yl)benzoate (2c)

A dichloromethane solution (10 mL) of *N*-chlorosuccinimide (600 mg, 4.5 mmol) was charged with dimethyl sulfide (0.3 mL, 4.5 mmol) at 0 °C, and the resulting white suspension was stirred for 5 min. After cooling to -25 °C, a dichloromethane solution (20 mL) of (E)-4-((hexyloxy)carbamoyl)benzyl 4-(3-hydroxyprop-1-en-1-yl)benzoate (640 mg, 1.6 mmol) was added, and the mixture was warmed to 0 °C and stirred for 2 h. The reaction mixture was diluted with water, and extracted with CH₂Cl₂. Combined organic layer was washed with brine and dried over Na₂SO₄. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 7/3) to give white solid (588 mg, 90%). ¹H NMR (CDCl₃, 400 MHz): δ 9.34 (br, 1H, NH), 8.01 (d, 2H, *J* = 7.3 Hz, Ar), 7.77 (d, 2H, *J* = 7.3 Hz, Ar), 7.49-7.41 (m, 4H, Ar), 6.69 (d, 2H, *J* = 15.8 Hz, Ar), 6.43 (dt, 1H, *J* = 15.8, 7.1 Hz, Ar), 5.36 (s, 2H, CH₂), 4.25 (d, 2H, *J* = 7.1 Hz, CH₂), 4.00 (br, 2H, CH₂), 1.37-1.26 (m, 6H, CH₂), 0.87 (s, 3H, CH₃). ¹³C NMR (CDCl₃, 100 MHz): δ 165.9, 140.6, 139.9, 132.6, 131.8, 130.0, 129.1, 127.9, 127.7, 127.4, 126.6, 65.9, 44.8, 31.5, 27.9, 25.4, 22.5, 14.0.

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Chapter 6: Summary

We have been studied on the development of novel asymmetric reaction systems by use of planar-chiral cyclopentadienyl ruthenium (Cp'Ru) complexes. In the thesis we have demonstrated development of a new reaction system using Cp'Ru catalysts toward *precise synthesis* of optically active compounds. Additionally, the high reactivity and selectivity of the system was applied to asymmetric polymerization for the synthesis of novel optically active polymers.

Chapter 2 and Chapter 3 described the first examples of asymmetric substitution reactions with novel types of nucleophiles, metal carboxylate and water, by using (*S*)-Cp'Ru complex as a catalyst. In Chapter 2, we have showed that controlling the ratio of substrates is crucial for achieving high regioselectivity and enantioselectivity of the allylic carboxylation reaction. The reaction have been successfully applied to asymmetric allylic substitution of a variety of allylic chlorides and carboxylates, which include not only aryl-substituted substrates but also alkyl ones to give branched allylic esters with high regio- and enantioselectivities. Synthetic methods using other transition-metal catalysts like palladium complexes may be difficult to realize the selective allylic carboxylation because the resulting allylic esters react again with the metal catalyst via oxidative addition and isomerize to thermodynamically stable linear allylic esters. In Chapter 3, we have found that on the basis of experimental results water works as a nucleophile in a manner similar to the case of allylic carboxylation. As highly useful allylic alcohols as a building block are obtained from the reaction, this direct allylic hydroxylation offers one of the most important synthetic methods. These reactions have been proved to proceed via π -allyl-ruthenium intermediate, which is generated by the oxidative addition of allylic chloride to Ru atom with a high diastereoselectivity. The catalytic system involving the *O*-nucleophiles is rare examples.

In Chapter 4, we described the example of asymmetric auto-tandem allylic amidation/ATRC reaction, which *involves two or more mechanistically distinct reactions* was promoted by only Cp'Ru complex. Ruthenium has a characteristic redox property of $\text{Ru}^{\text{II}}/\text{Ru}^{\text{IV}}$ and $\text{Ru}^{\text{II}}/\text{Ru}^{\text{III}}$ and this feature of ruthenium complexes may work expediently in different types of catalyses involving mechanistically distinct allylic substitution ($\text{Ru}^{\text{II}}/\text{Ru}^{\text{IV}}$) and atom transfer radical cyclization ($\text{Ru}^{\text{II}}/\text{Ru}^{\text{III}}$) leading to the present asymmetric auto-tandem reaction. The results exemplify that the asymmetric auto-tandem catalysis is an efficient and environmentally benign synthetic method for useful chiral γ -lactams with well-controlled

multi stereogenic centers. To best our knowledge, this is the first example of asymmetric auto-tandem catalysis.

Finally, in Chapter 5, we have applied the Cp'Ru-catalyzed asymmetric allylic substitution to the asymmetric allylic amidation, which has been successfully extended to an asymmetric polymerization to produce the poly(amide) with high regio- and enantioselectivity in the main chain. The precise synthesis of optically active polymers by means of asymmetric polymerization is generally very difficult, since highly enantioselective reaction has to be maintained throughout polymerization, but our results indicate that the planar-chiral Cp'Ru catalysts can work as a highly efficient catalyst for controlling the stereochemistry even in polymerization reaction. The Cp'Ru-catalyzed polymerization provides one of new and novel types of asymmetric polymerization. Additionally, as the resulting poly(amide) has still terminal double bond per monomer unit, the polymer may be transferred to a variety of functional polymers.

In conclusion, the asymmetric reaction catalyzed by planar-chiral cyclopentadienyl ruthenium (Cp'Ru) complexes, described in the thesis, should contribute the development of novel *precise synthesis* in the fields of both organic chemistry and polymer science.

List of Publication

1. Naoya Kanbayashi and Kiyotaka Onitsuka: Enantioselective Synthesis of Allylic Esters via Asymmetric Allylic Substitution with Metal Carboxylates Using Planar-Chiral Cyclopentadienyl Ruthenium Catalysts, *J. Am. Chem. Soc.* **2010**, *132*, 1206-1207. (**Chapter 2**)
2. Naoya Kanbayashi and Kiyotaka Onitsuka: Ruthenium-Catalyzed Regio- and Enantioselective Allylic Substitution with Water: Direct Synthesis of Chiral Allylic Alcohols, *Angew. Chem. Int. Ed.* **2011**, *50*, 5197-5199. (**Chapter 3**).
3. Naoya Kanbayashi, Tazuhiro Takenaka, Taka-aki Okamura and Kiyotaka Onitsuka: Asymmetric Auto-Tandem Catalysis by Planar-Chiral Cyclopentadienyl-Ruthenium Complex: Sequential Asymmetric Allylic Amidation and Atom Transfer Radical Cyclization, Submitted to *Angew. Chem. Int. Ed.* (**Chapter 4**).
4. Naoya Kanbayashi, Taka-aki Okamura and Kiyotaka Onitsuka: Asymmetric Polymerization by means of Asymmetric Allylic Substitution Catalyzed by Planar-Chiral Cyclopentadienyl Ruthenium Complex, to be submitted (**Chapter 5**).

Related Publications

1. Koichiro Takii, Naoya Kanbayashi and Kiyotaka Onitsuka: Modular synthesis of optically active lactones by Ru-catalyzed asymmetric allylic carboxylation and ring-closing metathesis reaction, *Chem. Commun.* **2012**, *48*, 3872-3874..