



Title	Construction of Quaternary Carbon Stereogenic Centers through Copper-Catalyzed Enantioselective Allylic Substitution Reactions
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**Construction of Quaternary Carbon Stereogenic Centers through
Copper-Catalyzed Enantioselective Allylic Substitution Reactions**

**Kentaro Hojoh
2018**

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General Introduction

Quaternary carbon stereogenic centers, which have four different carbon substituents, are attractive synthetic targets found in many bioactive compounds and pharmaceutical intermediates (Figure 1). Thus, development of efficient methods to provide quaternary carbon stereogenic centers in enantiomerically pure states is highly important. However, the enantioselective installation of quaternary carbon stereogenic centers, especially in a catalytic manner, represents one of the most challenging tasks in organic synthesis. This difficulty is due to the increased steric demands of the C–C bond forming process, and thus may require harsh reaction conditions. Moreover, the relatively similar steric environment presented by non-hydrogen substituents is an obstacle to achieving high levels of enantiotopic face selectivity.

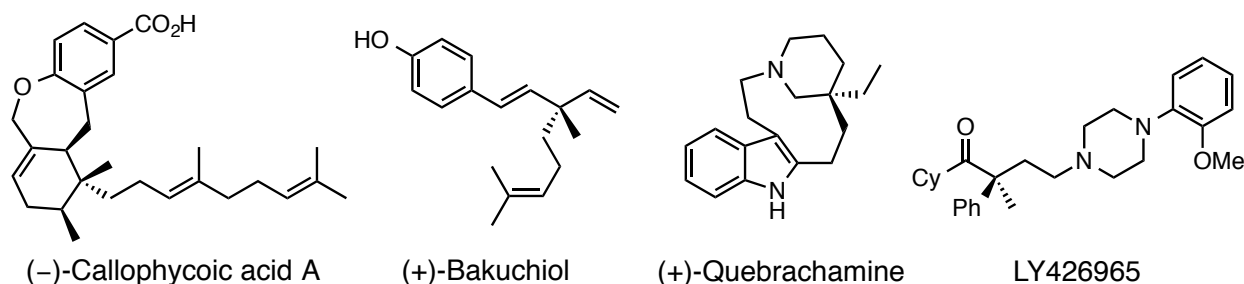


Figure 1. Bioactive Compounds Containing Quaternary Carbon Stereogenic Centers

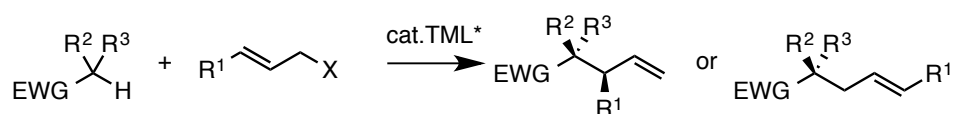
1. Construction of Quaternary Carbon Stereogenic Centers through Transition Metal Catalyzed Allylic Substitution Reactions

1.1. Introduction

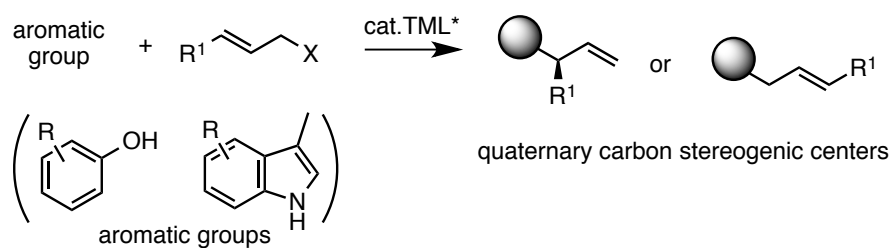
Since its first report in the 70s, transition metal catalyzed enantioselective allylic substitutions have been known to be a versatile method for a wide range of asymmetric C–C bond formation reactions.¹ Advances over the past two decades demonstrate that this protocol is one of the most powerful tools for producing quaternary carbon stereogenic centers. While this approach was historically carried out using Pd catalysts, it was subsequently expanded to Ir-, Rh-, Mo- and Cu-catalyzed reactions. The choice of metals leads to different regioselectivities and expansion of the scope of nucleophiles in the allylation reaction. The following sections outline these methods, categorized into the construction of quaternary carbon stereogenic centers on (i) the nucleophile side (Scheme 1), and (ii) the allyl electrophile side (Scheme 2).

Scheme 1. Construction of Quaternary Carbon Stereogenic Centers on Nucleophile Side

Allylic Substitution Reaction with Soft Carbon Nucleophiles (TM = Pd, Mo, Ir, Rh etc.)

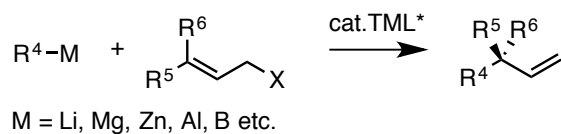


Allylic Dearomatization Reaction (TM = Pd, Ir)



Scheme 2. Construction of Quaternary Carbon Stereogenic Centers on Allyl Electrophile Side

Allylic Cross-Coupling with Organometallic Reagents (TM = Cu, Pd)



1.2. Construction of Quaternary Carbon Stereogenic Centers on Nucleophile Side

1.2.1. Allylic Substitution with Soft Carbon Nucleophiles

1.2.1.1. Pd-Catalysis

Pd-catalyzed enantioselective allylic substitution of “soft” stabilized or non-stabilized carbon nucleophiles such as carbonyl enolates and enamines is the most common method for construction of α -quaternary carbonyl compounds.¹ The typical reaction involves the well-known π -allylpalladium intermediate derived from the oxidative addition of allyl substrates to palladium(0) species (Figure 2). Subsequent attack of the carbon nucleophile to the electrophilic π -allylpalladium species results in the allylic substitution product and regeneration of the palladium(0) species.

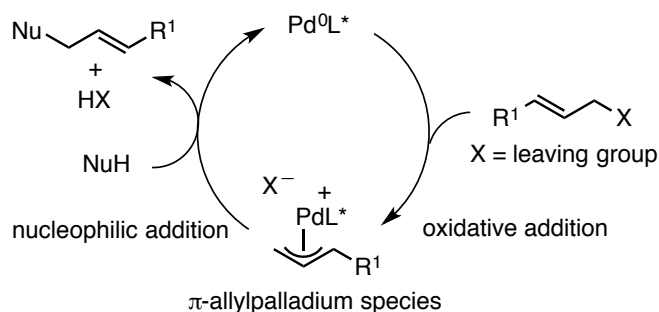
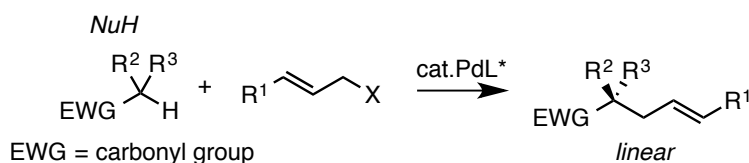


Figure 2. General Principle of Pd-Catalyzed Enantioselective Allylic Substitution

Since nucleophilic attack generally occurs at the sterically less hindered side of the π -allylpalladium species, the reaction of allylic electrophiles that are substituted at only one terminus provides linear and achiral products. Thus, quaternary carbon stereogenic centers are generated by the reaction of prochiral carbon nucleophiles bearing three distinct substituents. A typical example of such nucleophiles is a trisubstituted enolate, generated by deprotonation of the α -proton of a carbonyl compound (Scheme 3).

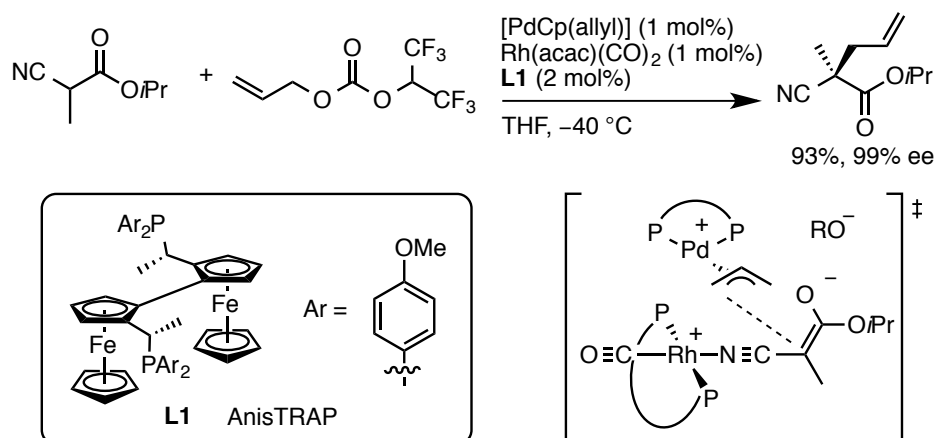
Scheme 3. Pd-Catalyzed Asymmetric Allylic Substitution



In 1996, Sawamura and Ito reported that the allylation of α -cyano esters proceeded with excellent enantioselectivity under the influence of a Pd/Rh-dual catalytic system using AnisTRAP

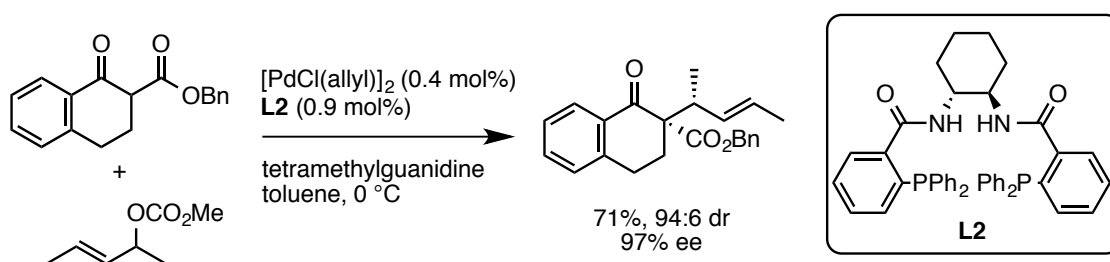
(**L1**) as a ligand (Scheme 4).² In this reaction, the palladium complex activates the allyl electrophile by forming the π -allylpalladium species, while the rhodium complex is coordinated by the cyano group of the cyanoester substrate and to control the enantioselectivity.

Scheme 4. Pd-Rh Two-Component Catalytic System



Soon after, Trost reported an asymmetric allylic substitution in cyclic systems. The use of the Trost-type ligand (**L2**) in the reaction between 2-carboalkoxycyclohexanone derivatives and allyl acetates afforded the corresponding product with high ee (Scheme 5).³ The author demonstrated the enantio- and diastereoselective reaction of 1,3-dimethyl allylic substrates, which could provide a symmetrical π -allyl intermediate.

Scheme 5. Asymmetric Allylic Substitution of β -Ketoester



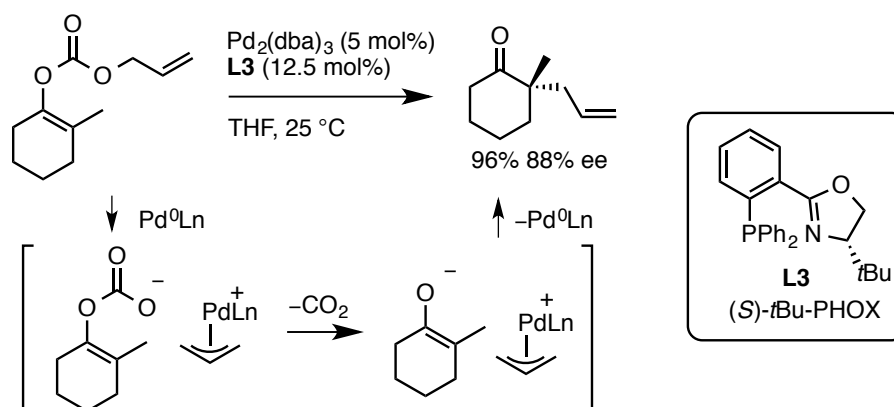
Inspired by these pioneering works, chemists have expanded the scope of nucleophiles to the use of α,α -disubstituted amides,⁴ β -hydroxyacrylate aldehydes,⁵ and α,α -disubstituted aldehydes.⁶

Compared with the aforementioned carbonyl compounds containing α' -blocking groups or α -electron withdrawing groups, position-selective enolate generation of unsymmetrical ketones with multiple acidic α -protons can be particularly challenging. Pd-catalyzed decarboxylative allylation of allyl enol carbonates or allyl β -ketoesters provides an efficient method to generate ketone

enolates as a single isomer.⁷

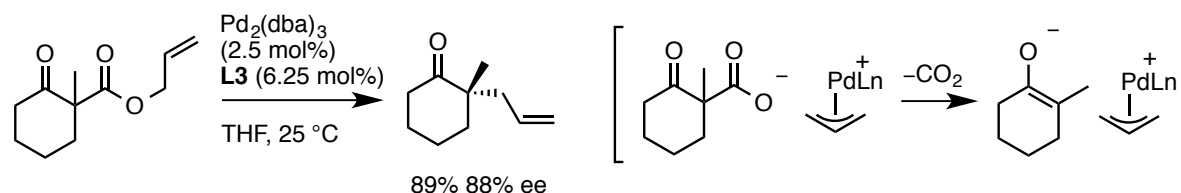
The first example of asymmetric decarboxylative allylic alkylation of allyl enol carbonates was reported by Stoltz in 2006.⁸ The reaction provides synthetically important α -quaternary cyclohexanones from simple alkanone derivatives in a highly enantioenriched form in the presence of the PHOX ligand (**L3**) (Scheme 6).

Scheme 6. Decarboxylative Allylation of Allyl Enol Carbonates

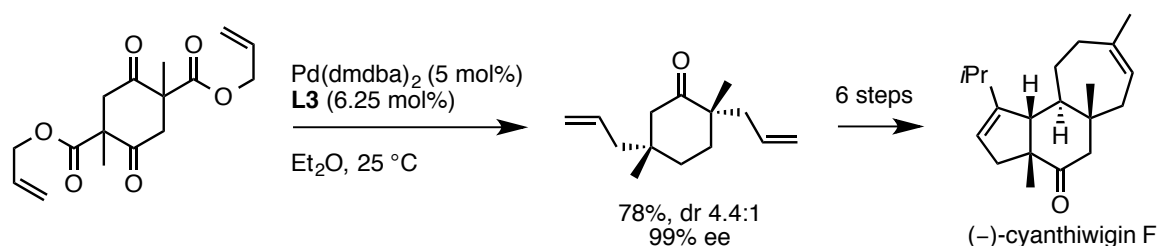


Pd-catalyzed decarboxylative allylic alkylations were expanded to the use of racemic allyl β -ketoesters (Scheme 7).⁹ Stoltz employed a catalytic double enantioselective decarboxylative allylation of the racemic bis- β -ketoester in the total synthesis of (–)-cyanthiwigin F (Scheme 8).^{10,11} This stereoconvergent approach allows the generation of two quaternary carbon stereogenic centers on the cyclohexadione ring with high enantioselectivity. A decarboxylative allylic alkylation in acyclic systems has also been reported.¹²

Scheme 7. Decarboxylative Allylation of β -Ketoesters



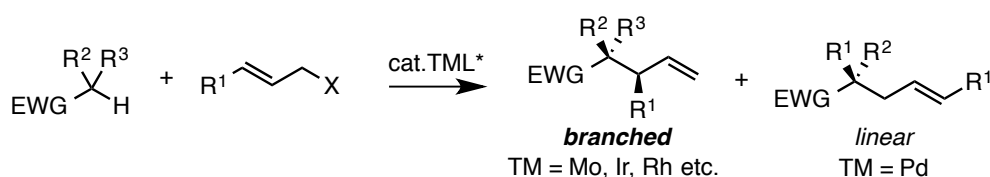
Scheme 8. Synthesis of Cyanthiwigin F through Double Decarboxylative Allylation



1.2.1.2. Mo, Ir, and Rh Catalysis

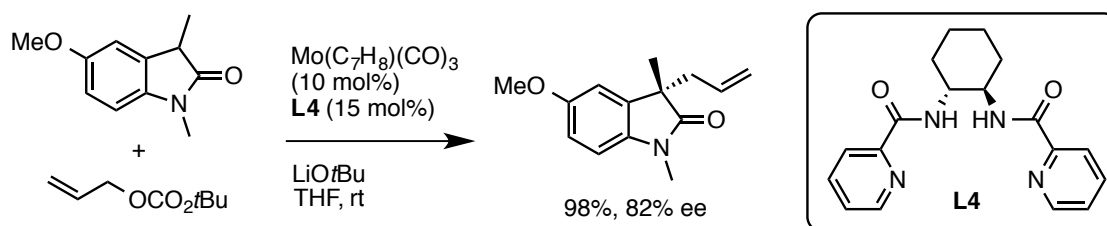
In contrast to the case of palladium, allylic substitutions with unsymmetric allylic substrates catalyzed by other transition metals preferentially form branched products through attack of the nucleophile at the more substituted carbon of the allylmetal moiety (Scheme 9).¹³ Therefore, these catalyst systems enable simultaneous stereocontrol of both prochiral carbon nucleophiles and prochiral allylic electrophiles under appropriate conditions. The reactions catalyzed by Mo, Ir and Rh are shown below.

Scheme 9. Branch-Selective Asymmetric Allylic Substitution

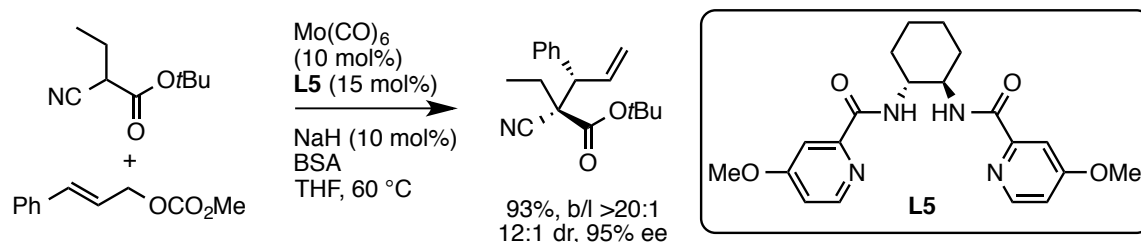


The Mo-catalyzed reaction was reported by Trost in 2006. The enantioselective allylation of prochiral 3-alkyl oxindole, with **L4** as a chiral ligand, provided chiral 3,3'-dialkyl oxindoles (Scheme 10).¹⁴ The author expanded this strategy to a regio-, diastereo- and enantioselective version with cinnamyl carbonate.¹⁵ This method was later extended to the use of β -cyanoesters as prochiral nucleophiles (Scheme 11).¹⁶

Scheme 10. Mo-Catalyzed Allylic Substitution of Oxindoles

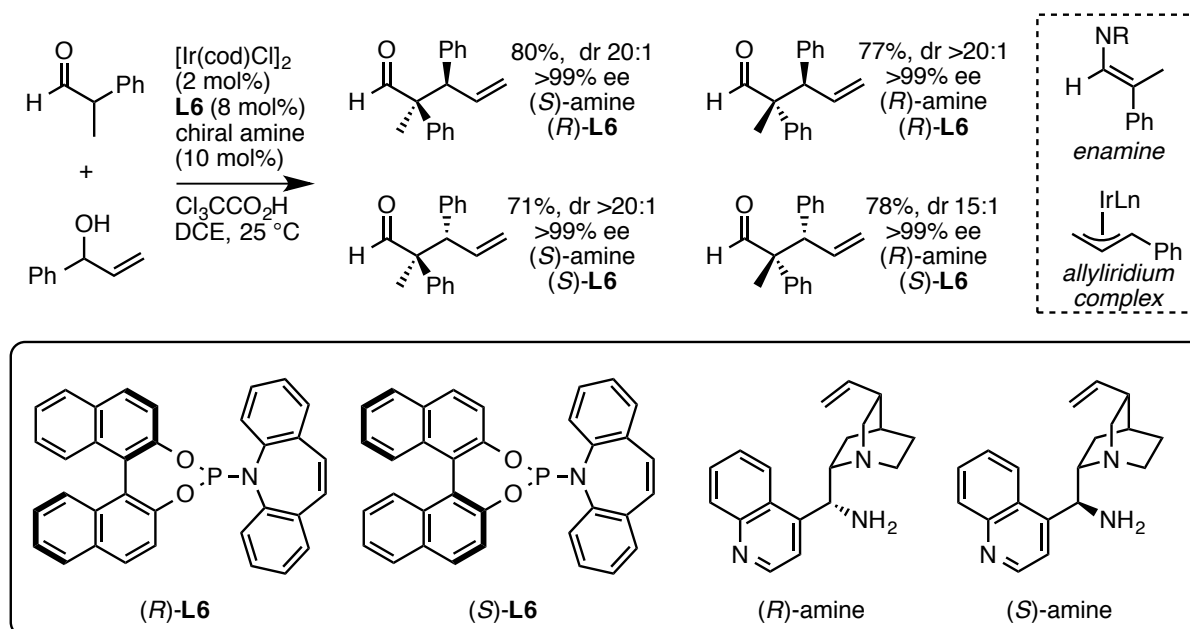


Scheme 11. Mo-Catalyzed Enantio- and Diastereoselective Allylic Substitution of Cyanoesters



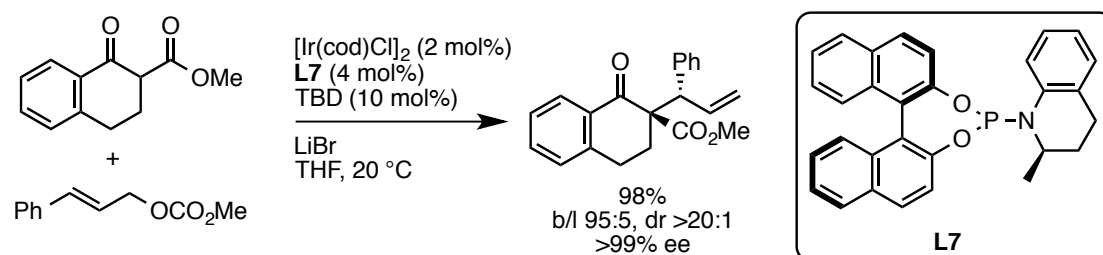
In 2013, Carreira developed the enantio- and diastereodivergent synthesis of γ,σ -unsaturated aldehydes bearing vicinal quaternary/tertiary carbon stereogenic centers (Scheme 12).¹⁷ The asymmetric α -allylation of allylic alcohols with α,α -disubstituted aldehydes was enabled by the dual catalyst system of the Ir/phosphoramidite (**L6**) complex and a cinchona-alkaloid-derived primary amine. All four stereoisomers of the product can be accessed through selection of the suitable pair of chiral iridium complex and chiral amine, which activate the allylic alcohol and aldehyde, respectively. The *in situ* generated chiral enamine attacks the allyliridium complex to give the desired product.

Scheme 12. Ir-Catalyzed Enantio- and Diastereodivergent Allylic Substitution of Aldehydes

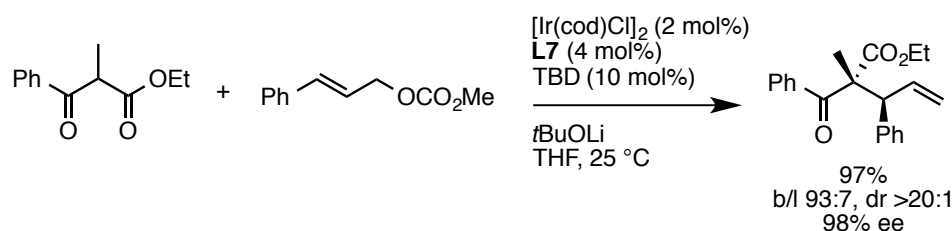


Shortly after this article was published, Stoltz developed the diastereo- and enantioselective allylation of α -substituted β -ketoesters catalyzed by the Ir/phosphoramidite complex (Scheme 13). The reaction provides vicinal quaternary/tertiary carbon stereogenic centers in cyclic systems.¹⁸ Linear β -ketoesters are also applicable to this protocol (Scheme 14).¹⁹

Scheme 13. Ir-Catalyzed Enantio- and Diastereoselective Allylic Substitution of β -Ketoesters

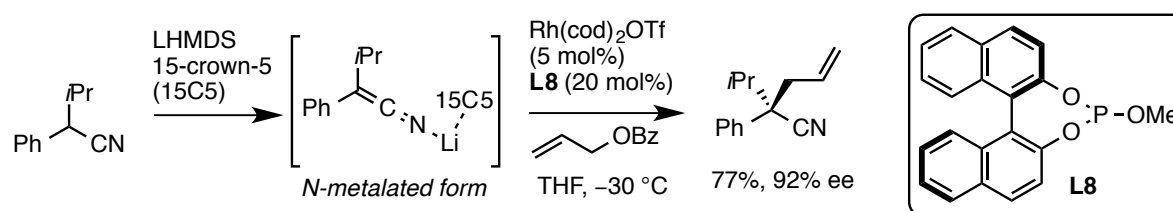


Scheme 14. Enantio- and Diastereoselective Allylic Substitution of Acyclic β -Ketoesters



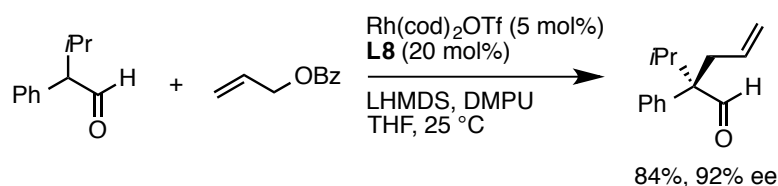
In 2015, Evans demonstrated the allylic alkylation of lithiated α -substituted benzyl nitriles with allyl carbonates using a rhodium complex that was modified by a chiral monodentate phosphite ligand (Scheme 15).²⁰ This is the first report of the direct asymmetric alkylation of a nitrile anion. 15-Crown-5 was used as a deaggregating agent to affect the equilibrium between the C- and N-metalated forms.

Scheme 15. Rh-Catalyzed Direct Asymmetric Alkylation of Nitrile Anions



Later, this strategy was expanded to the use of α -branched aldehydes by the same author.²¹ The direct asymmetric allylic substitution of aldehyde enolates affords synthetically useful α -quaternary aldehydes (Scheme 16). Mechanistic studies revealed that high levels of enantioselectivity could be achieved even from a mixture of (*E*)- and (*Z*)-enolates of the aldehydes.

Scheme 16. Direct Asymmetric Allylic Substitution of Aldehyde Enolate

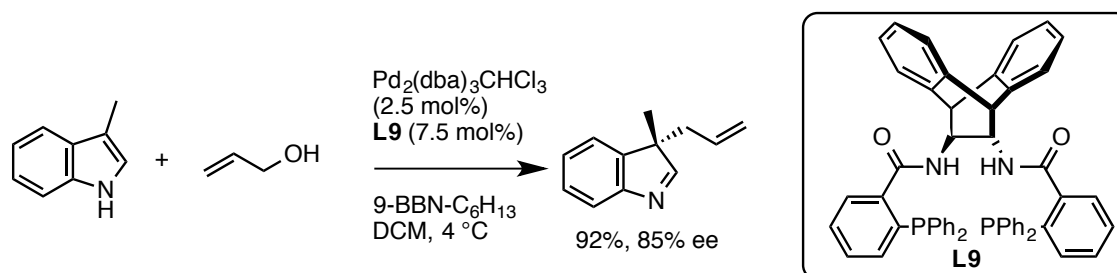


1.2.2. Asymmetric Allylic Dearomatization

Aromatic compounds are highly abundant and readily available materials. Transition metal catalyzed asymmetric allylic dearomatizations serve as a very attractive strategy for construction of polycyclic or spirocyclic compounds containing quaternary carbon stereogenic centers.^{13, 22}

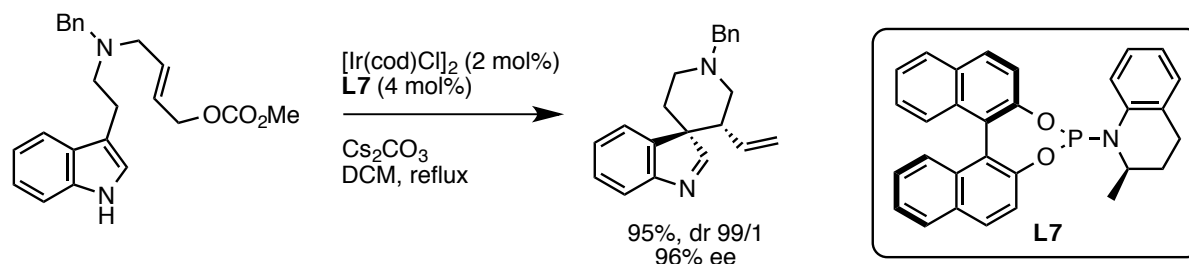
In 2006, Trost reported that the Pd-catalyzed enantioselective C3-allylation of 3-substituted indoles with allylic alcohols employing the chiral anthracene-derived ligand **L9** provided the corresponding chiral 3,3-disubstituted indolenines (Scheme 17).²³

Scheme 17. Pd-Catalyzed Asymmetric Allylic Dearomatization of 3-Substituted Indoles



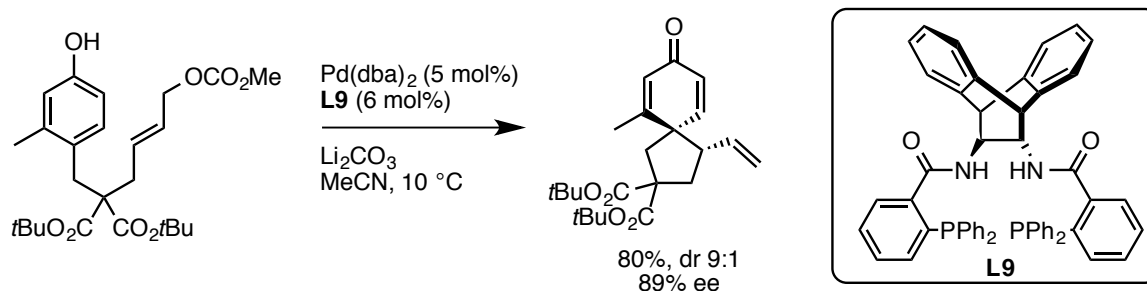
Inspired by Trost's pioneering work, You and co-workers developed an intramolecular allylic dearomatization with tryptamine-derived indolyl allyl carbonate under the influence of the Ir/phosphoramidite catalyst system (Scheme 18).²⁴ The reaction allowed the synthesis of chiral six-membered ring spirocyclic compounds from readily available starting materials and construction of two contiguous stereogenic centers. This protocol was later applied to the construction of enantioenriched five-membered ring spirocyclic compounds²⁵ and nine-membered rings.²⁶

Scheme 18. Asymmetric Synthesis of Six-Membered-Ring Spiroindolenines



Phenols are usually used as oxygen nucleophiles in transition metal catalyzed allylic substitution reactions, but there are few examples of C-allylation. Hamada developed the Pd-catalyzed asymmetric allylic dearomatization reaction of *para*-substituted phenol derivatives containing an allylic carbonate (Scheme 19).²⁷ The reaction gave spirocyclohexadienones with high enantioselectivity.

Scheme 19. Pd-Catalyzed Intramolecular Asymmetric Allylic Dearomatization of Phenols



Later, construction of quaternary carbon stereogenic centers through the asymmetric allylic dearomatization reaction of naphthols was also achieved.²⁸

1.3. Construction of Quaternary Carbon Stereogenic Centers on Allyl Electrophile Side

1.3.1. Cu-Catalyzed $\text{S}_{\text{N}}2'$ Allylic Cross-Coupling with Organometallic Reagents

Copper is one of the cheapest and most readily available transition metals. Cu-catalyzed allylic cross-coupling has enjoyed special attention to promote the coupling of organometallic reagents due to its high $\text{S}_{\text{N}}2'$ affinity (Figure 3, left).²⁹ Hence, Cu-catalysis is complementary to other metal-catalyzed processes. The general principle of Cu-catalyzed allylic cross-coupling is described in Figure 3 (right). The reaction proceeds via initial formation of the organocopper(I)

species, which is generated by transmetallation between the organometallic reagent and the Cu(I) complex. Subsequent S_N2' reaction between the organocopper(I) species and the prochiral allylic substrate provides the cross-coupling product containing a vinyl group. Quaternary carbon stereogenic centers are obtained by the reaction of isomerically pure γ,γ -disubstituted allylic substrates.

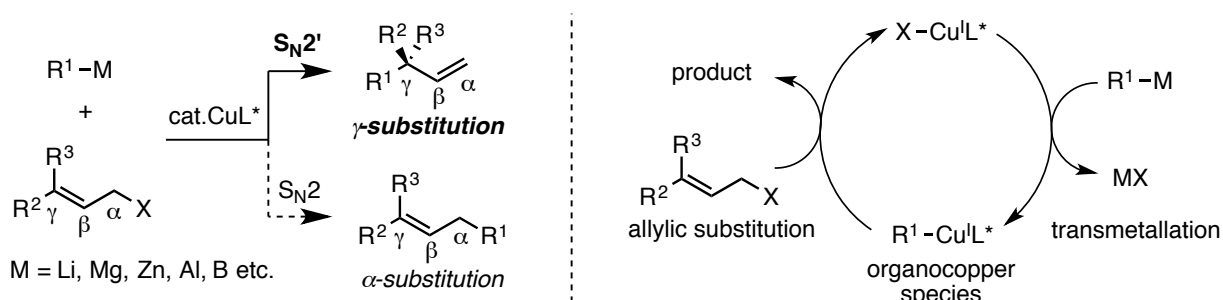


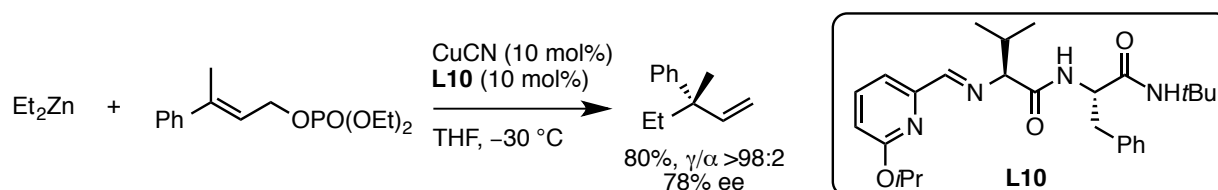
Figure 3. General Principle of Cu-Catalyzed Enantioselective Allylic Cross-Coupling

The last dozen years have witnessed significant progress in Cu-catalyzed enantioselective allylic cross-coupling of various carbon nucleophiles, which provide quaternary carbon stereogenic centers. In the early years in this research area, highly reactive organometallic reagents such as organolithium-, Grignard-, organoaluminum- and diorganozinc reagents attracted much attention.

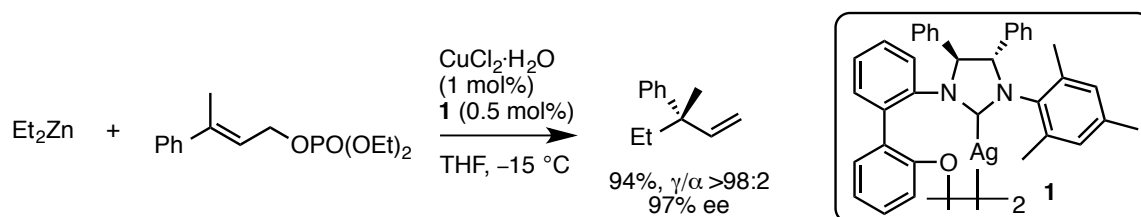
1.3.1.1 Cu-Catalyzed Allylic Cross-Coupling with Organolithium-, Grignard-, Organoaluminum-, and Diorganozinc Reagents

In 2001, Hoveyda reported the allylic alkylation of γ,γ -disubstituted allylic phosphates with dialkylzinc reagents using the peptide-base ligand (**L10**) (Scheme 20).³⁰ Later, the author improved the reaction system³¹ and found that the bidentate NHC-based chiral ligand Ag complex (**1**) enforced higher enantioselectivity with lower loading of the copper catalyst (Scheme 21).³²

Scheme 20. Dialkylzinc Reagents

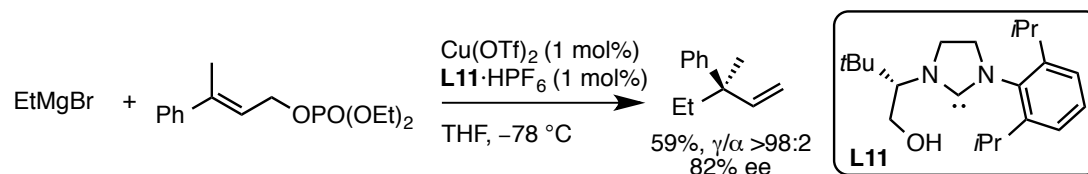


Scheme 21. Optimized Asymmetric Allylic Cross-Coupling with Dialkylzinc Reagents



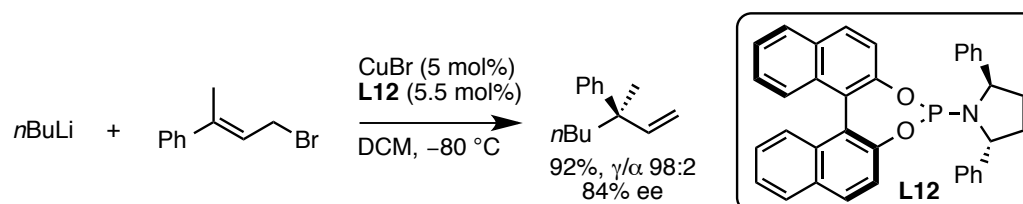
Crévisy and Mauduit demonstrated the allylation reaction with readily available alkylgrignards utilizing the bidentate hydroxyalkyl NHC ligand (**L11**) derived from a chiral amino acid pool (Scheme 22).³³ The reaction provides the corresponding products with high regio- and enantioselectivities.

Scheme 22. Alkylgrignard Reagents



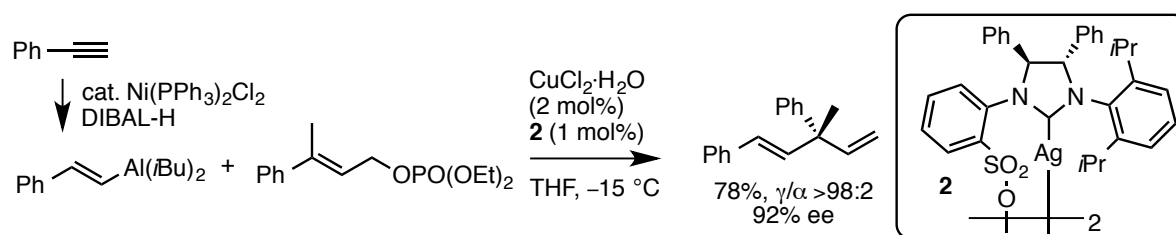
As described by Feringa, alkyllithium reagents also engaged in the Cu/phosphoramidite-catalyzed allylic substitution (Scheme 23).³⁴

Scheme 23. Alkyllithium Reagents



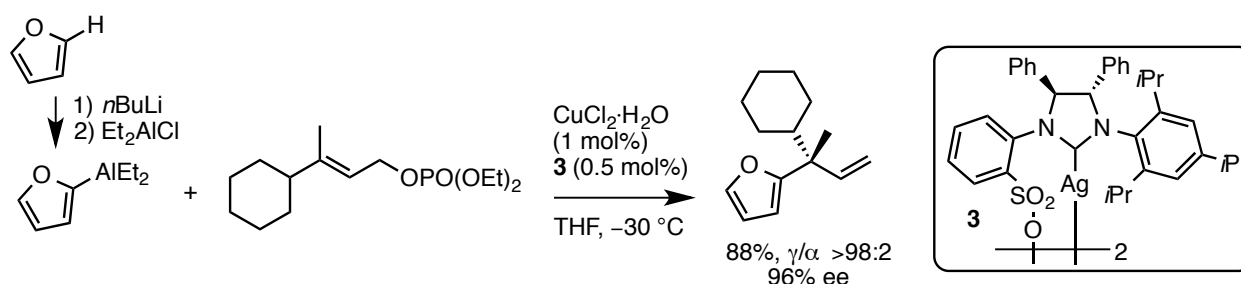
Not only $\text{C}(\text{sp}^3)$, but also $\text{C}(\text{sp}^2)$ and $\text{C}(\text{sp})$, organometallic reagents are able to participate in these reactions. Hoveyda showed that the allylic alkylation of *in situ* prepared alkenylaluminum reagents with γ,γ -disubstituted allylic phosphates provided 1,4-dienes bearing chiral quaternary centers (Scheme 24). High regio- and enantioselectivities were observed in the presence of the Cu catalyst, which were derived from the chiral bidentate sulfonate-based NHC (**2**).³⁵

Scheme 24. Alkenylaluminum Reagents

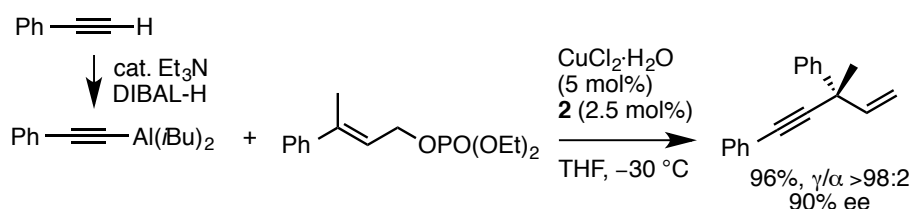


The same author applied this methodology to the use of aryl-³⁶ and alkynylaluminum³⁷ reagents. The reaction provides enantioenriched diaryl- or 1,4-enyne compounds (Schemes 25 and 26).

Scheme 25. Arylaluminum Reagents



Scheme 26. Alkynylaluminum Reagents



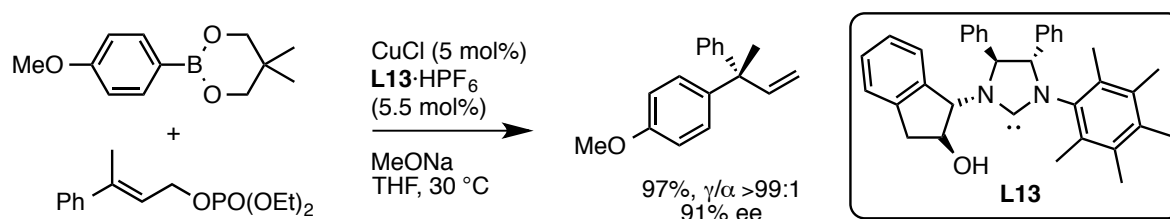
Recently, Feringa found that aryllithium reagents can be applied to the reaction with allyl bromides.³⁸

1.3.1.2 Cu-Catalyzed Allylic Cross-Coupling with Organoboron Reagents

While reactions with the aforementioned highly reactive nucleophiles provide the corresponding quaternary carbon stereogenic centers with high regio- and enantioselectivities, poor to moderate functional group tolerance even at cryogenic temperature can be a problem. To address this shortcoming, the use of organoboron reagents, which are much less reactive but easier to handle and more tolerant to functional groups, has recently emerged as a superior alternative.

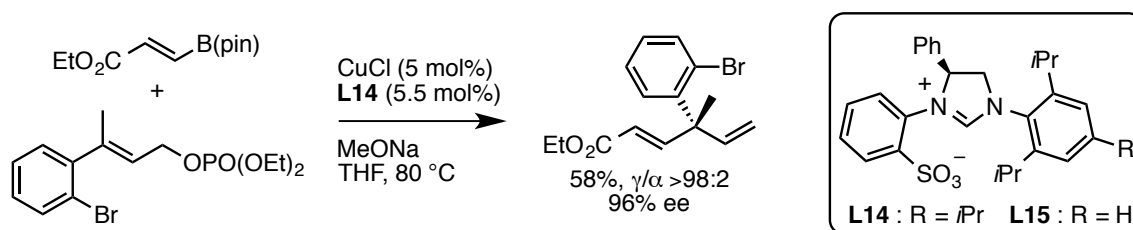
In 2011, Shintani and Hayashi discovered that a combination of a Cu-catalyst, which was modified by a Mauduit-type chiral NHC ligand,³⁹ and MeONa enabled the enantioselective allylic cross-coupling between arylboronic acid esters and allylic phosphates.⁴⁰ Improvement of enantioselectivity and expansion of substrate scope were later achieved with the new chiral NHC ligand (**L13**) (Scheme 27).⁴¹ Control experiments revealed that the hydroxy group in the ligand substituent was crucial for achieving high reactivity and selectivity.

Scheme 27. Arylboronates

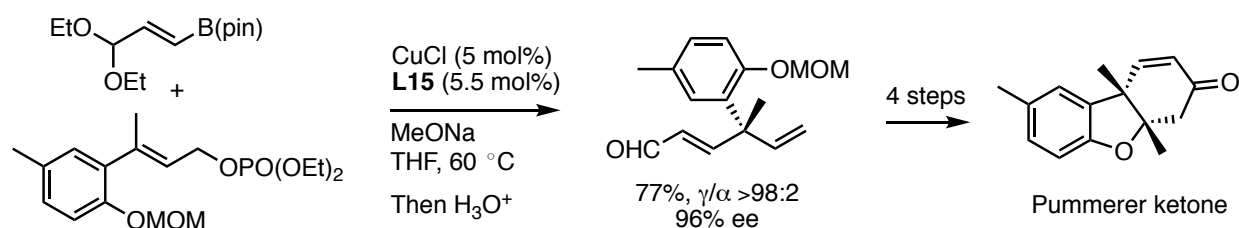


In addition to arylboronates, other types of organoboron reagents are also employed for Cu-catalyzed enantioselective allylic substitutions. In 2012, Hoveyda applied alkenylboronic acid esters to the coupling reaction with allylic phosphates, based on the author's previous work on alkenylaluminum reagents (see Scheme 24) (Scheme 28).⁴² The reaction allowed effective delivery of sensitive organic functional groups that were not compatible with organoaluminum chemistry. The utility of this protocol was demonstrated by the asymmetric synthesis of the Pummerer ketone from an enantioenriched 1,4-diene (Scheme 29).

Scheme 28. Alkenylboronates

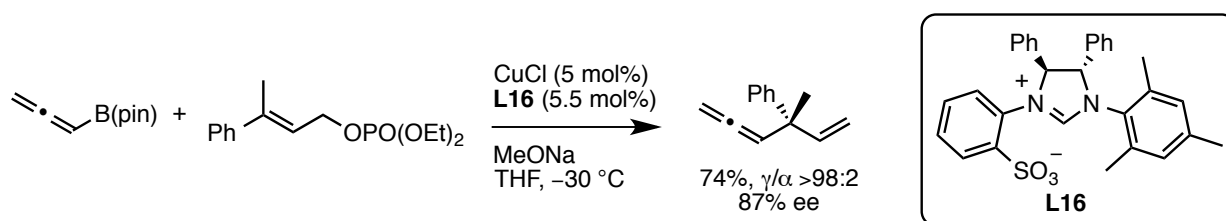


Scheme 29. Asymmetric Synthesis of Pummerer Ketone

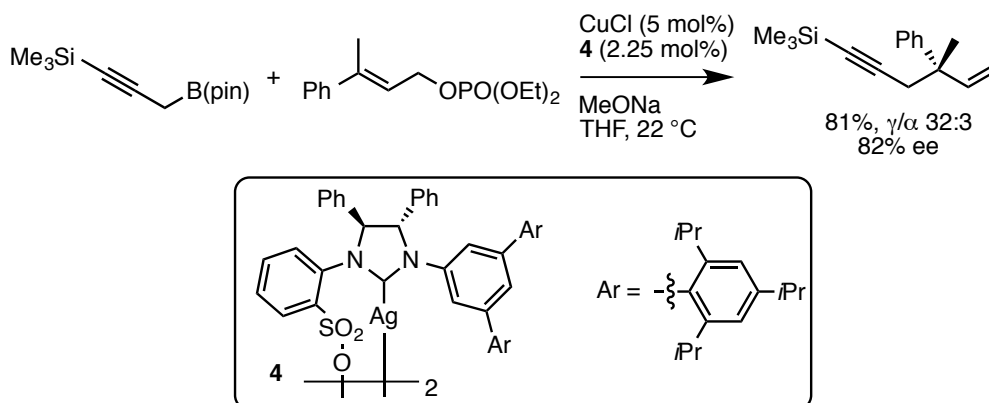


In a contemporaneous report, Hoveyda disclosed that the allylic cross-coupling of allenylboron reagents led to chiral allenes bearing quaternary carbon stereogenic centers with good to high enantioselectivity (Scheme 30).⁴³ More recently, Hoveyda utilized propargylboronic acid pinacol esters in the allylation reaction to afford 1,5-enynes containing quaternary carbon stereogenic centers (Scheme 31).⁴⁴

Scheme 30. Allenylboronates



Scheme 31. Propargylboronates

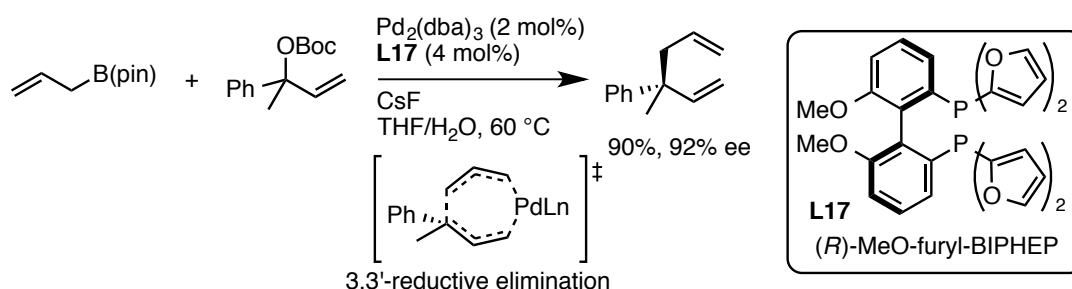


1.3.2. Pd-Catalyzed Branch-Selective Allyl-Allyl Coupling with Allylboronates

Morken found that allylboronates were useful reagents for Pd-catalyzed enantioselective allylic substitutions. The reaction between racemic tertiary allylic carbonates and allylboronic acid pinacol esters was effectively catalyzed by the Pd/MeO-furyl-BIPHEP complex to provide 1,5-

dienes containing quaternary carbon stereogenic centers in highly regio- and enantioselective fashion (Scheme 32).⁴⁵ Mechanistic experiments suggest that the reaction proceeded by way of 3,3'-reductive elimination of the bis-(η^1 -allyl)palladium intermediates.

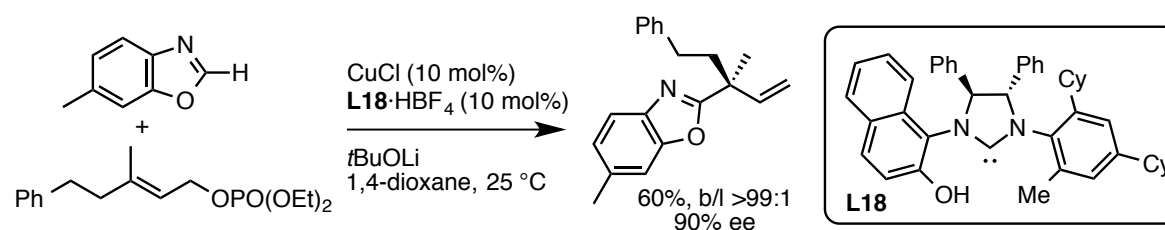
Scheme 32. Pd-Catalyzed Asymmetric Allylic Substitution with Allylboronates



1.3.3. Asymmetric $\text{C}(\text{sp}^2)\text{--H}$ Allylation with Azoles

In 2016, Ohmiya and Sawamura showed that azoles participate in the Cu-catalyzed asymmetric $\text{C}(\text{sp}^2)\text{--H}$ allylation of γ,γ -disubstituted allylic phosphates to form quaternary carbon stereogenic centers at the position α to the heteroaromatic ring (Scheme 33).⁴⁶ The use of the chiral naphthol-carbene ligand (**L18**), which was developed by the Ohmiya and Sawamura group, enabled the reaction. A variety of azoles were used directly without premetalation of the $\text{C}(\text{sp}^2)\text{--H}$ bond.

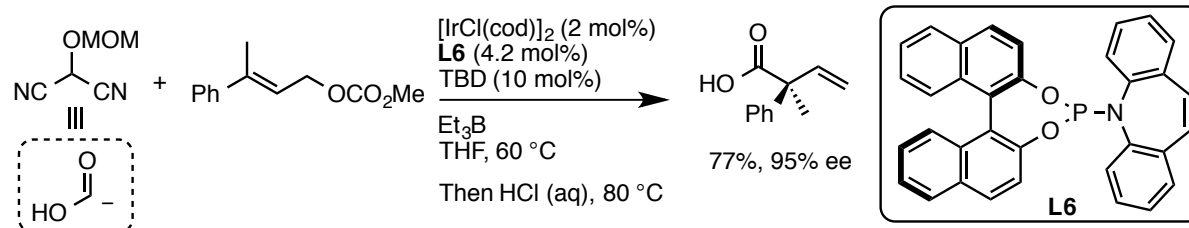
Scheme 33. Asymmetric $\text{C}(\text{sp}^2)\text{--H}$ allylation with Azoles



1.3.4. Ir-Catalyzed Enantioselective Synthesis of α -Quaternary Carboxylic Acids

Most recently, Stoltz achieved the construction of a quaternary carbon stereogenic center on the allyl electrophile side through an Ir-catalyzed enantioselective allylic alkylation of the masked acyl cyanide (MAC) reagent, which is an umpolung synthon of a carboxylic acid, with γ,γ -disubstituted allyl carbonates (Scheme 34).⁴⁷ Hydrolysis of the MAC-functionalized product provided direct access to the corresponding enantioenriched α -quaternary carboxylic acids.

Scheme 34. Ir-Catalyzed Enantioselective Synthesis of α -Quaternary Carboxylic Acid



2. Overview of this Thesis

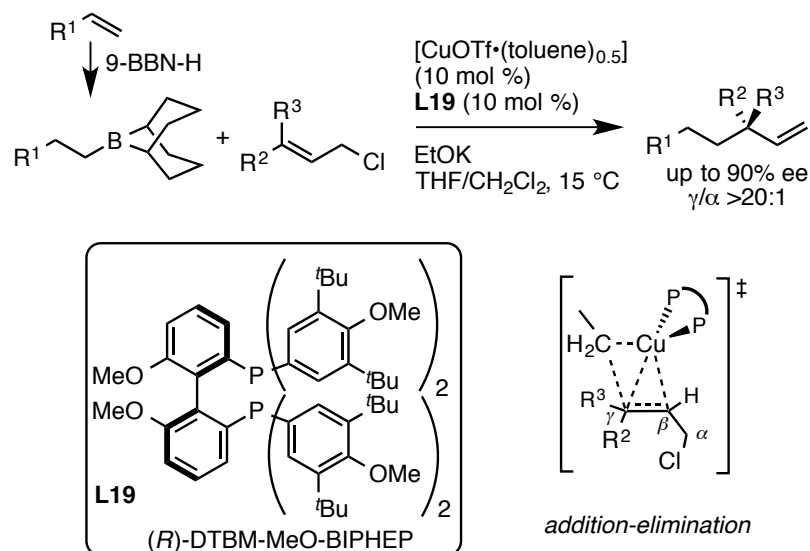
The author developed Cu-catalyzed enantioselective allylic substitution reactions for the construction of quaternary carbon stereogenic centers. All of them proceeded under mild conditions with good to excellent enantioselectivities and showed high functional group compatibility. In chapters 1 and 2, the author discusses the reactions between alkyl-9-BBN, an alkylboron reagent, and allyl chlorides. In chapter 1, intermolecular allylic cross-coupling under the catalysis of a Cu(I) system is described. In chapter 2, construction of chiral cyclic compounds through intramolecular allylic cross-coupling of alkyl-9-BBN reagents with allyl chlorides is shown. In chapter 3, a highly regio- and enantioselective three-component coupling of isocyanides, hydrosilanes, and γ,γ -disubstituted allylic phosphates is described.

2.1. Construction of Quaternary Stereogenic Carbon Centers through Copper-Catalyzed Enantioselective Allylic Cross-Coupling with Alkylboranes (Chapter 1)

As mentioned in section 1.3.1.2., Cu-catalyzed allylic cross-coupling of organoboron reagents is a powerful synthetic method for functionalized quaternary carbon stereogenic centers. Despite many efforts, the applicable reagents have been limited to aryl-, alkenyl-, allenyl- and propargylboron compounds. The use of alkylboron reagents has not been achieved.

In chapter 1, the author describes an enantioselective allylic cross-coupling of primary γ,γ -disubstituted allyl chlorides with alkyl-9-BBN reagents under the influence of an *in situ* generated chiral Cu(I)/DTBM-MeO-BIPHEP catalyst and EtOK system (Scheme 35). 3,5-Di-*t*-butyl-4-methoxyphenyl (DTBM) substituents on the phosphorus atoms were essential not only for enantiocontrol but also for catalytic activity. The reaction provides quaternary carbon stereogenic centers containing three sp³-alkyl groups and a vinyl group. A possible reaction pathway involving addition/elimination of a neutral alkylcopper(I) species with the allyl chloride substrate is proposed.

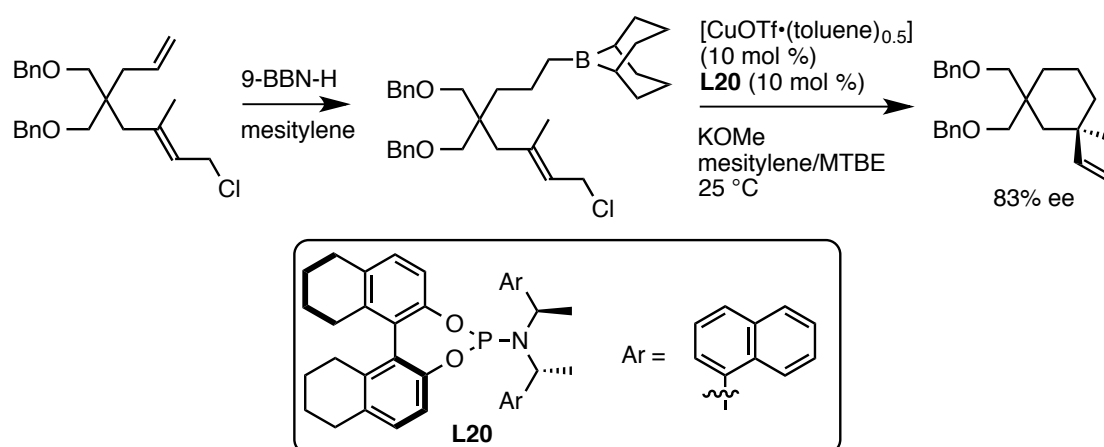
Scheme 35. Cu-Catalyzed Enantioselective Allylic Substitution with Alkylboranes



2.2. Copper-Catalyzed Enantioselective Intramolecular Alkylboron Allylic Alkylation (Chapter 2)

In chapter 2, the author describes enantioselective reductive cyclization of allyl chlorides tethered to a terminal alkene that goes through 9-BBN hydroboration of the terminal alkene followed by copper-catalyzed enantioselective intramolecular allylic alkylation with a new chiral phosphoramidite ligand (Scheme 36). The reaction afforded functionalized chiral six-membered ring compounds containing tertiary or quaternary carbon stereogenic centers substituted with a vinyl group with high enantioselectivities.

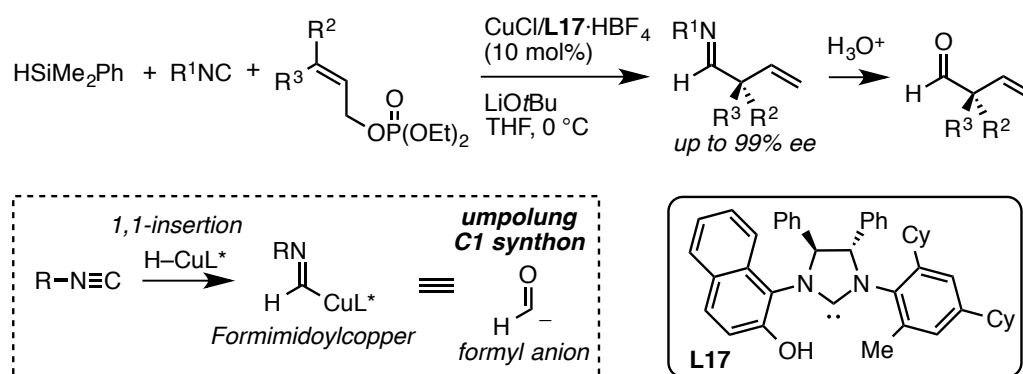
Scheme 36. Cu-Catalyzed Enantioselective Intramolecular Allylic Substitution



2.3. Synthesis of α -Quaternary Formimides and Aldehydes through Copper-Catalyzed Asymmetric Three-Component Coupling Reaction of Isocyanides, Hydrosilanes, and Allylic Electrophiles (Chapter 3)

In chapter 3, the author describes that a highly regio- and enantioselective Cu-catalyzed three component coupling reaction of hydrosilane, isocyanide, and γ,γ -disubstituted allyl phosphate was enabled by the use of the chiral naphthol-carbene ligand (**L17**), developed by Sawamura and Ohmiya group (Scheme 37). α -Quaternary formimides and aldehydes were provided by allylic alkylation with a formimidoyl copper species, which is a formyl anion equivalent produced by 1,1-insertion of isocyanide to a hydride copper species. Due to the mild reaction conditions, high functional group compatibility was observed. The formimidoyl group and the vinyl group in the three component coupling product can be utilized for further chemical transformations.

Scheme 37. Cu-catalyzed Three-Component Coupling Reaction



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Chapter 1

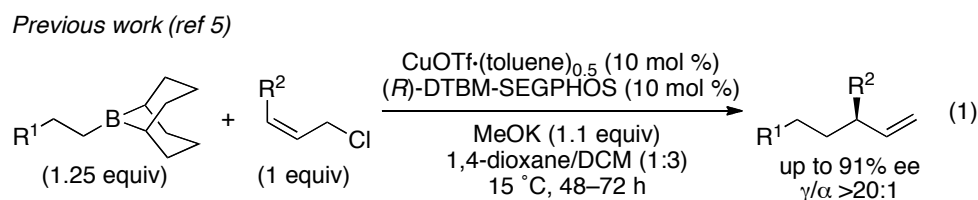
Construction of Quaternary Stereogenic Carbon Centers through Copper-Catalyzed Enantioselective Allylic Cross-Coupling with Alkylboranes

A combination of an in-situ generated Cu(I)-DTBM-MeO-BIPHEP chiral catalyst system and the EtOK base enabled the enantioselective S_N2'-type allylic cross-coupling between alkylborane (alkyl-9-BBN) reagents and γ,γ -disubstituted primary allyl chlorides with enantiocontrol at a useful level. This protocol allowed the use of terminal alkenes as nucleophile precursors, thus representing a formal reductive allylic cross-coupling of terminal alkenes. A reaction pathway involving addition-elimination of a neutral alkylcopper(I) species with the allyl chloride substrate is proposed.

Introduction

Catalytic enantioselective construction of all-carbon quaternary stereogenic centers in acyclic systems is one of the biggest challenges in organic synthesis.¹ One of the obstacles is a low reactivity due to the steric repulsion that occurs in the carbon–carbon bond formation step. It is also difficult to discriminate the enantiotopic faces due to steric congestion and the diminished steric difference between the non-hydrogen substituents. To this end, transition metal catalyzed enantioselective allylic substitutions with organometallic nucleophiles such as organolithium, Grignard, diorganozinc or triorganoaluminum reagents have proven to be effective strategies.² Organoboron compounds have also been used for enantioselective construction of all-carbon quaternary stereogenic centers through allylic substitution, making this strategy more tolerant to various functional groups.³ However, applied organoboron reagents are limited to aryl-, alkenyl-, allenyl-, and allylboron (propargyl) compounds; the methodology has not yet been generalized to allow the reaction of non-allylic alkylboron nucleophiles.⁴

Earlier, Sawamura and Ohmiya reported the enantioselective S_N2' -type reaction between alkylboron compounds (alkyl-9-BBN) and substituted allyl chlorides under catalysis of the Cu(I)-DTBM-SEGPHOS system (eq. 1).⁵ However, the protocol was limited to the construction of tertiary carbon stereogenic centers using γ -monosubstituted primary allylic substrates. The authors reported that a combination of an in situ generated Cu(I)-DTBM-MeO-BIPHEP chiral catalyst system and the EtOK base enabled the enantioselective S_N2' -type allylic cross-coupling between alkylborane (alkyl-9-BBN) reagents and γ,γ -disubstituted primary allyl chlorides with enantiocontrol at a useful level.^{6–8} The reaction generates a quaternary carbon stereogenic center branched with three sp^3 -alkyl groups and a vinyl group. The overall protocol employs terminal alkenes as nucleophile precursors, thus representing a formal reductive allylic cross-coupling of terminal alkenes.



Results and Discussion

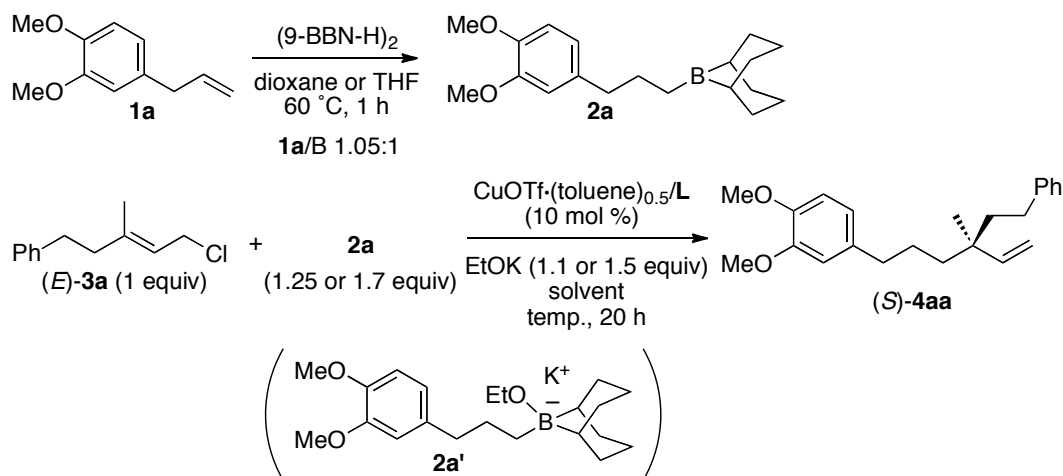
Discovery of the reaction and screening of conditions

The author's earlier investigation on the copper-catalyzed enantioselective reaction between alkylboranes and γ -monosubstituted primary allyl chlorides indicated that introducing 3,5-di-*t*-butyl-4-methoxyphenyl (DTBM) substituents on the phosphorus atoms of chiral bisphosphines was important for promotion of the reaction.⁵ The author assumed that the introduction of the

DTBM substituents would induce the deaggregation of the alkylcopper(I) species to form a catalytically active monomeric copper complex.⁹ On the basis of this consideration, he examined copper complexes prepared from CuOTf·(toluene)_{0.5} (10 mol %) and various DTBM-substituted chiral bisphosphine ligands for catalytic activity, γ -regioselectivity, and enantioselectivity in the reaction of γ,γ -disubstituted allyl chloride (E)-**3a** with alkylborane **2a** in the presence of EtOK in 1,4-dioxane/dichloromethane (DCM) (1:3) at 25 °C over 20 h (**3a/2a**/EtOK 1:1.25:1.1) (Table 1, entries 1–4).^{5,10,11} As in the previous study with γ -monosubstituted allyl chlorides, the alkylborane **2a** was prepared in advance through hydroboration of 3,4-dimethoxy-1-allylbenzene (**1a**) with (9-BBN-H)**2** (**3a/1a/B** 1:1.3:1.25) at 60 °C over 1 h and was used without purification. The conversion of **1a** into **2a** with a full consumption of 9-BBN-H was confirmed by ¹H and ¹¹B NMR spectroscopy. The amount of EtOK base was adjusted so that the borane **2a** was in a slightly excess (**2a**/EtOK 1.1:1) to ensure a full consumption of EtOK for the formation of CuOEt and borate (**2a'**) species (see below).¹² Accordingly, yields of allylation product **4aa** were calculated based on the allyl chloride **3a**. Specifically, the catalyst prepared from the DTBM-substituted TunePHOS-type chiral bisphosphine (**L1**) did not promote the reaction at all (entry 1).¹³ (R)-DTBM-BINAP (**L2**) induced only low catalytic activity, γ -selectivity, and enantioselectivity (entry 2). (R)-DTBM-SEGPPOS (**L3**), which exhibited high performance in the previously reported reaction with γ -monosubstituted primary allyl chlorides (eq. 1), imparted moderate γ -selectivity (γ/α 6:1) and enantioselectivity (47% ee), but the product yield was lower than that with **L2** (entry 3). To the author's delight, the use of (R)-DTBM-MeO-BIPHEP (**L4**) led to a significant improvement in the regioselectivity and enantioselectivity (entry 4).¹⁴ The alkylation occurred at the disubstituted γ -carbon atom of **3a** (γ/α >20:1), constructing the all-carbon quaternary stereogenic center with 83% ee in favor of the formation of (*S*)-**4aa** (si-face attack), albeit still with a low product yield. These results suggest that the catalytic activity, γ -selectivity, and enantioselectivity of this reaction are very sensitive to the dihedral angle of the axially chiral biaryl scaffolds in the Cu(I)-bisphosphine complexes.

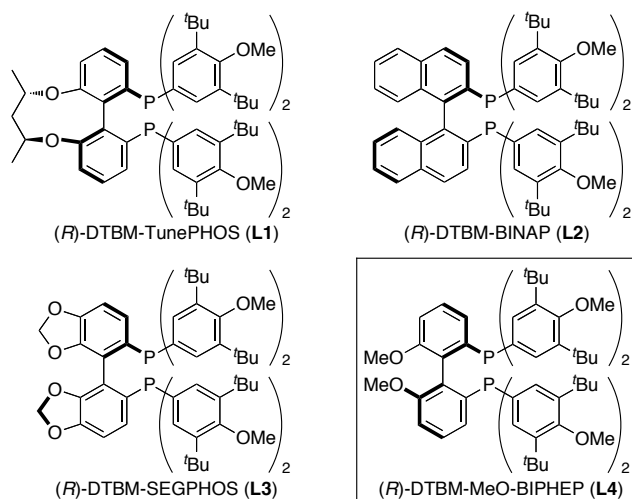
The product yield with the Cu-**L4** system could be increased to 56% by changing the solvent to THF/DCM (1:3) with the enantioselectivity almost unchanged (81% ee) (Table 1, entry 5). The yield was further improved to 65% by conducting the reaction at 15 °C with a increased amount of the **2a**/EtOK reagent (**3a/2a**/EtOK 1/1.7/1.5) (entry 6).

Table 1. Copper-catalyzed enantioselective cross-coupling between **2a** and (*E*)-**3a** under various conditions.^[a]



entry	Ligand (L)	solvent	temp (°C)	yield (%) ^[b]	γ/α ^[c]	ee (%) ^[d]
1	L1	dioxane/DCM	25	0	—	—
2	L2	dioxane/DCM	25	38	3.5:1	21
3	L3	dioxane/DCM	25	15	6:1	47
4	L4	dioxane/DCM	25	26	>20:1	83
5	L4	THF/DCM	25	56	>20:1	81
6 ^[e]	L4	THF/DCM	15	65	>20:1	81

[a] Conditions of hydroboration: **1a**, 0.26 mmol; $(9\text{-BBN-H})_2$, 0.125 mmol (**1a/B** 1.05:1); 60 °C, 1 h. **2a** (0.25 mmol) was used without purification. Conditions of enantioselective coupling reaction: (*E*)-**3a**, 0.2 mmol; **2a**, 0.25 mmol; EtOK, 0.22 mmol; $\text{CuOTf}\cdot(\text{toluene})_{0.5}$, 10 mol %; ligand (**L**), 10 mol %; solvent, 0.8 mL; 20 h. [b] Yield of the isolated product. [c] Determined by ^1H NMR analysis of the crude product. [d] The enantiomeric excess was determined by HPLC analysis. [e] Reaction at 0.3 mmol scale. **2a** (0.52 mmol) and EtOK (0.45 mmol) were used.



NMR Studies

The mixture of (9-BBN-H)₂ (12.1 mg, 0.05 mmol) and 3,4-dimethoxy-1-allylbenzene (18.1 μ l, 0.11 mmol) in THF (0.04 mL) was stirred at 60 °C for 1 hour to prepare **2a** [δ 69.6 (¹¹B), Figure 1. See also Figure 4 for the ¹H NMR spectrum].^{6a} Next, the THF solution of **2a** was added to a vial containing EtOK (8.8 mg, 0.1 mmol) and CH₂Cl₂ (0.12 mL) at 25 °C, and the resulting yellow suspension was stirred at 25 °C for 10 min. The ¹¹B NMR spectrum of the suspension showed a peak that corresponds to a tetravalent borate **2a'** (δ -3.1) (Figure 2. See also Figure 5. for the ¹H NMR spectrum).^{6a} Subsequently, the suspension was added to a vial containing CuOTf·(toluene)_{0.5} (25.8 mg, 0.1 mmol, B/Cu 1:1) and **L4** (115.2 mg, 0.1 mmol), and the resulting yellow suspension was stirred at 25 °C for 15 min: the peak of the borate **2a'** disappeared completely and a signal that corresponds to 9-BBN-OEt appeared at δ 55.6 as a major peak in a ¹¹B NMR spectrum (Figure 3. see also Figure 6. for a ¹H NMR spectrum).¹⁵

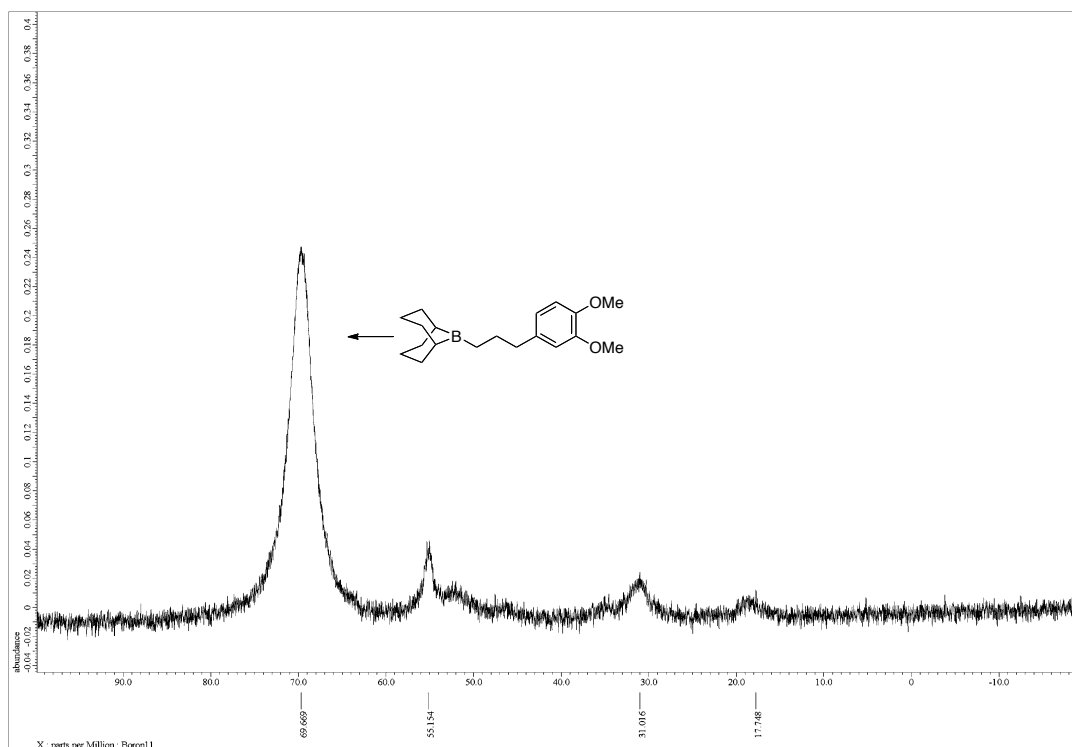


Figure 1. ¹¹B NMR spectrum of **2a** (128 MHz, rt, THF-*d*₈)

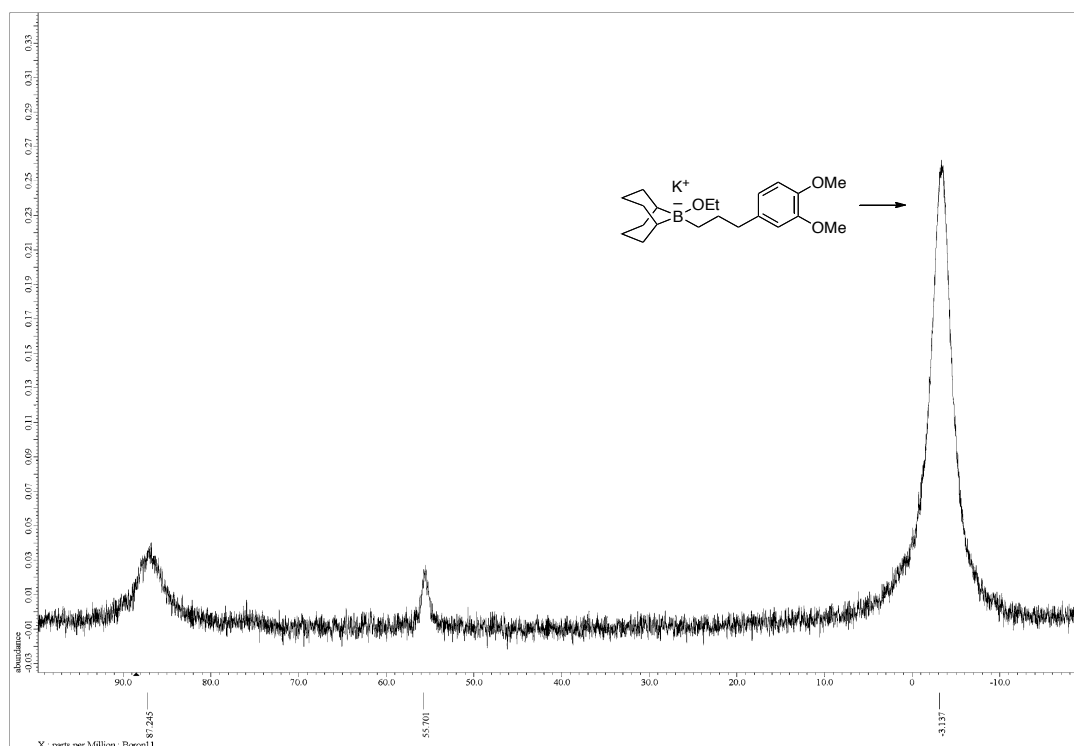


Figure 2. ^{11}B NMR spectrum of **2a'** (128 MHz, rt, CD_2Cl_2)

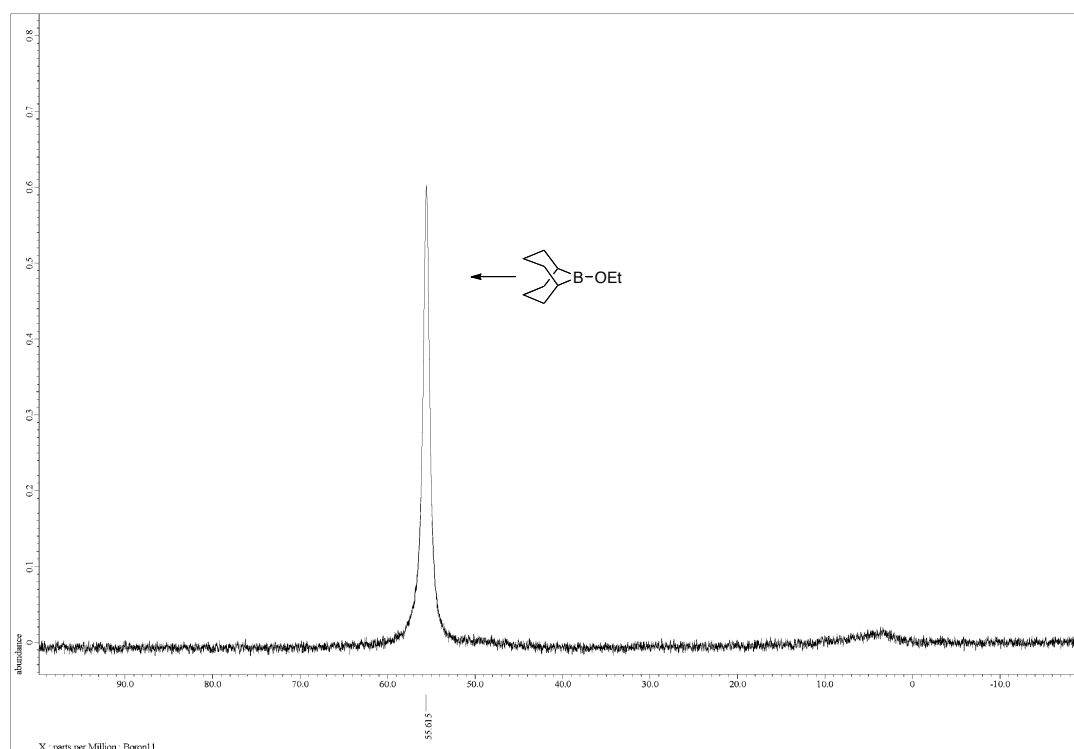


Figure 3. [^{11}B NMR spectrum of 9-BBN-OEt (128 MHz, rt, CD_2Cl_2)]

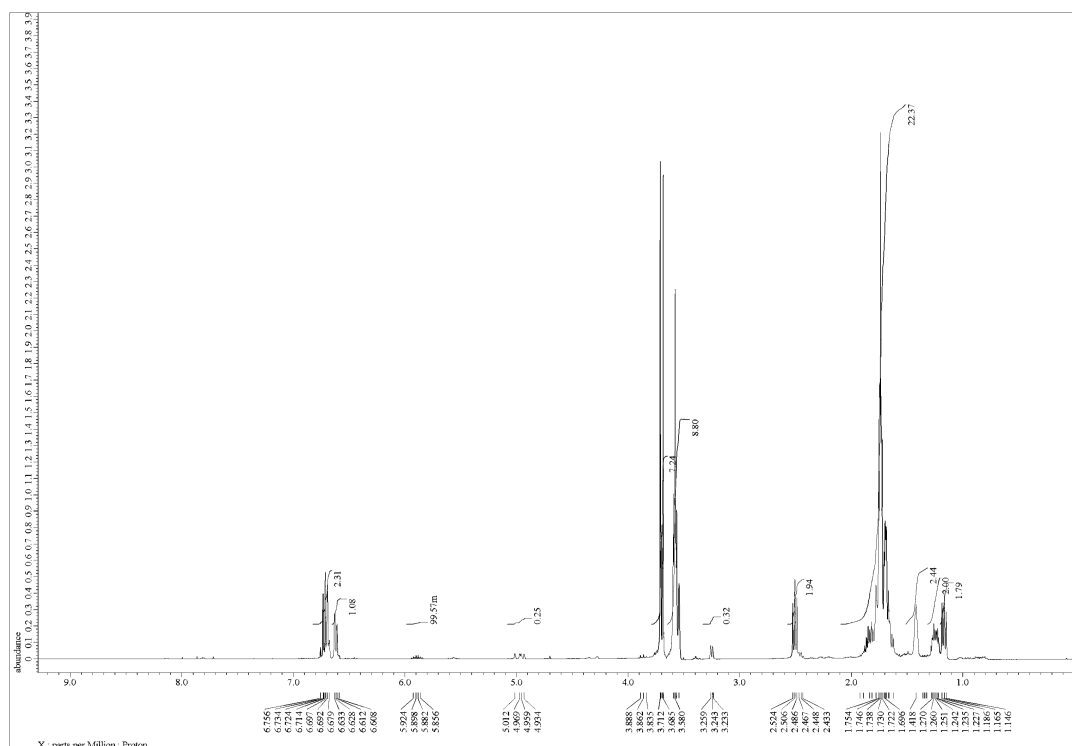


Figure 4. ^1H NMR spectrum of **2a** (400 MHz, $\text{THF-}d_8$)

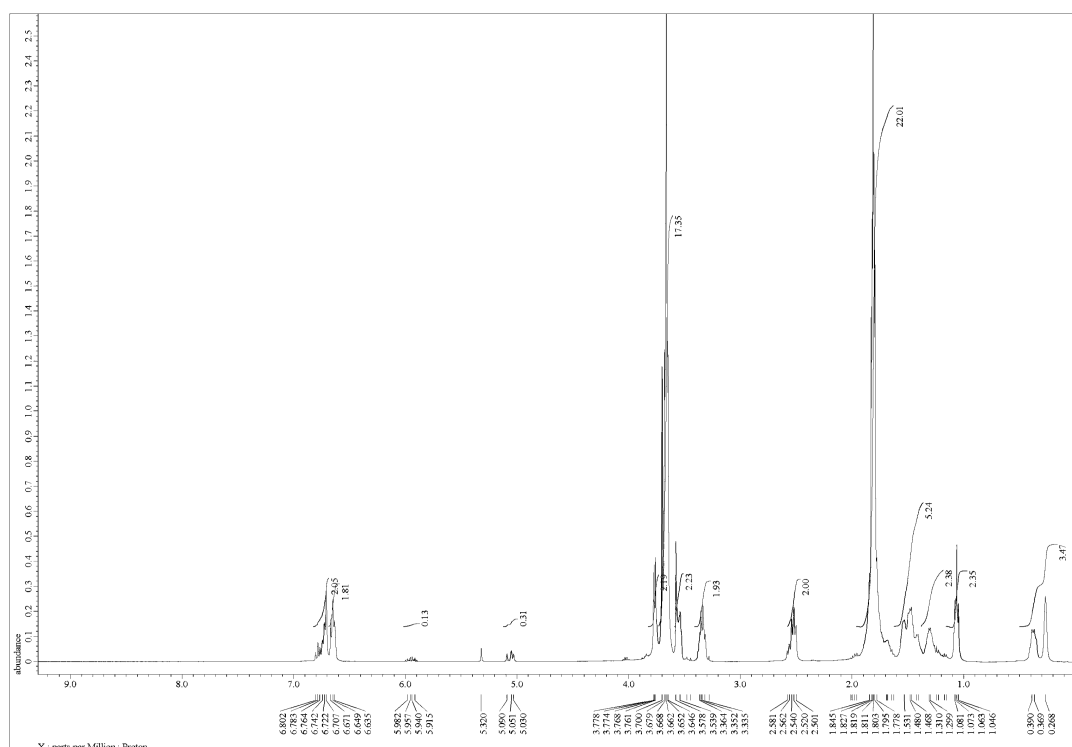


Figure 5. ^1H NMR spectrum of **2a'** (400 MHz, CD_2Cl_2)

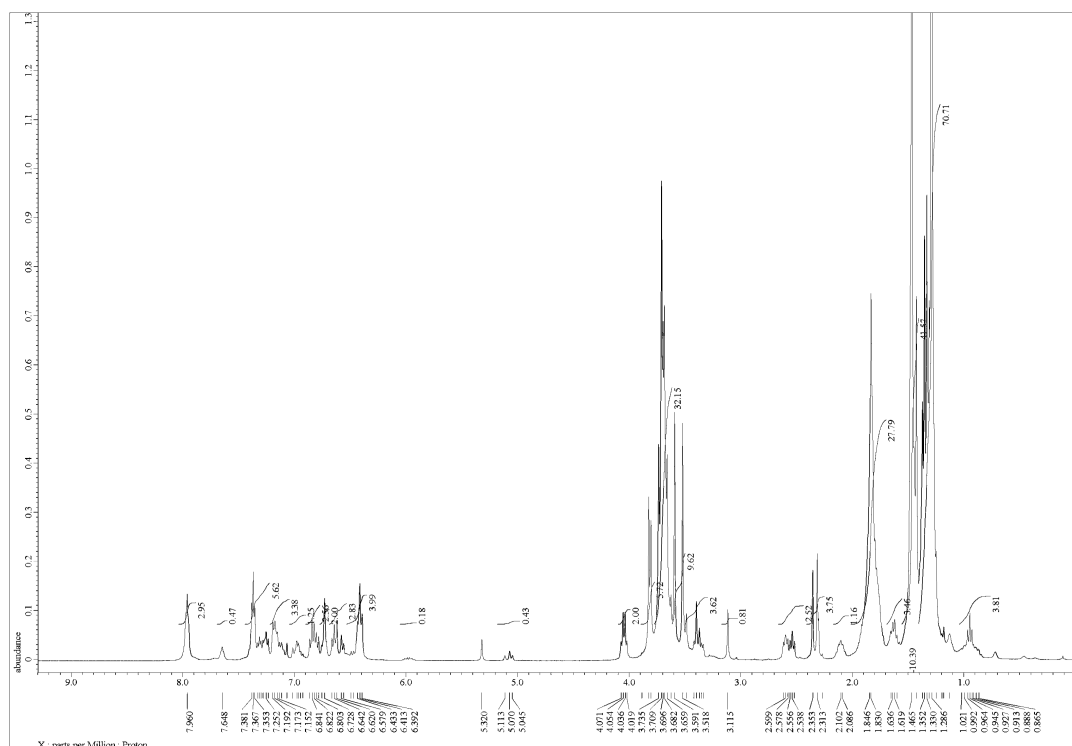
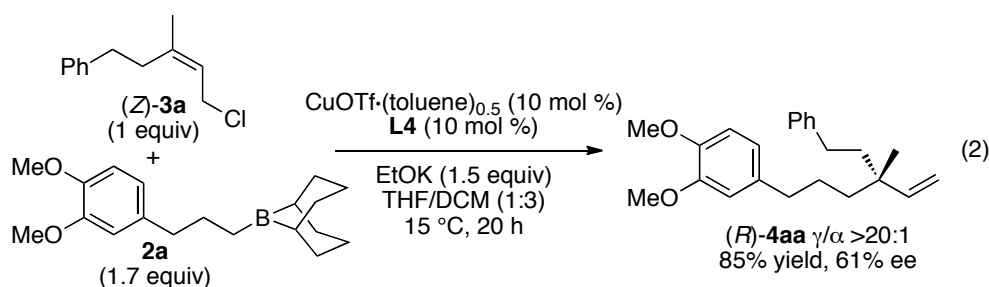


Figure 6. ^1H NMR spectrum of 9-BBN-OEt (400 MHz, CD_2Cl_2)

Substrates

The reaction of *Z*-configured allyl chloride (*Z*)-**3a** under the conditions optimal for the reaction of (*E*)-**3a** (Table 1, entry 6) provided (*R*)-**4aa**, the antipode of the product derived from (*E*)-**3a**, with 61% ee in 85% yield (eq. 2).^{10,11} This enantioselectivity is lower than that for the reaction of (*E*)-**3** (*vide infra* for discussion on enantioselection models).



Various terminal alkenes were subjected to 9-BBN-hydroboration and were used for coupling with γ,γ -disubstituted *E*-allyl chloride (*E*)-**3a** using $\text{CuOTf} \cdot (\text{toluene})_{0.5}$ (10 mol %), **L4** (10 mol %) and EtOK in THF/DCM (1:3) at 15 °C over 20 h (Table 2, entries 1–7).^{10,11} The Cu-catalyzed coupling reactions proceeded with excellent γ -selectivity and good-to-high enantioselectivities. Various terminal alkenes having different functional groups such as acetal, ester, chloro, silyl ether

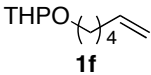
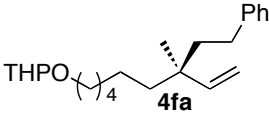
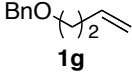
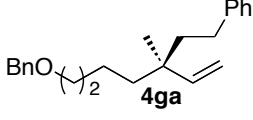
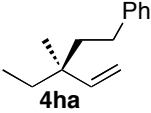
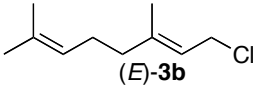
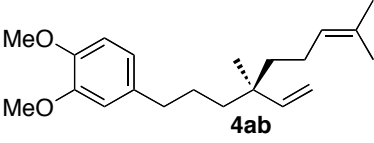
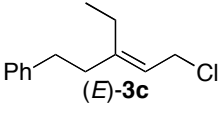
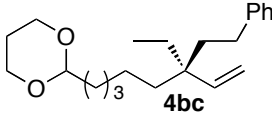
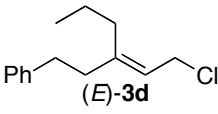
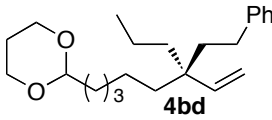
and benzyl ether moieties in the aliphatic chain were compatible with this protocol (entries 1–6).

Ethylene also served as a suitable substrate (Table 2, entry 7).^{10,11} This reaction delivered an ethyl group to the fully substituted γ -carbon atom of **3a** with enantioselectivity at a useful level.

The scope of γ,γ -disubstituted allyl chlorides (**3**) is also shown in Table 2 (entries 8–10).^{10,11} An additional trisubstituted alkene moiety in the allylic substrate **3b** was tolerated for the formation of diene **4ab** (entry 8). The copper catalyst system enabled the enantioselective coupling of allyl chlorides having two alkyl substituents of almost equal steric demands at the γ -position (entries 9 and 10). For example, allyl chloride **3c** having ethyl and phenylethyl groups at the γ -position reacted with a high enantioselectivity (81% ee) (entry 9). Replacing the ethyl group at the γ -position of **3c** with a propyl group caused only a slight reduction in the enantioselectivity (entry 10).

Table 2. Scope of enantioselective allylic cross-coupling with alkylboranes.^[a]

entry	alkene	chloride	product	yield (%) ^[b,c]	ee (%) ^[d]
1		(<i>E</i>)- 3a		79	90
2		(<i>E</i>)- 3a		66	81
3 ^[e]		(<i>E</i>)- 3a		80	86
4		(<i>E</i>)- 3a		85	83

5 ^[f]	 1f	(<i>E</i>)- 3a	 4fa	70	86
6	 1g	(<i>E</i>)- 3a	 4ga	68	81
7	 1h	(<i>E</i>)- 3a	 4ha	63	71
8	1a  (<i>E</i>)- 3b		 4ab	54	73
9 ^[e]	1b  (<i>E</i>)- 3c		 4bc	75	81
10 ^[e]	1b  (<i>E</i>)- 3d		 4bd	67	71

[a] Conditions of hydroboration: **1**, 0.35 mmol; (9-BBN-H)₂, 0.17 mmol (**1**/B 1.05:1); 60 °C, 1 h. **2** (0.34 mmol) was used without purification. Conditions of enantioselective coupling reaction: (*E*)-**3**, 0.2 mmol; **2**, 0.34 mmol; EtOK, 0.3 mmol; CuOTf·(toluene)_{0.5}, 10 mol %; (*R*)-DTBM-MeO-BIPHEP (**L4**), 10 mol %; THF/DCM (1:3, 0.8 mL); 15 °C, 20 h. [b] Yield of the isolated product. [c] Constitutional isomer ratio γ/α > 20:1 (determined by ¹H NMR analysis of the crude product). [d] The enantiomeric excess was determined by HPLC analysis. [e] Constitutional isomer ratio γ/α > 10:1. [f] Diastereomeric ratio (1:1).

Considerations for reaction pathways

A possible catalytic cycle for the γ-selective allylic coupling is illustrated in Figure 7.^{5,6a-c} As proposed for the Cu-catalyzed enantioselective reaction between alkylboranes and γ-monosubstituted primary allyl chlorides, the active organocopper species is likely in the form of a neutral organocopper(I) species (**C**) rather than a monoorganoheterocuprate, as EtOK is consumed for the formation of borate **2'** and the copper center bearing the alkyl ligand and the bisphosphine ligand (**L4**) is coordinatively saturated upon alkene coordination.¹² Therefore, the reaction would proceed through addition-β-elimination with the neutral organocopper(I) species **B**. The enantioselection would occur at transition states of the R¹-Cu addition across the C-C double bond of **3** (**C** → **D-TS** → (**E** →) **A** + **4** + 9-BBN-OEt).

The formation of the α -coupling product in the reaction with (*R*)-DTBM-BINAP (**L2**) or (*R*)-DTBM-SEGPHOS (**L3**) might be due to the formation of alkyl(ethoxo)cuprate species upon dissociation of one or two P atoms of the chiral ligands. Such cuprate species would undergo oxidative addition with **3** to form an isomeric mixture of ($[\sigma+\pi]$ -allyl)copper(III) species with a C–Cu σ bond either at the α or γ carbon atoms. Reductive elimination of these allylcopper(III) intermediates may form a mixture of the α - and γ -coupling product as a minor product.^{16,17}

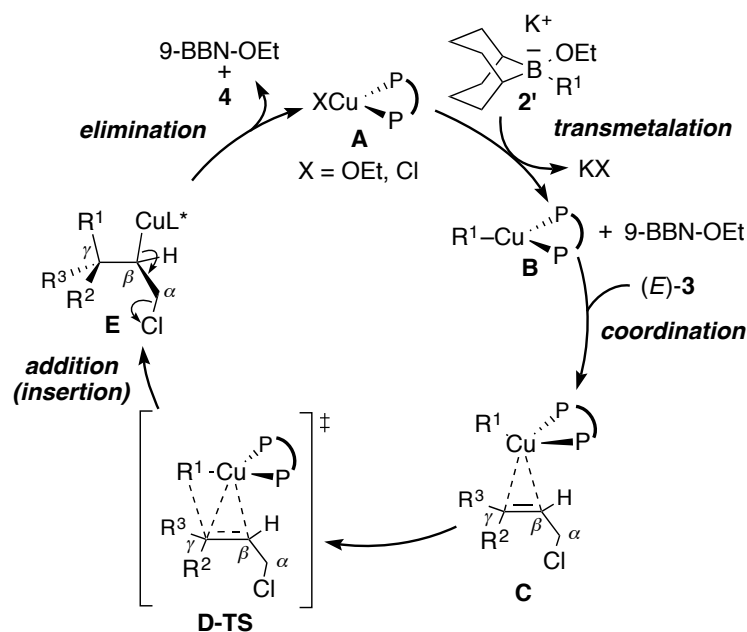


Figure 7. Possible Catalytic Cycle.

The author proposes enantioselection models depicted in Figure 8 based on the fact that the reactions of *E*- and *Z*-isomers of **3a** gave the antipodes of **4**, respectively, the former showing higher enantioselectivity (Table 1, entry 6 vs. eq 2). In the π -complex **C** (see Figure 1), the allyl chloride substrate (**3**) bound to the tetrahedral copper center is in proximity to the two P-substituents Ar^1 and Ar^3 , which are axial and equatorial substituents, respectively, of the bisphosphine-Cu chelate ring. The axial substituent Ar^1 points toward the substrate more than the equatorial Ar^3 . R_L and R_S indicate the larger and smaller γ -substituents of **3**, respectively. **C-1**, which leads to the major enantiomer of **4** in the reaction of (*E*)-**3**, has steric repulsion only between R_S and Ar^3 , while the corresponding π -complex (**C-2**) leading to the minor enantiomer has larger steric repulsions between the ClCH_2 group and Ar^1 and between Ar^3 and R_L . A similar discussion should be applicable for the transition state **D-TS**.

In the case of the reaction of (*Z*)-**3**, the π -complex (**C-3**) leading to the major enantiomer, the antipode of the product from **C-1**, has a steric repulsion between Ar^3 and R_L , which should be larger than the steric repulsion that occurs in **C-1** (R_L vs. R_S). On the other hand, the steric repulsion

between Ar^3 and R_s in **C-4** should be smaller than that between Ar^3 and R_l in **C-2**. These considerations also match the observed trend that the enantioselectivity gradually decreased with the increase of the size of the R_s substituent of (*E*)-**3** (Table 2, entries 1, 9, and 10). This can be explained by the increasing steric repulsion between Ar^3 and R_s in **C-1**.

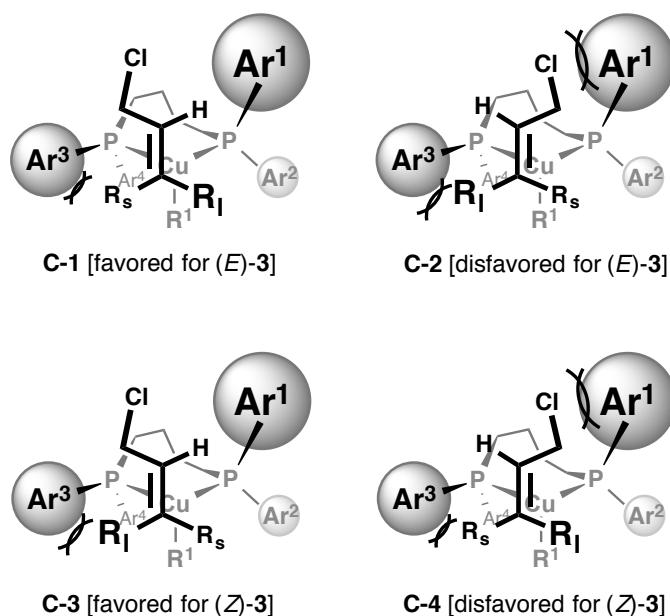


Figure 8. Models for Enantiodiscrimination.

Conclusion

In summary, the author have developed an $\text{S}_{\text{N}}2'$ -type enantioselective allylic cross-coupling between alkyl-9-BBN reagents and γ,γ -disubstituted primary allyl chlorides under catalysis of a Cu(I)-DTBM-MeO-BIPHEP system to deliver enantioenriched chiral products containing quaternary carbon stereogenic centers branched with three sp^3 -alkyl groups and a vinyl group. This protocol allowed the use of terminal alkenes as nucleophile precursors, thus representing a formal reductive allylic cross-coupling of terminal alkenes.

Experimental Section

Instrumentation and Chemicals

NMR spectra were recorded on a Varian Gemini 2000 spectrometer, operating at 300 MHz for ^1H NMR, and a JEOL ECX-400, operating at 100.5 MHz for ^{13}C NMR, 128 MHz for ^{11}B NMR and 161.8 MHz for ^{31}P NMR. Chemical shift values for ^1H and ^{13}C are referenced to Me_4Si and the residual solvent resonances, respectively. Chemical shift values for ^{11}B is referenced to $\text{BF}_3\cdot\text{OEt}_2$ (δ 0 ppm). Chemical shifts are reported in δ ppm. Mass spectra were obtained with Thermo Fisher Scientific Exactive, JEOL JMS-T100LP or JEOL JMS-700TZ at the Instrumental

Analysis Division, Equipment Management Center, Creative Research Institution, Hokkaido University. Elemental analysis was performed at the Instrumental Analysis Division, Equipment Management Center, Creative Research Institution, Hokkaido University. HPLC analyses were conducted on a HITACHI ELITE LaChrom system with a HITACHI L-2455 diode array detector. IR spectra were recorded on a Perkin-Elmer Spectrum One. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F₂₅₄. Silica gel (Kanto Chemical Co., Silica gel 60 N, spherical, neutral) was used for column chromatography. Melting points were measured on a Yanaco MP-500D apparatus. Gel permeation chromatography (GPC) was performed by LC-908 (Japan Analytical Industry Ltd., two in-line JAIGEL-2H, CHCl₃, 3.5 mL/min, UV and RI detectors).

All reactions were carried out under nitrogen or argon atmosphere. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. 9-Borabicyclo[3,3,1]nonane dimer (9-BBN-H)₂, CuOTf·(toluene)_{0.5}, EtOK, (*R*)-DTBM-MeO-BIPHEP and (*R*)-DTBM-BINAP were purchased from Aldrich Chemical Co., stored under nitrogen, and used as it is. (*R*)-DTBM-SEGPPOS was purchased from Strem Chemicals Inc., stored under nitrogen, and used as it is. Dichloromethane (DCM) was purchased from Kanto Chemical Co., stored over 4Å molecular sieves under nitrogen. 1,4-Dioxane was purchased from Kanto Chemical Co., distilled from sodium/benzophenone and stored over 4Å molecular sieves under nitrogen. Terminal alkenes **1a–h** are known compounds.

Preparation of Allyl Chlorides (3)

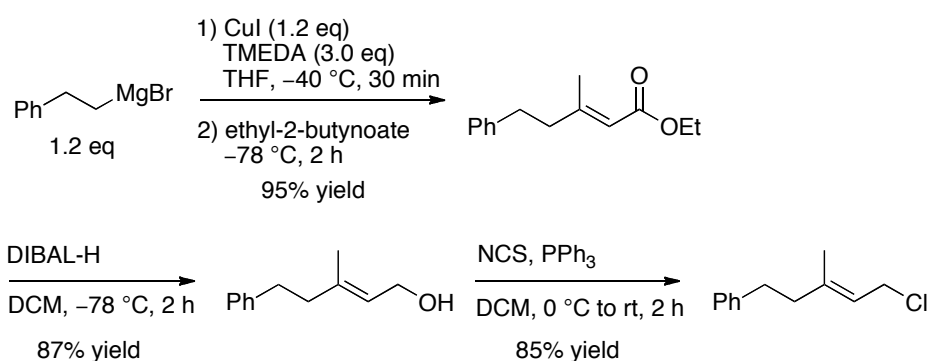
Preparation of γ,γ -disubstituted (*E*)-allyl chlorides **3a, **c** and **d** (Scheme 1).** The preparation of **3a** is representative (Scheme 1). To a solution of CuI (1.8 g, 9.6 mmol) and TMEDA (3.6 mL, 24 mmol) in THF (1.0 mL) was added 2-phenylethylmagnesium bromide (0.7 M in THF, 13.7 mL, 9.6 mmol) at –40 °C, and the resulting mixture was stirred at –40 °C for 30 min. To the mixture was added ethyl 2-butynoate (0.9 g, 8 mmol) at –78 °C, and the mixture was stirred at –78 °C for 2 h. Saturated NH₄Cl aq was added and the mixture was allowed to warm to room temperature. The resulting slurry was diluted with EtOAc (50 mL) and washed with H₂O and brine. The organic layer was separated and dried over MgSO₄. Then, the drying agent was removed by filtration, and the resulting solution was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (0–10% EtOAc/hexane) provided alkynoate (1.7 g, 7.6 mmol) in 95% yield.

To a stirred solution of alkynoate (1.7 g, 7.6 mmol) in DCM was dropped DIBAL-H (16.4 mL in 1.02 M hexane solution, 16.7 mmol) at –78 °C and the reaction was continued for 30 min at the same temperature. Sat. NH₄Cl was added and the mixture was vigorously stirred for 10 min. Solid

was filtered through celite pad and the filtrate was extracted with ether. The crude product was purified by flash chromatography on silica gel (10–20% EtOAc/hexane) to give allylic alcohol (1.2 g, 6.6 mmol) in 87% yield.

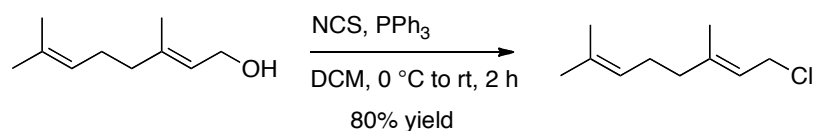
To a solution of allylic alcohol (1.2g, 6.6 mmol) in DCM (13.2 mL), NCS (1.0 g, 7.3 mmol) and PPh₃ (2.0 g, 7.9 mmol) were sequentially added at 0 °C. After being stirred at rt for 2 h, the solvent was removed under reduced pressure, and then residue was filtered through a pad of celite with EtOAc as an eluent. The filtrate was evaporated under reduced pressure. The residue was purified through flash chromatography on silica gel (hexane) followed by Kugelrohr distillation provided **3a** (1.1 g, 5.6 mmol) in 80% yield.

Scheme 1. Preparation of γ,γ -disubstituted (*E*)-allyl chlorides **3a**, **c** and **d**



Preparation of γ,γ -disubstituted (*E*)-allyl chloride **3b (Scheme 2).** To a solution of geraniol (1.5 g, 10 mmol) in DCM (20 mL), NCS (1.5 g, 11 mmol) and PPh₃ (3.1 g, 12 mmol) were sequentially added at 0 °C. After being stirred at rt for 2 h, the solvent was removed under reduced pressure, and then residue was filtered through a pad of celite with hexane as an eluent. The filtrate was evaporated under reduced pressure. The residue was purified by Kugelrohr distillation to provide **3b** (1.4 g, 8 mmol) in 80% yield.

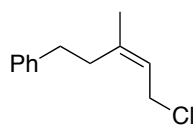
Scheme 2. Preparation of γ,γ -Disubstituted (*E*)-Allyl Chloride **3b**



Characterization Data for Allyl Chlorides

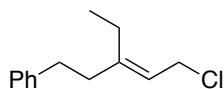
Allyl chlorides (*E*)-**3a**, **b** are found in the literature.^{18,19}

(Z)-(5-Chloro-3-methyl-3-penten-1-yl)benzene [(Z)-3a]



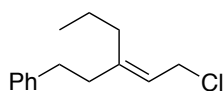
Colorless Oil. **IR** (neat) 697, 1253, 1454, 1495, 2940, 3027 cm^{-1} . **^1H NMR** (300 MHz, CDCl_3) δ 0.93 (s, 3H), 2.38–2.43 (m, 2H), 2.70–2.77 (m, 2H), 3.88 (d, $J = 8.1$ Hz, 2H), 5.46 (t, $J = 8.1$ Hz, 1H), 7.17–7.22 (m, 3H), 7.26–7.32 (m, 2H). **^{13}C NMR** (100.5 MHz, CDCl_3) δ 23.51, 33.92, 34.28, 40.65, 121.74, 126.05, 128.38 (2C), 141.45, 141.76. **HRMS–EI** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{12}\text{H}_{15}\text{Cl}$, 194.08623; found, 194.08630.

(E)-(5-Chloro-3-ethyl-3-penten-1-yl)benzene (3c)



Colorless Oil. **IR** (neat) 697, 739, 1252, 1454, 2935, 2967 cm^{-1} . **^1H NMR** (300 MHz, CDCl_3) δ 1.05 (t, $J = 7.5$ Hz, 3H), 2.14–2.21 (m, 2H), 2.33–2.38 (m, 2H), 2.70–2.76 (m, 2H), 4.11 (d, $J = 8.1$ Hz, 2H), 5.44 (t, $J = 8.1$ Hz, 1H), 7.17–7.21 (m, 3H), 7.25–7.31 (m, 2H). **^{13}C NMR** (100.5 MHz, CDCl_3) δ 13.31, 23.44, 34.33, 38.18, 40.68, 120.13, 125.88, 128.33 (2C), 141.77, 147.86. **HRMS–EI** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{Cl}$, 208.10188; found, 208.10202.

(E)-[3-(2-Chloroethylidene)hexyl]benzene (3d)



Colorless Oil. **IR** (neat) 697, 746, 1315, 1454, 2870, 2959 cm^{-1} . **^1H NMR** (300 MHz, CDCl_3) δ 0.93 (t, $J = 7.5$ Hz, 3H), 1.40–1.53 (m, 2H), 2.10–2.15 (m, 2H), 2.31–2.37 (m, 2H), 2.70–2.76 (m, 2H), 4.11 (d, $J = 8.1$ Hz, 2H), 5.47 (t, $J = 8.1$ Hz, 1H), 7.16–7.21 (m, 3H), 7.25–7.31 (m, 2H). **^{13}C NMR** (100.5 MHz, CDCl_3) δ 14.08, 21.65, 32.38, 34.36, 38.51, 40.85, 120.95, 125.87, 128.32 (2C), 141.78, 145.96. **HRMS–EI** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{Cl}$, 222.11753; found, 222.11773.

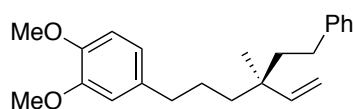
Procedure for Copper-Catalyzed Enantioselective Allylic Cross-Coupling with Alkylboranes.

The reaction in Table 1, entry 6 is representative. 3,4-Dimethoxy-1-allylbenzene (**1a**) (93.4 μL , 0.54 mmol) and (9-BBN-H)₂ (64.2 mg, 0.26 mmol) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon[®]-coated silicon rubber septum and the vial was evacuated and filled with argon. THF (0.3 mL) was added to the vial, and then the mixture was stirred at 60 °C for 1 h to prepare an alkylborane. Meanwhile, $\text{CuOTf} \cdot (\text{toluene})_{0.5}$ (7.8 mg, 0.03

mmol), (*R*)-DTBM-MeO-BIPHEP (**L4**) (35.5 mg, 0.03 mmol) and EtOK (39.9 mg, 0.45 mmol) were placed in another vial. This vial was sealed with a Teflon[®]-coated silicon rubber septum and then evacuated and filled with argon. After DCM (0.9 mL) was added to the vial, the mixture was stirred at 25 °C for 1 h. Next, the alkylborane solution was transferred to the vial containing the Cu(I)–**L4** complex. Next, allyl chloride (*E*)-**3a** (58.5 mg, 0.3 mmol) was added. After 20 h stirring at 15 °C, diethyl ether was added to the mixture. The mixture was filtered through a short plug of silica gel, which was then washed with diethyl ether. After the solvent was removed under reduced pressure, flash chromatography on silica gel (0–3% EtOAc/hexane) provided **4aa** (66.0 mg, 0.20 mmol) at 81% ee in 65% yield.

Characterization Data for Allylic Cross-Coupling Products

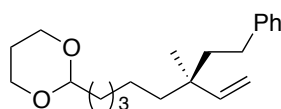
(*S*)-1,2-Dimethoxy-4-(4-methyl-4-phenethyl-5-hexen-1-yl)benzene (**4aa**)



The product (*S*)-**4aa** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) followed by GPC (CHCl₃) (65% isolated yield). Colorless Oil. **IR** (neat) 698, 1030, 1236, 1260, 1515, 2935 cm⁻¹. **¹H NMR** (300 MHz, CDCl₃) δ 1.03 (s, 3H), 1.35–1.40 (m, 2H), 1.55–1.65 (m, 4H), 2.45–2.55 (m, 4H), 3.85 (s, 3H), 3.87 (s, 3H), 4.94 (d, *J* = 17.4 Hz, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 5.74 (dd, *J* = 17.4, 10.8 Hz, 1H), 6.70–6.72 (m, 2H), 6.79 (m, 1H), 7.13–7.18 (m, 3H), 7.24–7.29 (m, 2H). **¹³C NMR** (100.5 MHz, CDCl₃) δ 22.50, 26.21, 30.67, 36.20, 39.58, 40.51, 42.93, 55.78, 55.88, 111.08, 111.64, 111.99, 120.11, 125.54, 128.29 (2C), 135.30, 143.28, 146.86, 146.99, 148.68. **HRMS–EI** (*m/z*): [*M*]⁺ calcd for C₂₃H₃₀O₂, 338.22458; found, 338.22391. [α]_D²³ +5.81 (*c* 1.10, CHCl₃).

HPLC analysis [CHIRALCEL[®] OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99.5:0.5, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 106.7 min for *R* isomer and 112.5 min for *S* isomer] revealed that the enantiomeric excess of **4aa** was 81% ee. The absolute configuration of **4aa** was assigned by consideration of the stereochemical pathway.

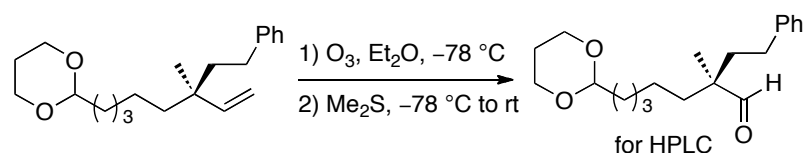
(*S*)-2-(6-Methyl-6-phenethyl-7-octen-1-yl)-1,3-dioxane (**4ba**)



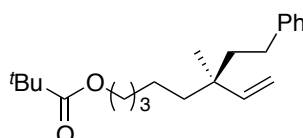
The product **4ba** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (79% isolated yield). Colorless Oil. **IR** (neat) 698, 909, 996, 1143, 2849, 2929 cm^{-1} . **^1H NMR** (300 MHz, CDCl_3) δ 1.01 (s, 3H), 1.26–1.43 (m, 8H), 1.54–1.64 (m, 5H), 2.08 (m, 1H), 2.46–2.52 (m, 2H), 3.76 (dt, $J = 12.0, 2.4$ Hz, 2H), 4.08–4.13 (m, 2H), 4.50 (t, $J = 5.1$ Hz, 1H), 4.93 (dd, $J = 17.4, 1.5$ Hz, 1H), 5.02 (dd, $J = 10.8, 1.5$ Hz, 1H), 5.74 (dd, $J = 17.4, 10.8$ Hz, 1H), 7.15–7.19 (m, 3H), 7.25–7.30 (m, 2H). **^{13}C NMR** (100.5 MHz, CDCl_3) δ 22.55, 23.87, 23.96, 25.84, 30.26, 30.70, 35.23, 39.58, 40.71, 42.97, 66.88, 102.39, 111.76, 125.49, 128.28 (2C), 143.37, 147.09. **HRMS–EI** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{21}\text{H}_{32}\text{O}_2$, 316.24023; found, 316.24002. $[\alpha]_{\text{D}}^{26} +2.06$ (c 1.08, CHCl_3).

The ee value (90% ee) was determined by chiral HPLC analysis of the aldehyde derivative obtained by the ozonolysis followed by reduction with Me_2S from **4ba** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm $\times$ 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 96:4, 0.7 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 54.1 min for *R* isomer and 55.7 min for *S* isomer]. The absolute configuration of **4ba** was assigned by consideration of the stereochemical pathway.

Derivatization of 4ba. Ozone was bubbled into a solution of **4ba** (15.8 mg, 0.05 mmol) in diethyl ether (5.0 mL) at -78 $^\circ\text{C}$. After the starting material was completely disappeared (monitored by TLC), dimethyl sulfide (0.1 mL) was added and the mixture was allowed to warm to room temperature and it was further stirred at the room temperature for 2 h. The mixture was diluted with EtOAc and washed with H_2O and brine. The organic layer was separated and dried over MgSO_4 . Then, the drying agent was removed by filtration, and the resulting solution was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (0–4% diethyl ether /DCM) provided the aldehyde derivative (3.2 mg, 0.01 mmol).



(*S*)-6-Methyl-6-phenethyl-7-octen-1-yl Pivalate (4ca)

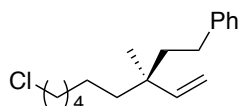


The product **4ca** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (66% isolated yield). Colorless Oil. **IR** (neat) 698, 1284, 1151, 1727, 2862, 2935 cm^{-1} . **^1H NMR** (300 MHz, CDCl_3) δ 1.03 (s, 3H), 1.19 (s, 9H), 1.29–1.32 (m, 6H), 1.52–1.64 (m, 4H), 2.47–2.53 (m, 2H), 4.04 (t, $J = 6.6$ Hz, 2H), 4.95 (d, $J = 17.4$ Hz, 1H), 5.04 (d, $J = 11.1$ Hz, 1H), 5.75 (dd, J

= 17.4, 11.1 Hz, 1H), 7.15–7.19 (m, 3H), 7.25–7.30 (m, 2H). ¹³C NMR (100.5 MHz, CDCl₃) δ 22.46, 23.72, 26.77, 27.20, 28.64, 30.70, 38.72, 39.61, 40.87, 43.02, 64.44, 111.95, 125.55, 128.30 (2C), 143.31, 146.94, 178.69. HRMS–EI (*m/z*): [M]⁺ calcd for C₂₂H₃₄O₂, 330.25588; found, 330.25630. [α]_D²⁵ +7.36 (*c* 0.58, CHCl₃).

The ee value (81% ee) was determined by chiral HPLC analysis of the aldehyde derivative obtained by the ozonolysis followed by reduction with Me₂S from **4ca** [CHIRALCEL[®] OD-3 column, 4.6 mm × 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm × 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 96:4, 0.7 mL/min, 40 °C, 220 nm UV detector, retention time = 29.7 min for *R* isomer and 30.6 min for *S* isomer] (**4ca** was converted to the corresponding aldehyde according to the procedure for the derivatization of **4ba**). The absolute configuration of **4ca** was assigned by consideration of the stereochemical pathway.

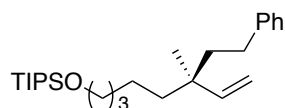
(*S*)-(9-Chloro-3-methyl-3-vinylnonyl)benzene (**4da**)



The product **4da** was purified by flash chromatography on silica gel (hexane) followed by GPC (CHCl₃) (80% isolated yield). Colorless Oil. IR (neat) 696, 909, 1453, 1495, 2858, 2930 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 1.03 (s, 3H), 1.26–1.48 (m, 6H), 1.52–1.61 (m, 4H), 1.72–1.79 (m, 2H), 2.47–2.53 (m, 2H), 3.53 (t, *J* = 6.6 Hz, 2H), 4.95 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.04 (dd, *J* = 11.1, 1.5 Hz, 1H), 5.75 (dd, *J* = 17.4, 11.1 Hz, 1H), 7.15–7.20 (m, 3H), 7.25–7.30 (m, 2H). ¹³C NMR (100.5 MHz, CDCl₃) δ 22.49, 23.85, 26.87, 29.67, 30.70, 32.62, 39.60, 40.82, 42.98, 45.16, 111.89, 125.53, 128.29 (2C), 143.32, 146.99. HRMS–EI (*m/z*): [M]⁺ calcd for C₁₈H₂₇Cl, 278.1803; found, 278.18100. [α]_D²⁶ +6.49 (*c* 0.30, CHCl₃).

The ee value (86% ee) was determined by chiral HPLC analysis of the aldehyde derivative obtained by the ozonolysis followed by reduction with Me₂S from **4da** [CHIRALCEL[®] OD-3 column, 4.6 mm × 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm × 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 96:4, 0.7 mL/min, 40 °C, 220 nm UV detector, retention time = 39.6 min for *R* isomer and 41.3 min for *S* isomer] (**4da** was converted to the corresponding aldehyde according to the procedure for the derivatization of **4ba**). The absolute configuration of **4da** was assigned by consideration of the stereochemical pathway.

(S)-Triisopropyl[(6-methyl-6-phenethyl-7-octen-1-yl)oxy]silane (4ea)

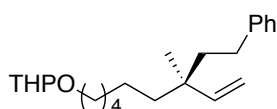


The product **4ea** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (85% isolated yield). Colorless Oil. **IR** (neat) 679, 910, 1106, 1463, 2864, 2938 cm^{-1} . **^1H NMR** (300 MHz, CDCl_3) δ 1.05–1.12, (m, 24H), 1.21–1.32 (m, 6H), 1.50–1.64 (m, 4H), 2.47–2.53 (m, 2H), 3.66 (t, J = 6.6 Hz, 2H), 4.94 (dd, J = 17.4, 1.5 Hz, 1H), 5.04 (dd, J = 11.1, 1.5 Hz, 1H), 5.75 (dd, J = 17.4, 11.1 Hz, 1H), 7.15–7.17 (m, 3H), 7.24–7.29 (m, 2H). **^{13}C NMR** (100.5 MHz, CDCl_3) δ 11.99, 18.03, 22.56, 23.85, 26.62, 30.71, 33.01, 39.60, 40.92, 42.97, 63.41, 111.76, 125.50, 128.28 (2C), 143.39, 147.14. **HRMS–ESI** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{26}\text{H}_{47}\text{OSi}$, 403.33907; found, 403.33838. $[\alpha]_{\text{D}}^{27} +6.31$ (c 0.92, CHCl_3).

The ee value (83% ee) was determined by chiral HPLC analysis of the aldehyde derivative obtained by the ozonolysis, reduction with Me_2S from **4ea** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm $\times$ 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 98:2, 0.3 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 17.9 min for *R* isomer and 18.6 min for *S* isomer] (**4ea** was converted to the corresponding aldehyde according to the procedure for the derivatization of **4ba**). The absolute configuration of **4ea** was assigned by consideration of the stereochemical pathway.

2-[(S)-7-Methyl-7-phenethyl-8-nonen-1-yl]oxy]tetrahydro-2H-pyran (4fa)

(Diastereomeric ratio 1:1)



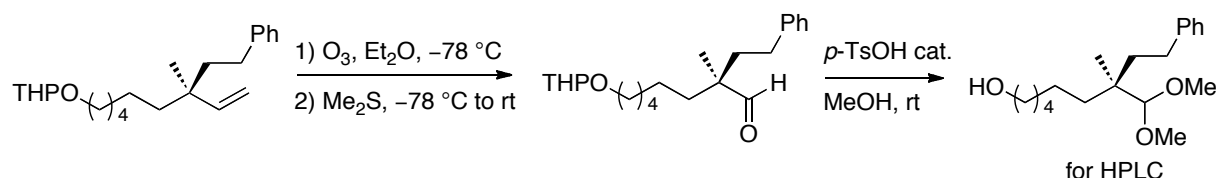
The product **4fa** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (70% isolated yield). Colorless Oil. **IR** (neat) 1022, 1032, 1119, 2859, 2931 cm^{-1} . **^1H NMR** (300 MHz, CDCl_3) δ 1.02 (s, 3H), 1.23–1.36 (m, 6H), 1.54–1.87 (m, 12H), 2.47–2.53 (m, 2H), 3.38 (m, 1H), 3.51 (m, 1H), 3.73 (m, 1H), 3.87 (m, 1H), 4.58 (m, 1H), 4.94 (d, J = 17.4 Hz, 1H), 5.03 (d, J = 11.1 Hz, 1H), 5.75 (dd, J = 17.4, 11.1 Hz, 1H), 7.15–7.18 (m, 3H), 7.25–7.30 (m, 2H). **^{13}C NMR** (100.5 MHz, CDCl_3) δ 19.70, 22.57, 23.96, 25.49, 26.25, 29.75, 30.29, 30.72, 30.78, 39.61, 40.86, 42.97, 62.36, 67.67, 98.84, 111.76, 125.51, 128.29 (2C), 143.39, 147.14. **HRMS–EI** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{36}\text{O}_2$, 344.27153; found, 344.27045. $[\alpha]_{\text{D}}^{28} +5.94$ (c 0.87, CHCl_3).

The ee value (86% ee) was determined by chiral HPLC analysis of the acetal derivative obtained by the ozonolysis, reduction with Me_2S followed by acetalization from **4fa**

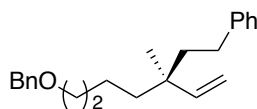
[CHIRALCEL[®] OD-3 column, 4.6 mm × 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm × 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 96:4, 0.7 mL/min, 40 °C, 220 nm UV detector, retention time = 39.6 min for *R* isomer and 41.2 min for *S* isomer]. The absolute configuration of **4fa** was assigned by consideration of the stereochemical pathway.

Derivatization of 4fa. Ozone was bubbled into a solution of **4fa** (34.4 mg, 0.1 mmol) in diethyl ether (5.0 mL) at −78 °C. After the starting material was completely disappeared (monitored by TLC), dimethyl sulfide (0.1 mL) was added and the mixture was allowed to warm to room temperature and it was further stirred at the room temperature for 2 h. The mixture was diluted with EtOAc and washed with H₂O and brine. The organic layer was separated and dried over MgSO₄. Then, the drying agent was removed by filtration, and the resulting solution was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (50–75% DCM/hexane) provided the aldehyde derivative (13.9 mg, 0.04 mmol).

To a solution of the aldehyde (13.9 mg, 0.04 mmol) in MeOH (0.1 mL) was added *p*-TsOH (4.6 mg, 0.0024 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h (monitored by TLC) and diluted with H₂O. The aqueous layer was extracted with EtOAc (three times). The combined organic layer was washed with water and brine, and then was dried and concentrated. The crude product was purified by flash column chromatography (DCM) yielded the acetal derivative (9.3 mg, 0.03 mmol).



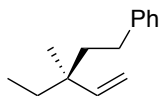
(*S*)-[7-(Benzyloxy)-3-methyl-3-vinylheptyl]benzene (**4ga**)



The product **4ga** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (68% isolated yield). Colorless Oil. **IR** (neat) 696, 733, 1102, 1454, 2862, 2936 cm^{−1}. **¹H NMR** (300 MHz, CDCl₃) δ 1.03 (s, 3H), 1.23–1.37 (m, 4H), 1.52–1.64 (m, 4H), 2.47–2.52 (m, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 4.50 (s, 2H), 4.94 (d, *J* = 17.4 Hz, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 5.75 (dd, *J* = 17.4, 10.8 Hz, 1H), 7.14–7.18 (m, 3H), 7.24–7.34 (m, 7H). **¹³C NMR** (100.5 MHz, CDCl₃) δ 20.68, 22.51, 30.47, 30.70, 39.62, 40.69, 42.94, 70.34, 72.87, 111.93, 125.53, 127.48, 127.65 (2C), 128.30 (2C), 138.64, 143.33, 146.97. **HRMS–ESI** (*m/z*): [M+Na]⁺ calcd for C₂₃H₃₀ONa, 345.21889; found, 345.21869. [α]_D²² +8.32 (*c* 0.43, CHCl₃).

HPLC analysis [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 95:5, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 49.1 min for *R* isomer and 51.7 min for *S* isomer] revealed that the enantiomeric excess of **4ga** was 81% ee. The absolute configuration of **4ga** was assigned by consideration of the stereochemical pathway.

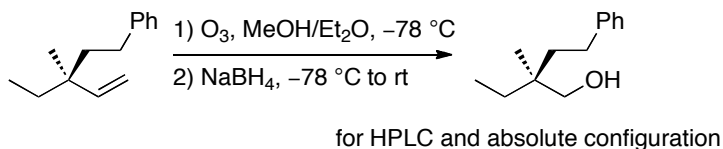
(*S*)-(3-Ethyl-3-methyl-4-penten-1-yl)benzene (4ha**)**



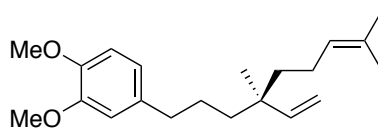
The product **4ha** was purified by flash chromatography on silica gel (hexane) followed by GPC (CHCl₃) (63% isolated yield). Colorless Oil. **IR** (neat) 696, 752, 910, 1454, 2933, 2965 cm⁻¹. **¹H NMR** (300 MHz, CDCl₃) δ 0.82 (t, *J* = 7.5 Hz, 3H), 1.01 (s, 3H), 1.39 (q, *J* = 7.5 Hz, 2H), 1.51–1.61 (m, 2H), 2.47–2.53 (m, 2H), 4.95 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.05 (dd, *J* = 10.8, 1.5 Hz, 1H), 5.74 (dd, *J* = 17.4, 10.8 Hz, 1H), 7.15–7.21 (m, 3H), 7.25–7.29 (m, 2H). **¹³C NMR** (100.5 MHz, CDCl₃) δ 8.38, 21.99, 30.74, 33.07, 39.77, 42.62, 112.02, 125.52, 128.30 (2C), 143.44, 146.83. **HRMS–EI** (*m/z*): [M]⁺ calcd for C₁₄H₂₀, 188.15650; found, 188.15651. [α]_D²² +16.69 (*c* 0.63, CHCl₃)

The ee value (71% ee) was determined by chiral HPLC analysis of the alcohol derivative obtained by the ozonolysis followed by reduction with NaBH₄ from **4ha** [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm/CHIRALCEL® OD-H column, 4.6 mm × 250 mm/CHIRALCEL® OD-H column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 96:4, 0.7 mL/min, 40 °C, 220 nm UV detector, retention time = 39.6 min for *R* isomer and 44.5 min for *S* isomer]. The absolute configuration of **4ha** was determined by optical rotation of the alcohol derivative. [α]_D²² –8.91 (*c* 0.10, CHCl₃). {lit²⁰, (*S*) isomer, 96% ee, [α]_D²⁰ –12.48 (*c* 0.125, CH₂Cl₂)}.

Derivatization of 4ha. Ozone was bubbled into a solution of **4ha** (7.4 mg, 0.04 mmol) in MeOH/diethyl ether (1:10, 5.0 mL) at –78 °C. After the starting material was completely disappeared (monitored by TLC), NaBH₄ (15.1 mg, 0.4 mmol) was added and the mixture was allowed to warm to room temperature and it was further stirred at the room temperature for 1 h. The mixture was quenched with water. The aqueous layer was extracted with EtOAc (three times). The combined organic layer was washed with water and brine, and then was dried and concentrated. Purification by column chromatography (silica gel, 5–15% EtOAc/hexane) yielded the alcohol derivative (3.8 mg, 0.02 mmol).



(S)-4-(4,8-Dimethyl-4-vinyl-7-nonen-1-yl)-1,2-dimethoxybenzene (4ab)

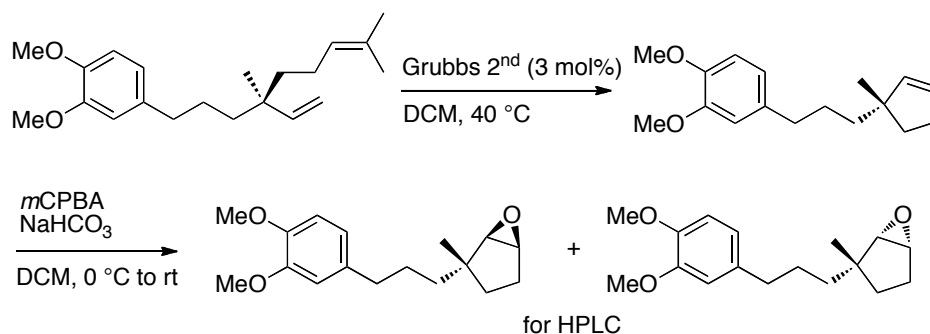


The product **4ab** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) followed by GPC (CHCl₃) (54% isolated yield). Colorless Oil. **IR** (neat) 1031, 1235, 1260, 1515, 2854, 2933 cm⁻¹. **¹H NMR** (300 MHz, CDCl₃) δ 0.95 (s, 3H), 1.25–1.35 (m, 4H), 1.46–1.61 (m, 5H), 1.67 (s, 3H), 1.80–1.89 (m, 2H), 2.51 (t, J = 7.5 Hz, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 4.87 (dd, J = 17.4, 1.5 Hz, 1H), 4.97 (dd, J = 10.8, 1.5 Hz, 1H), 5.08 (m, 1H), 5.68 (dd, J = 17.4, 10.8 Hz, 1H), 6.69–6.72 (m, 2H), 6.79 (m, 1H). **¹³C NMR** (100.5 MHz, CDCl₃) δ 17.56, 22.50, 22.77, 25.69, 26.25, 36.27, 39.41, 40.44, 40.71, 55.79, 55.90, 111.09, 111.54, 111.66, 120.11, 125.00, 131.03, 135.42, 146.97, 147.18, 148.68. **HRMS–EI** (m/z): [M]⁺ calcd for C₂₁H₃₂O₂, 316.24023; found, 316.24053. [α]_D²³ +8.40 (c 0.50, CHCl₃).

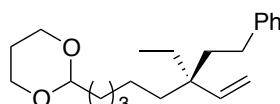
The ee value (73% ee) was determined by chiral HPLC analysis of the epoxy derivative obtained by the ring closing metathesis followed by epoxidation from **4ab** [CHIRALCEL® OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 46.0 min and 65.7 min for *R* isomer and 48.2 min and 85.3 min for *S* isomer]. The absolute configuration of **4ab** was assigned by consideration of the stereochemical pathway.

Derivatization of 4ab. **4ab** (37.9 mg, 0.12 mmol) was dissolved in DCM (0.7 mL), and then Grubbs 2nd catalyst (3.3 mg, 0.004 mmol) was added. After 4 h stirring at 40 °C, diethyl ether was added to the mixture. The mixture was filtered through a short plug of silica gel, which was then washed with diethyl ether. After the solvent was removed under reduced pressure, flash chromatography on silica gel (0–3% EtOAc/hexane) provided the corresponding cyclization product (18.2 mg, 0.07 mmol).

To a solution of the cyclization product (18.2 mg, 0.07 mmol) in DCM (5 mL) was added *m*CPBA (18.1 mg, 0.105 mmol) and NaHCO₃ (17.6 mg, 0.21 mmol) at 0 °C. After being stirred at rt for 2 h, the mixture was diluted with EtOAc, washed with Na₂S₂O₃, sat. NaHCO₃ aq, water, and brine. After the solvent was removed under reduced pressure, flash chromatography on silica gel (5–10% EtOAc/hexane) provided the epoxy derivative (8.3 mg, 0.03 mmol).



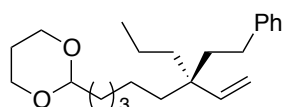
(S)-2-(6-Ethyl-6-phenethyl-7-octen-1-yl)-1,3-dioxane (4bc)



The product **4hg** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) followed by GPC (CHCl_3) (75% isolated yield). Colorless Oil. **IR** (neat) 698, 909, 998, 1143, 2851, 2929 cm^{-1} . **^1H NMR** (300 MHz, CDCl_3) δ 0.79 (t, $J = 7.2$ Hz, 3H), 1.20–1.45 (m, 10H), 1.53–1.63 (m, 5H), 2.08 (m, 1H), 2.41–2.47 (m, 2H), 3.76 (td, $J = 12.0, 2.4$ Hz, 2H), 4.08–4.13 (m, 2H), 4.51 (t, $J = 5.1$ Hz, 1H), 4.91 (dd, $J = 17.4, 1.5$ Hz, 1H), 5.08 (dd, $J = 11.1, 1.5$ Hz, 1H), 5.64 (dd, $J = 17.4, 11.1$ Hz, 1H), 7.15–7.19 (m, 3H), 7.25–7.30 (m, 2H). **^{13}C NMR** (100.5 MHz, CDCl_3) δ 7.83, 23.26, 24.01, 25.85, 28.43, 30.12, 30.35, 35.29, 35.64, 38.26, 42.12, 66.90, 102.39, 112.68, 125.52, 128.29 (2C), 143.45, 146.63. **HRMS–EI** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{22}\text{H}_{34}\text{O}_2$, 330.25588; found, 330.25466. $[\alpha]_{\text{D}}^{26} -5.63$ (c 0.48, CHCl_3).

The ee value (81% ee) was determined by chiral HPLC analysis of the aldehyde derivative obtained by the ozonolysis followed by reduction with Me_2S from **4bc** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm $\times$ 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 96:4, 0.7 mL/min, 40 °C, 220 nm UV detector, retention time = 37.4 min for *S* isomer and 42.5 min for *R* isomer] (**4bc** was converted to the corresponding aldehyde according to the procedure for the derivatization of **4ba**). The absolute configuration of **4bc** was assigned by consideration of the stereochemical pathway.

(S)-2-(6-Phenethyl-6-vinylnonyl)-1,3-dioxane (4bd)

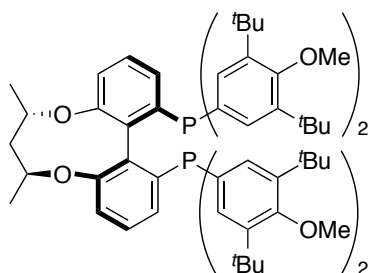


The product **4bd** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) followed by GPC (CHCl_3) (67% isolated yield). Colorless Oil. **IR** (neat) 698, 908, 998, 1144,

2850, 2929 cm^{-1} . ^1H NMR (300 MHz, CDCl_3) δ 0.89 (t, J = 6.9 Hz, 3H), 1.19–1.47 (m, 12H), 1.53–1.62 (m, 5H), 2.04 (m, 1H), 2.41–2.47 (m, 2H), 3.76 (t, J = 12.0 Hz, 2H), 4.08–4.13 (m, 2H), 4.51 (t, J = 5.1 Hz, 1H), 4.90 (d, J = 17.4 Hz, 1H), 5.06 (d, J = 11.1 Hz, 1H), 5.65 (dd, J = 17.4, 11.1 Hz, 1H), 7.14–7.18 (m, 3H), 7.24–7.29 (m, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ 14.92, 16.64, 23.31, 24.03, 25.86, 30.14, 30.36, 35.30, 36.22, 38.72, 38.79, 42.08, 66.91, 102.40, 112.40, 125.52, 128.29 (2C), 143.44, 146.93. HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{23}\text{H}_{36}\text{O}_2$, 344.27153; found, 344.27039. $[\alpha]_{\text{D}}^{22}$ –3.06 (c 0.23, CHCl_3).

The ee value (71% ee) was determined by chiral HPLC analysis of the aldehyde derivative obtained by the ozonolysis followed by reduction with Me_2S from **4bd** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm $\times$ 250 mm/CHIRALCEL[®] OD-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 96:4, 0.7 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 29.9 min for *S* isomer and 32.6 min for *R* isomer] (**4bd** was converted to the corresponding aldehyde according to the procedure for the derivatization of **4ba**). The absolute configuration of **4bd** was assigned by consideration of the stereochemical pathway.

(*R*)-DTBM-TunePHOS (**L1**)



L1 was prepared according to the literature procedure.²¹ White solid. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{77}\text{H}_{109}\text{O}_6\text{P}_2$, 1191.7706; found, 1191.76939. $[\alpha]_{\text{D}}^{23}$ –85.69 (c 0.53, CHCl_3).

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- (11) The absolute configuration of **4ha** was determined by transforming it to a known compound. See Supporting Information for details. Absolute configurations of **4aa** and the other products listed in Table 2 were assigned by consideration of the stereochemical pathway.
- (12) Rapid and quantitative formation of a tetravalent borate (**2a'**) was confirmed by ¹¹B NMR spectroscopy. Treatment of **2a** with EtOK in THF/DCM (1:3) at 25 °C for 10 min caused a complete disappearance of the signal for **2a** (δ 69.6, rt), and a new signal appeared at the higher magnetic field (δ –3.1), which was assigned to **2a'** (ref 6a). Subsequent mixing of the borate with one equiv of CuOTf·(toluene)_{0.5}/(*R*)-DTBM-MeO-BIPHEP (**L4**) at 25 °C for 15 min formed 9-BBN-OEt (δ 55.6, rt). See Supporting Information for details of the NMR studies.
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Chapter 2

Copper-Catalyzed Enantioselective Intramolecular Alkylboron

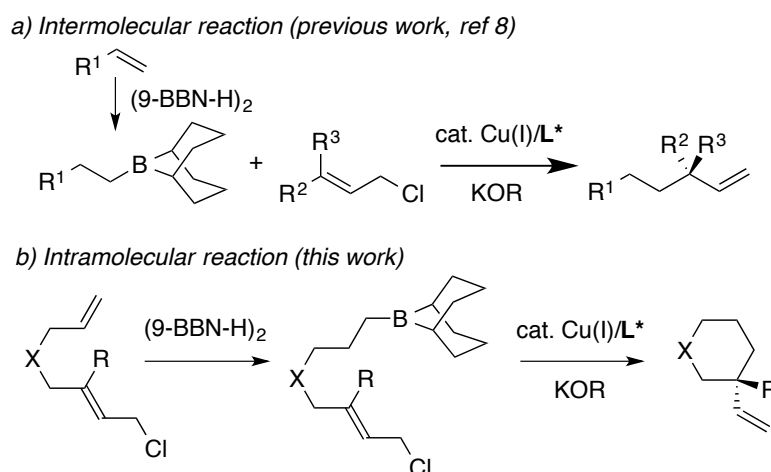
Allylic Alkylation

A reductive C–C-bond-forming cyclization of vinyl-terminated allyl chlorides via alkene hydroboration with 9-BBN-H followed by Cu-catalyzed asymmetric intramolecular allylic alkylation with a new chiral phosphoramidite ligand produced six-membered ring compounds with a tertiary or quaternary stereogenic center in the ring with high enantioselectivity.

Introduction

Transition metal catalyzed enantioselective allylic substitution of organometallic reagents is one of the most powerful and versatile methods for asymmetric C–C bond formation.¹ Recently, allylic substitution reactions utilizing organoboron compounds have made a remarkable advance, allowing the expansion of substrate scopes with great functional group compatibilities.^{2–6} Although the applicable organoboron reagents had been limited to aryl-, alkenyl-, allyl-, propargyl-, and allenylboron derivatives, more recently Sawamura and Ohmiya introduced protocols for using alkyl-9-BBN reagents for stereoselective γ -selective allylic alkylation.^{7–8}

Scheme 1. Copper-Catalyzed Enantioselective Inter- and Intramolecular Allylic Substitution Reactions.



In the reported intermolecular copper-catalyzed enantioselective allylic alkylation reactions with alkyl-9-BBN reagents, Sawamura and Ohmiya identified C_2 -symmetric bisphosphine ligands with axially chiral biaryl backbone and bulky *P*-aryl substituents to be suitable for producing highly active and enantioselective copper catalysts (Scheme 1a).⁸ The reactions afforded enantioenriched chiral terminal alkenes containing tertiary or quaternary carbon stereogenic centers branched with sp^3 -alkyl groups at the allylic position. The wide availability of alkylboranes *via* alkene hydroboration and their great functional group compatibility are attractive features of these transformations. Based on this knowledge, the author sought to develop a method for synthesizing cyclic compounds with a stereogenic carbon center in a ring through intramolecular enantioselective reductive allylic alkylation of bifunctional molecules with a terminal alkene and an allyl (pseudo)halide moiety with a possibility for coexistence of the trialkylborane and the electrophilic allyl moiety in mind.¹⁰

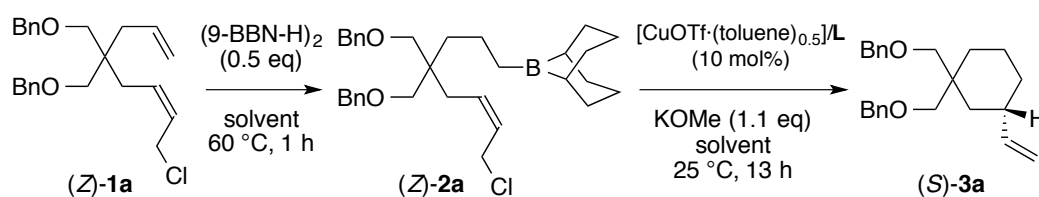
This chapter describes enantioselective reductive cyclization of allyl chlorides tethered to a terminal alkene that goes through 9-BBN hydroboration of the terminal alkene followed by copper-catalyzed enantioselective intramolecular allylic alkylation with a new chiral phosphoramidite ligand (Scheme 1b). The reaction afforded functionalized chiral six-membered ring compounds containing tertiary or quaternary carbon stereogenic centers substituted with a vinyl group with high enantioselectivities.

Results and Discussion

Discovery of the reaction and screening of conditions

An initial screening of chiral ligand for the enantioselective copper-catalyzed cyclization was conducted with alkylborane (*Z*)-**2a**, which was prepared by hydroboration of (*Z*)-**1a**, in the presence of [CuOTf·(toluene)_{0.5}] (10 mol%) and KOMe in toluene at 25 °C (Table 1). (*R*)-DTBM-SEGPHOS (**L1**), which exhibited high performance in the intermolecular reaction, induced low enantioselectivity (74% yield, 43% ee) (entry 1).^{8a} On the other hand, the screening has revealed that some phosphoramidite-type chiral monodentate phosphine ligand are more suitable than the bidentate phosphine ligands in terms of both catalytic activity and enantioselectivity.¹¹ The reaction proceeded most efficiently (82% yield, 85% ee) in the presence of a newly synthesized phosphoramidite ligand (**L2**), which consists of a (*S*)-H₈-binaphthol backbone and two *N*-(*R*)-1-(α -naphthyl)ethyl groups (entry 2). Changing the α -naphthyl groups of **L2** to sterically less hindered phenyl groups slightly reduced the product yield and enantioselectivity (78% yield, 80% ee) (entry 3).¹² While a ligand (**L4**) with an achiral biphenol backbone instead of the (*S*)-H₈-binaphthol backbone of **L2** retained some enantioselectivity (30% yield, 39% ee) (entry 4),¹³ replacement of the *N*-(*R*)-1-(α -naphthyl)ethyl groups of **L2** with *N*-methyl groups (**L5**) resulted in complete loss of enantioselectivity (entry 5).¹⁴ Thus, the chiral amine moiety is more important than the diol moiety for the enantiocontrol.

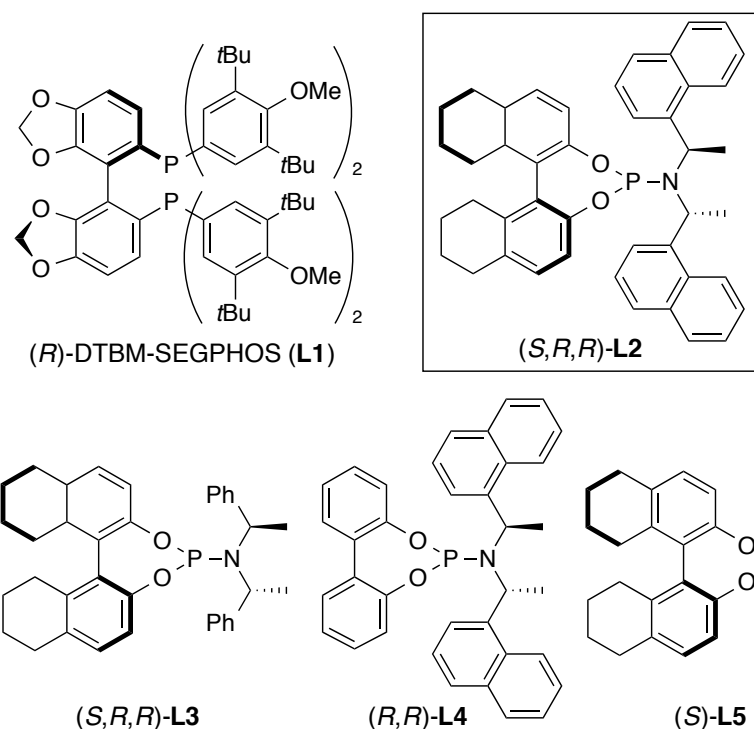
Table 1. Hydroboration of (*Z*)-**1a** and Subsequent Copper-Catalyzed Enantioselective Intramolecular Allylic Alkylation of (*Z*)-**2a** under Various Conditions.^a



entry	ligand	solvent	yield (%) ^b	ee (%) ^c
1	L1	toluene	73	43

2	L2	toluene	82	85
3	L3	toluene	78	80
4	L4	toluene	30	39
5	L5	toluene	57	racemic
6	L2	mesitylene	85	90
7	L2	THF	5	–
8	L2	CPME	70	87
9	L2	mesitylene/MTBE (1:3)	84	91

^aReaction conditions for hydroboration: (Z)-**1a** (0.1 mmol), (9-BBN-H)₂ (0.05 mmol; (Z)-**1a**/B 1:1); 60 °C, 1 h. (Z)-**2a** (0.1 mmol) was used without purification. Reaction conditions for enantioselective coupling reaction: (Z)-**2a** (0.1 mmol), KOMe (0.11 mmol), [CuOTf·(toluene)_{0.5}] (10 mol%), **L** (10 mol%), solvent (0.4 mL), 25 °C, 13 h. ^bYield of the isolated product. ^cThe enantiomeric excess was determined by HPLC analysis.

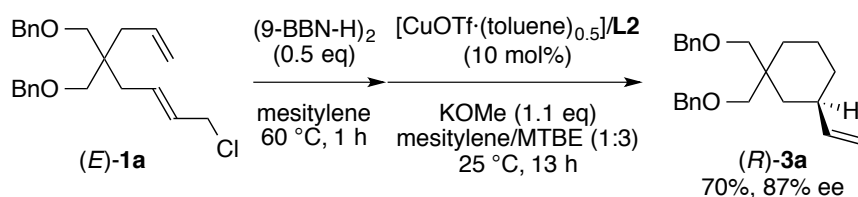


Using **L2** as the optimal chiral ligand, effects of solvents were examined (Table 1, entries 6–9). Mesitylene gave better product yield and enantioselectivity (85% yield and 90% ee) than toluene (entry 6). THF inhibited the reaction almost completely (entry 7). In contrast, cyclopentyl methyl ether (CPME) was suitable for the reaction (70% yield and 87% ee), suggesting that weaker coordination ability or lower polarity of solvent is favorable (entry 8). The highest

enantioselectivity (91% ee) was observed with a mixed solvent system mesitylene/methyl *tert*-butyl ether (MTBE) (1:3) (entry 9).

The reaction with (*E*)-**1a** under the optimal conditions (Table 1, entry 9) provided (*R*)-**3a**, the antipode of the product from (*Z*)-**1a**, with 87% ee in 70% yield (Scheme 2). Thus, *Z*-configuration is more favorable than *E*-configuration in the allyl chloride moiety, and the substitution pattern at the position β to the chlorine atom is more important than that at the γ -position for enantiodiscrimination by the catalyst.

Scheme 2. Cu-catalyzed Enantioselective Intramolecular Allylic Substitution of (*E*)-**1a**.



Substrates

Other substrates with different linkers between the vinyl group and allyl chloride moiety were subjected to the hydroboration-cyclization protocol under the same conditions. The results are summarized in Table 2.^{15–17} This study demonstrates good functional group tolerance of the protocol. For example, the reaction of diethyl malonate-tethered substrate **1b** afforded the corresponding product **3b** in good enantioselectivity (85% ee), albeit in moderate yield (50% yield) (entry 1). The reaction of sulfone derivative **1c** gave **3c** with 89% ee (entry 2). The protocol is applicable for the synthesis of a chiral *N*-tritylpiperidine derivative (**3d**, 90% ee) through the reaction of the corresponding *N*-tethered substrate (**1d**) (entry 3). The five-membered ring formation with a 1,1-dibenzylmethylene tethered substrate **1e** gave the expected cyclic product (**3e**) in low yield and low enantioselectivity (34% yield, 33% ee) (entry 4). A restricted coordination geometry of the alkene may be unfavorable for enantioselection by the catalyst.¹⁸

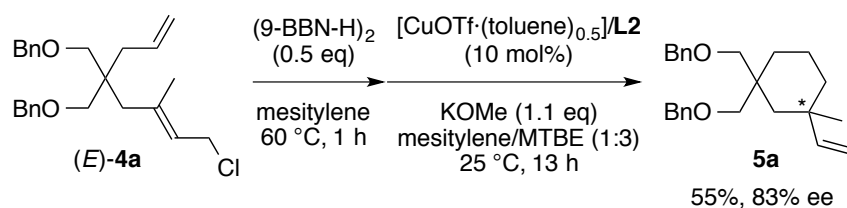
Table 2. Scope of (*Z*)-Allyl Chlorides

(<i>Z</i>)-1 $n = 0-2$ $(9\text{-BBN-H})_2$ (0.5 eq) mesitylene, 60 °C, 1 h $[\text{CuOTf} \cdot (\text{toluene})_{0.5}]/\text{L2}$ (10 mol%) KOMe (1.1 eq) mesitylene/MTBE (1:3) 25 °C, 13 h 3				
entry	isocyanide	allylic substrate	yield (%) ^b	ee (%) ^c
1	(<i>Z</i>)-1b	(<i>S</i>)-3b	50 ^d	85
2	(<i>Z</i>)-1c	(<i>S</i>)-3c	40 ^d	89
3	(<i>Z</i>)-1d	(<i>R</i>)-3d	60	90
4	(<i>Z</i>)-1e	3e	34	33

^aReaction conditions for hydroboration: (*Z*)-**1** (0.1 mmol), (9-BBN-H)₂ (0.05 mmol); (*Z*)-**1**/B 1:1; mesitylene, 60 °C, 1 h. (*Z*)-**2** (0.1 mmol) was used without purification. Reaction conditions for enantioselective coupling reaction: (*Z*)-**2** (0.1 mmol), KOMe (0.11 mmol), [CuOTf·(toluene)_{0.5}] (10 mol%), **L2** (10 mol%), mesitylene/MTBE (1:3, 0.4 mL), 25 °C, 13 h. ^bYield of the isolated product. ^cThe enantiomeric excess was determined by HPLC analysis. ^d The isolated products were contaminated with traces amount of unidentified materials.

Next, the applicability of the protocol toward the construction of a quaternary carbon stereogenic center was tested with γ,γ -disubstituted allyl chloride (*E*)-**4** as a model substrate.^{8b,19} The corresponding six-membered ring containing an all carbon quaternary stereogenic center was obtained with an enantioselectivity as high as 83% ee (Scheme 3).²⁰

Scheme 3. Construction of a Quaternary Carbon Stereogenic Center.



Considerations for reaction pathways

A possible reaction pathway for the intramolecular allylic alkylation catalyzed by the CuX-**L2** system (**A**, CuX-P, X = Cl or OMe) is proposed in Figure 1.⁸ Similarly to the intermolecular reaction reported previously, this intramolecular reaction should be initiated by transmetalation between the copper(I) complex **A** and borate **B**, which is formed from **2** and KOMe, to produce a neutral alkylcopper(I) complex (**C**) coordinated with the monophosphine **L2** (P) and the alkene moiety of the allylic substrate.²¹ The intramolecular η^2 -coordination of the alkene in **C** should be more feasible than the coordination of alkene in the intermolecular allylic alkylation. This difference in alkene coordination may be a cause of the experimentally observed difference in preferred denticity for phosphine coordination. Next, the alkylcopper(I) intermediate **C** undergoes C–Cu addition across the bound C=C double bond, forming **E**. Then, Cu–Cl elimination affords **3** and regenerates **A** for the next catalytic cycle.

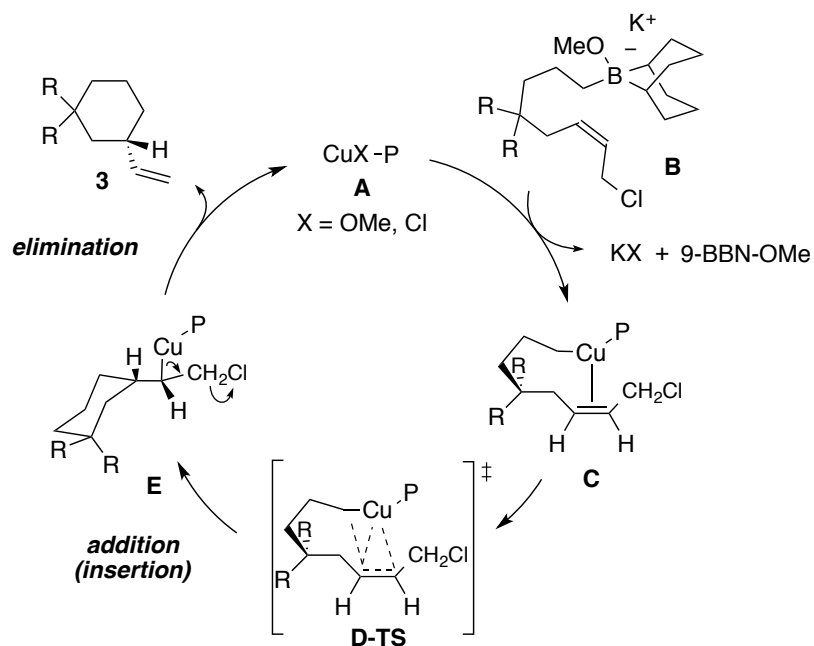


Figure 1. A possible reaction pathway for the copper-catalyzed intramolecular allylic alkylation of an alkyl-9-BBN derivative.

Conclusion

In summary, the author developed the reductive cyclization reaction of allyl chlorides tethered to a terminal alkene *via* alkene hydroboration followed by in-situ enantioselective intramolecular allylic alkylation of organoboron intermediates catalyzed by a copper(I)-phosphoramidite system. The reaction afforded functionalized chiral cyclic compounds bearing enantioenriched tertiary or quaternary carbon stereogenic centers.

Experimental Section

Instrumentation and Chemicals

NMR spectra were recorded on a JEOL ECX-400, operating at 400 MHz for ^1H NMR, 100.5 MHz for ^{13}C NMR and 168 MHz for ^{31}P NMR. Chemical shift values for ^1H and ^{13}C are referenced to Me_4Si and the residual solvent resonances, respectively, while H_3PO_4 was used as the reference for ^{31}P NMR. Chemical shifts are reported in δ ppm. Mass spectra were obtained with Thermo Fisher Scientific Exactive, JEOL JMS-T100LP or JEOL JMS-700TZ at the Instrumental Analysis Division, Global Facility Center, Creative Research Institution, Hokkaido University. HPLC analyses were conducted on a HITACHI ELITE LaChrom system with a HITACHI L-2455 diode array detector or a HITACHI Chromaster with a HITACHI 5430 diode array detector. Optical rotations were measured on a JASCO P-2200. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F₂₅₄. Silica gel (Kanto Chemical Co., Silica gel 60 N, spherical, neutral) was used for column chromatography. Gel permeation chromatography (GPC) was performed by LC-908 (Japan Analytical Industry Ltd., two in-line JAIGEL-2H, CHCl_3 , 3.5 mL/min, UV and RI detectors). Melting points were measured on a Yanaco MP-500D apparatus.

All reactions were carried out under nitrogen or argon atmosphere. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. 9-Borabicyclo[3,3,1]nonane dimer (9-BBN-H)₂, $\text{CuOTf} \cdot (\text{toluene})_{0.5}$, KOMe, were purchased from Aldrich Chemical Co., stored under nitrogen, and used as it is. (*R*)-DTBM-SEGPHOS was purchased from Strem Chemicals Inc., stored under nitrogen, and used as it is. Toluene, mesitylene, CPME and MTBE were purchased from Kanto Chemical Co., stored over 4Å molecular sieves under nitrogen. THF was purchased from Kanto Chemical Co., stored over 5Å molecular sieves under nitrogen.

Preparation of (Z)-allyl chloride **1a** and (E)-allyl chloride **1a** and **4a** (Scheme 4)

(Z)-**1a**, (E)-**1a** and (E)-**4a** were prepared through same procedure. The preparation of (Z)-**1a** is representative (Scheme 4). To a suspension of NaH (55% in mineral oil, 785.1 mg, 18.0 mmol) in DMF (20 mL) at 0 °C was added a solution of **6** (3.0 g, 15.0 mmol) in DMF (10 mL). After stirring for 30 min, allylbromide derivative **7** (3.52 g, 15.0 mmol) was added. After being stirred at room temperature for 12 h, the reaction was quenched with aqueous saturated NH₄Cl solution (15 mL) and extracted with EtOAc (30 mL × 3). The organic layers were combined and dried over MgSO₄. The filtrate was concentrated in vacuo, and was used for next step without further purification.

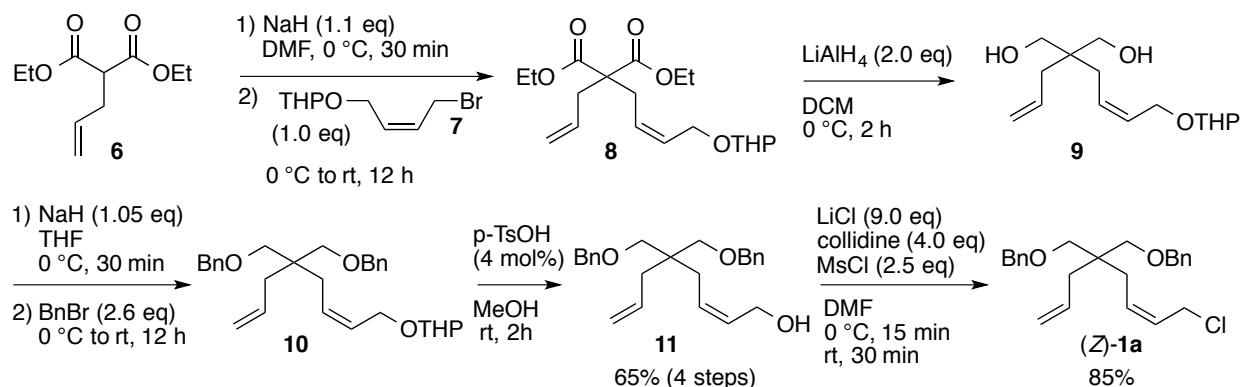
8 was added to a suspension of LiAlH₄ (1.19 g, 30 mmol) in DCM (15 mL) at 0 °C. The mixture was stirred at this temperature for 2 h. After quenching with NaOH aq, the mixture was filtered and concentrated. The corresponding diol product **9** was used for next step without further purification.

The diol compound **9** was added dropwise to a suspension of NaH (55 wt.%, 1.56 g, 36.0 mmol) in THF (20 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. Subsequently, BnBr (4.7 mL, 39 mmol) was added, and the reaction was stirred for 12 h. After quenching with sat. NH₄Cl aq., the mixture was extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The residue was used for next step without further purification.

A solution of benzyl ether **10** and *p*-TsOH (57 mg, 0.3 mmol) in MeOH (15 mL) was stirred at room temperature for 2 h. H₂O was added to quench the reaction. The resulting mixture was extracted with CH₂Cl₂ (50 mL × 3). The combined organic phase was washed with brine, dried over MgSO₄ and filtered. After removal of solvent, the crude compound was purified by flash chromatography on silica gel (5–20% EtOAc/hexane) to give allyl alcohol **11** (3.57 g, 9.8 mmol) in 65% yield (4 steps).

To a suspension of allyl alcohol **11** (1.10 g, 3.0 mmol) in DMF (9.0 mL) at 0 °C, LiCl (1.14 g, 27.0 mmol), and collidine (1.6 mL, 12.0 mmol) in DMF (9 mL) were added MsCl (580.5 μL, 7.5 mmol). The mixture was stirred at this temperature for 15 min before the temperature was allowed to rise to room temperature. After being stirred at room temperature for 30 min, the reaction was quenched with aqueous saturated NH₄Cl solution (15 mL) and extracted with EtOAc (18 mL × 3). The organic layers were combined and dried over MgSO₄. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (0–1% EtOAc/hexane) to yield 981.6 mg (2.6 mmol, 85%) of **1a** as a colorless oil.

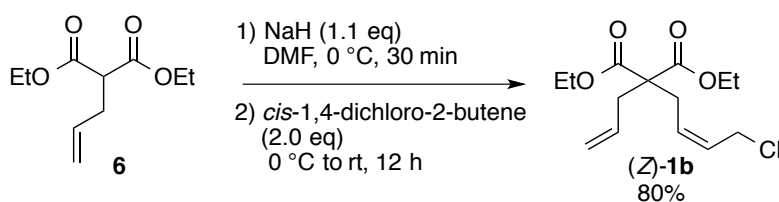
Scheme 4. Preparation of (Z)-1a



Preparation of (Z)-allyl chlorides 1b (Scheme 5).

To a suspension of NaH (55% in mineral oil, 287.9 mg, 6.6 mmol) in DMF (8 mL) at 0 °C was added a solution of diethyl allylmalonate **6** (1.2 mL, 6.0 mmol) in DMF (4 mL). After stirring for 30 min, *cis*-1,4-dichloro-2-butene (1.2 mL, 12 mmol) was added. After being stirred at room temperature for 12 h, the reaction was quenched with aqueous saturated NH₄Cl solution (6 mL) and extracted with EtOAc (12 mL × 3). The organic layers were combined and dried over MgSO₄. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (1–2% EtOAc/hexane) to yield 1.39 g (4.8 mmol, 80%) of **1b** as a colorless oil.

Scheme 5. Preparation of (Z)-1b



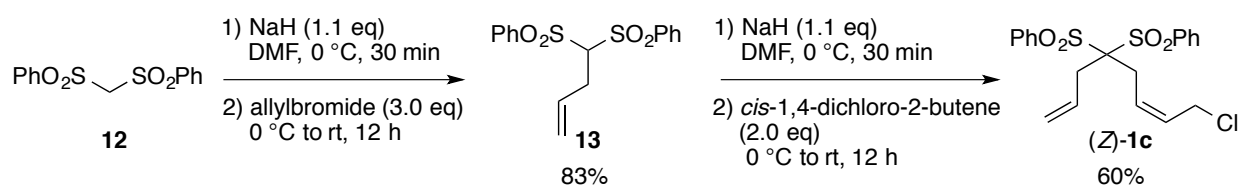
Preparation of (Z)-allyl chlorides 1c (Scheme 6).

To a suspension of NaH (55% in mineral oil, 287.9 mg, 6.6 mmol) in DMF (8 mL) at 0 °C was added a solution of bisphenylsulfonylmethane **12** (1.78 g, 6.0 mmol) in DMF (4 mL). After stirring for 30 min, allylbromide (533 μL, 6.3 mmol) was added. After being stirred at room temperature for 12 h, the reaction was quenched with aqueous saturated NH₄Cl solution (7 mL) and extracted with EtOAc (12 mL × 3). The organic layers were combined and dried over MgSO₄. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (15–30% EtOAc/hexane) to yield 260 mg (5.0 mmol, 83%, 2 steps)

of allyl bisphenylsulfonylmethane **13** as a white solid.

To a suspension of NaH (55% in mineral oil, 96.0 mg, 2.2 mmol) in DMF (6 mL) at 0 °C was added a solution of **13** (672.8 mg, 2.0 mmol) in DMF (2 mL). After stirring for 30 min, *cis*-1,4-dichloro-2-butene (420 µL, 4.0 mmol) was added. After being stirred at room temperature for 12 h, the reaction was quenched with aqueous saturated NH₄Cl solution (6 mL) and extracted with EtOAc (8 mL × 3). The organic layers were combined and dried over MgSO₄. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (5–20% EtOAc/hexane) and GPC to yield 509.9 mg (1.2 mmol, 60%) of **1c** as a white solid.

Scheme 6. Preparation of (Z)-1c



Preparation of (Z)-allyl chlorides **1d** (Scheme 7).

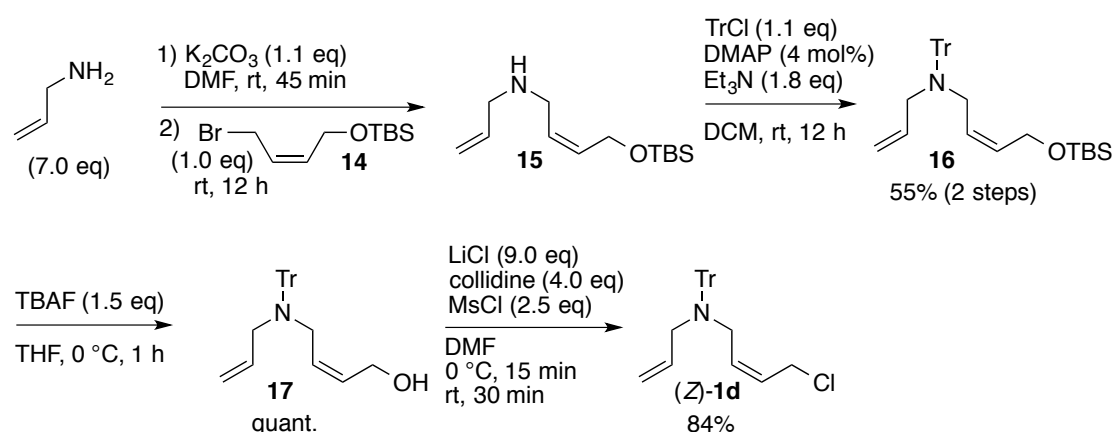
To a stirred suspension of K₂CO₃ (608.1 mg, 4.4 mmol) in allylamine (2.1 mL, 28.0 mmol) at room temperature, **14** (1.06 g, 4.0 mmol) was added dropwise over 45 min. After stirring at room temperature for 12 h the reaction mixture was filtered through a pad of Celite followed by evaporation of excess allylamine in vacuo. The residue was used for next step without further purification.

A solution of the corresponding crude amine **15** (2.0 mmol) in DCM (1 mL) was added to a solution of trityl chloride (613.3 mg, 2.2 mmol), Et₃N (502 µL, 3.6 mmol) and DMAP (9.8 mg, 0.08 mmol) at room temperature and the mixture was stirred for 12 h. The reaction was then quenched with H₂O (1 mL) and extracted with EtOAc (15 mL × 3) and the combined organic phases were washed with brine (5 mL) and dried over Na₂SO₄. After evaporation of the solvents, the resulting residue was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) to give **16** (532.1 mg, 1.1 mmol) in 55% yield (2 steps).

To a solution of **16** (532.1 mg, 1.1 mmol) in THF (5.5 mL) was added TBAF (1.7 mL of 1.0 M in THF solution, 1.7 mmol) at 0 °C. The mixture was stirred for 1 h. The reaction was then quenched with H₂O (5 mL) and extracted with EtOAc (15 mL × 3) and the combined organic phases were washed with brine (5 mL) and dried over Na₂SO₄. After evaporation of the solvents, the resulting residue was purified by flash chromatography on silica gel (5–20% EtOAc/hexane) to give allyl alcohol **17**.

To a suspension of **17** (168 mg, 0.75 mmol) in DMF (5 mL) at 0 °C, LiCl (500 mg, 11.8 mmol), and collidine (500 μ L, 547 mg, 4.5 mmol) in DMF (5 mL) were added MsCl (250 mL, 170 mg, 1.5 mmol). The mixture was stirred at this temperature for 15 min before the temperature was allowed to rise to room temperature. After being stirred at room temperature for 30 min, the reaction was quenched with aqueous saturated NH_4Cl solution (3 mL) and extracted with EtOAc (4 mL $\times$ 3). The organic layers were combined and dried over MgSO_4 . The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (0–2% EtOAc/hexane) to yield 244 mg (0.63 mmol, 84%) of **1d** as a pale yellow oil.

Scheme 7. Preparation of (Z)-1d



Preparation of (Z)-allyl chlorides 1e (Scheme 8).

A suspension of diethyl dibenzylmalonate **18** (4.45 g, 13.0 mmol) and LiCl (3.86 g, 91.0 mmol) in DMSO (38 mL) was stirred at 170 °C for 6 h. The reaction mixture was allowed to stirred at room temperature, treated with water (1.3 mL), stirred for another 1 h, diluted with EtOAc (30 mL) and extracted with EtOAc (30 mL $\times$ 3). The organic layers were combined and dried over MgSO_4 . The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (0–2% EtOAc/hexane) to yield 2.44 g (9.1 mmol, 70%) of 2-benzyl-3-phenylpropanoate **19** as pale yellow oil.

To a solution of **19** (1.74 g, 6.5 mmol) in dry THF (13 mL), LDA (7.8 mmol) was added at –78 °C. The resultant solution was stirred at –78 °C for 15 min and then **14** (2.07 g, 7.8 mmol) in THF (10 mL) was added. The mixture was stirred at this temperature for 6 h. The reaction was quenched with aqueous saturated NH_4Cl solution (6 mL) and extracted with EtOAc (13 mL $\times$ 3). The organic layers were combined and dried over MgSO_4 . The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (0–3% EtOAc/hexane)

to yield 2.27 g (5.0 mmol, 77%) of **20** as a pale yellow oil.

20 (2.27 g, 5.0 mmol) was added to a suspension of LiAlH₄ (247.5 mg, 6.0 mmol) in Et₂O (50 mL) at 0 °C. The mixture was allowed to stirred at room temperature for 2 h. After quenching with NaOH aq at 0 °C, the mixture was filtered and concentrated. The crude primary alcohol **21** was used for next step without further purification.

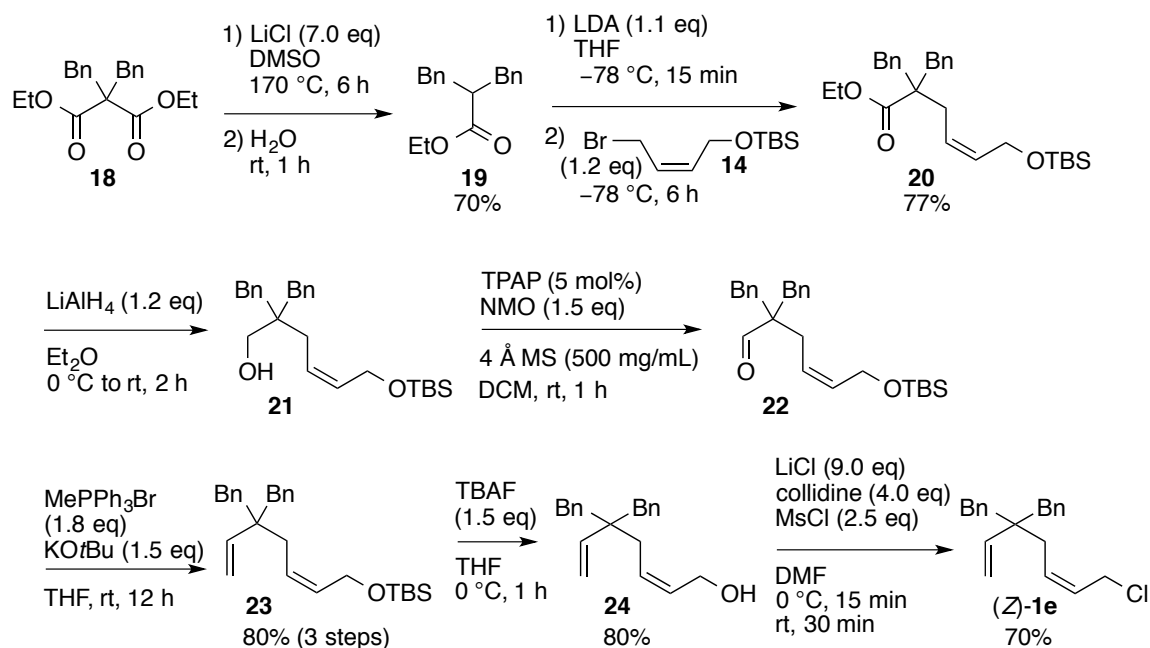
Powdered 4 Å molecular sieves and NMO (878.6 mg, 7.5 mmol) were added to a solution of the crude primary alcohol **21** in DCM (6 mL). The resultant solution was stirred at room temperature for 10 min and then TPAP (88.0 mg, 0.25 mmol) in DCM (3 mL) was added at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h, then loaded onto silica and eluted using hexane until all aldehyde had been collected. The crude aldehyde **22** was used for next step without further purification.

Methyltriphenylphosphonium bromide (3.21 g, 9.0 mmol) was suspended in THF (6 mL) and cooled to 0 °C. KO^tBu (841.6 mg, 7.6 mmol) was added in one portion, and the reaction mixture was stirred at 0 °C for 30 min. The crude aldehyde **22** was dissolved in THF (4 mL) and added to the ylide. After the mixture was stirred for room temperature for 12 h, hexane (25 mL) was added, and the resulting thick suspension was filtered through Celite. The filter cake was washed with Et₂O and the solution concentrated then purified by flash column chromatography on silica gel (0–1% EtOAc/hexane) to yield 1.63 g (4.0 mmol, 80% in 3 steps) of **23** as pale yellow oil.

To a solution of **23** (813.4 mg, 2.0 mmol) in THF (10 mL) was added TBAF (3.0 mL of 1.0 M in THF solution, 3.0 mmol) at 0 °C. The mixture was stirred for 1 h. The reaction was then quenched with H₂O (5 mL) and extracted with EtOAc (10 mL × 3) and the combined organic phases were washed with brine (5 mL) and dried over MgSO₄. After evaporation of the solvents, the resulting residue was purified by flash chromatography on silica gel (5–20% EtOAc/hexane) to give allyl alcohol **24** (467.9 mg, 1.6 mmol) in 80% yield.

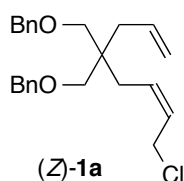
To a suspension of **24** (292.4 mg, 1.0 mmol) in DMF (3 mL) at 0 °C, LiCl (381.5 mg, 9.0 mmol), and collidine (530 µL, 4.0 mmol) in DMF (3 mL) were added MsCl (154.8 µL, 2.0 mmol). The mixture was stirred at this temperature for 15 min before the temperature was allowed to rise to room temperature. After being stirred at room temperature for 30 min, the reaction was quenched with aqueous saturated NH₄Cl solution (5 mL) and extracted with EtOAc (7 mL × 3). The organic layers were combined and dried over MgSO₄. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (0–1% EtOAc/hexane) to yield 217.6 mg (0.7 mmol, 70%) of **1e** as a colorless oil.

Scheme 8. Preparation of (Z)-1e



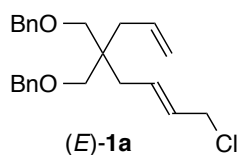
Characterization Data for Allylic Substrates

(Z)-({[2-Allyl-2-(4-chlorobut-2-en-1-yl)propane-1,3-diyl]bis(oxy)}bis(methylene))dibenzene (1a)



Colorless Oil. **IR** (neat) 734, 969, 1095, 1204, 1250, 1638, 1662, 2857, 3030 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 2.12–2.17 (m, 4H), 3.29 (s, 4H), 4.09 (d, $J = 7.2$ Hz, 2H), 4.47 (s, 4H), 5.03–5.07 (m, 2H), 5.61–5.83 (m, 3H), 7.26–7.33 (m, 10H). **^{13}C NMR** (100 MHz, CDCl_3) δ 29.5, 36.5, 39.7, 42.4, 72.0, 73.2, 117.9, 127.4, 127.8 ($\times 2\text{C}$), 128.2, 129.9, 134.0, 138.6. **HRMS–ESI** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{30}\text{O}_2\text{Cl}$, 385.19288; found, 385.19283.

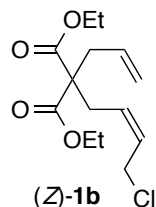
(E)-({[2-Allyl-2-(4-chlorobut-2-en-1-yl)propane-1,3-diyl]bis(oxy)}bis(methylene))dibenzene (1a)



Colorless Oil. **^1H NMR** (400 MHz, CDCl_3) δ 2.09–2.12 (m, 4H), 3.28 (s, 4H), 3.99 (d, $J = 6.8$

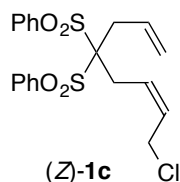
Hz, 2H), 4.47 (s, 4H), 5.02–5.06 (m, 2H), 5.59–5.82 (m, 3H), 7.27–7.34 (m, 10H). ^{13}C NMR (100 MHz, CDCl_3) δ 34.7, 36.6, 42.3, 45.4, 72.2, 73.2, 117.8, 127.4, 127.4, 128.2, 128.9, 131.6, 134.1, 138.7.

(Z)-Diethyl-2-allyl-2-(4-chlorobut-2-en-1-yl)malonate (1b)



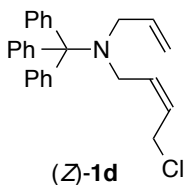
Colorless Oil. **IR** (neat) 749, 1191, 1211, 1287, 1642, 1728, 2982, 3030 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.25 (t, $J = 6.8$ Hz, 6H), 2.65 (d, $J = 7.6$ Hz, 2H), 2.70 (dd, $J = 8.0, 1.6$ Hz, 2H), 4.08 (d, $J = 7.6$ Hz, 2H), 4.14–4.25 (m, 4H), 5.11–5.15 (m, 2H), 5.48 (m, 1H), 5.59–5.78 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 30.0, 36.9, 39.1, 57.1, 61.5, 119.5, 127.8, 128.9, 132.1, 170.5. **HRMS–ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{21}\text{O}_4\text{ClNa}$, 311.10206; found, 311.10178.

(Z)-(8-Chloroocta-1,6-diene-4,4-diylbisulfonylethyl)dibenzene (1c)



White Solid. **M.p.** 89.2–92.3 $^{\circ}\text{C}$ **IR** (neat) 682, 727, 921, 1076, 1143, 1307, 1447, 1583, 1639, 2919, 3032 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 3.02–3.06 (m, 4H), 4.00 (d, $J = 7.6$ Hz, 2H), 5.20 (dd, $J = 17.2, 1.6$ Hz, 1H), 5.26 (dd, $J = 10.0, 1.6$ Hz, 1H), 5.82 (m, 1H), 5.90–6.02 (m, 2H), 7.61 (t, $J = 8.0$ Hz, 4H), 7.74 (t, $J = 8.0$ Hz, 2H), 8.06 (d, $J = 8.0$ Hz, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 26.8, 33.1, 38.8, 89.6, 121.4, 125.5, 128.7, 128.9, 129.4, 131.5, 134.8, 136.2. **HRMS–ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{21}\text{O}_4\text{ClNaS}_2$, 447.04630; found, 447.04620.

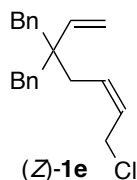
(Z)-N-allyl-4-chloro-N-tritylbut-2-en-1-amine (1d)



Pale Yellow Oil. **IR** (neat) 682, 727, 921, 1076, 1143, 1307, 1254, 1447, 1583, 2920 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 3.01 (d, $J = 6.0$ Hz, 2H), 3.09 (d, $J = 6.4$ Hz, 2H), 3.83 (d, $J = 8.0$ Hz, 2H), 4.94 (dd, $J = 10.0, 1.6$ Hz, 1H), 4.99 (dd, $J = 16.8, 1.6$ Hz, 1H), 5.47 (m, 1H), 5.79–5.97 (m,

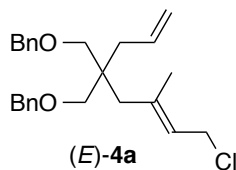
2H), 7.17 (t, $J = 7.2$ Hz, 3H), 7.27 (t, $J = 7.2$ Hz, 6H), 7.52 (d, $J = 7.2$ Hz, 6H). ^{13}C NMR (100 MHz, CDCl_3) δ 39.8, 49.6, 56.7, 78.5, 115.8, 124.6, 126.1, 127.7, 129.2, 135.1, 138.0, 143.5. HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{26}\text{H}_{26}\text{ClN}$, 387.17538; found, 387.17455.

(Z)-[2-(4-Chlorobut-2-en-1-yl)-2-vinylpropane-1,3-diyl]dibenzene (1e)



Colorless Oil. IR (neat) 699, 724, 915, 1076, 1249, 1495, 1601, 1637, 2923, 3028 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 2.07 (d, $J = 6.4$ Hz, 2H), 2.74 (s, 4H), 3.97 (d, $J = 7.6$ Hz, 2H), 4.82 (d, $J = 17.6$ Hz, 1H), 5.12 (d, $J = 11.2$ Hz, 1H), 5.75–5.89 (m, 3H), 7.12–7.77 (m, 10H). ^{13}C NMR (100 MHz, CDCl_3) δ 31.0, 39.9, 44.0, 44.3, 113.8, 126.2, 127.0, 127.7, 130.9, 131.1, 137.6, 144.2. HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{21}\text{H}_{23}\text{Cl}$, 310.14883; found, 310.14739.

(E)-([2-Allyl-2-(4-chloro-2-methylbut-2-en-1-yl)propane-1,3-diyl]bis(oxy))bis(methylene)dibenzene (4a)



Colorless Oil. IR (neat) 735, 969, 1093, 1207, 1254, 1638, 1662, 2856, 3030 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.76 (s, 3H), 2.16–2.18 (m, 4H), 3.27 (s, 4H), 4.06 (d, $J = 8.0$ Hz, 2H), 4.46 (s, 4H), 5.03–5.08 (m, 2H), 5.49 (t, $J = 8.0$ Hz, 1H), 5.80 (m, 1H), 7.25–7.35 (m, 10H). ^{13}C NMR (100 MHz, CDCl_3) δ 18.3, 37.4, 41.1, 41.2, 43.1, 72.3, 73.1, 117.8, 124.7, 127.4, 127.4, 128.2, 134.4, 138.7, 139.7. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{31}\text{O}_2\text{ClNa}$, 421.19048; found, 421.19107.

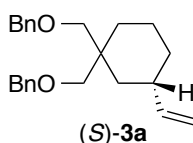
Procedure for Copper-Catalyzed Enantioselective Intramolecular Allylic Alkylation.

The reaction in Table 1, entry 9 is representative. (Z)-1a (38.4 mg, 0.1 mmol) and (9-BBN-H)₂ (12.2 mg, 0.05 mmol) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon[®]-coated silicon rubber septum and the vial was evacuated and filled with argon. mesitylene (0.1 mL) was added to the vial, and then the mixture was stirred at 60 °C for 1 h to prepare an alkylborane. Meanwhile, CuOTf·(toluene)_{0.5} (2.6 mg, 0.01 mmol), L2 (6.5 mg, 0.01 mmol) and KOMe (7.7 mg, 0.11 mmol) were placed in another vial. This vial was sealed with a Teflon[®]-coated silicon rubber septum and then evacuated and filled with argon. After MTBE (0.3

mL) was added to the vial, the mixture was stirred at 25 °C for 1 h. Next, the alkylborane solution was transferred to the vial containing the Cu(I)–**L2** complex. After 13 h stirring at 25 °C, diethyl ether was added to the mixture. The mixture was filtered through a short plug of silica gel, which was then washed with diethyl ether. After the solvent was removed under reduced pressure, flash chromatography on silica gel (0–1% EtOAc/hexane) provided **3a** (29.4 mg, 0.84 mmol) at 91% ee in 84% yield.

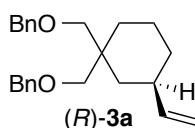
Characterization Data for Chiral Cyclic Compounds

(*S*)-({[(3-Vinylcyclohexane-1,1-diyl)bis(methylene)]bis(oxy)}bis(methylene))dibenzene (**3a**)



The product **3a** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (29.4 mg, 0.084 mmol, 84% isolated yield from (*Z*)-**1a**). Pale Yellow Oil. **IR** (neat) 696, 732, 906, 1027, 1096, 1205, 1363, 1452, 1635, 2852, 2922, 3029 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 0.92–1.15 (m, 3H), 1.37 (m, 1H), 1.59 (m, 1H), 1.69–1.78 (m, 3H), 2.04 (m, 1H), 3.27–3.32 (m, 2H), 3.48 (s, 2H), 4.49–4.50 (m, 4H), 4.87 (d, *J* = 10.8 Hz, 1H), 4.93 (d, *J* = 17.6 Hz, 1H), 5.71 (ddd, *J* = 17.6, 10.8, 6.4 Hz, 1H), 7.23–7.34 (m, 10H). **¹³C NMR** (100 MHz, CDCl₃) δ 21.1, 29.6, 32.2, 36.2, 36.5, 39.2, 70.1, 73.1, 73.2, 77.5, 111.9, 127.2 ($\times 2$ C), 127.3 ($\times 2$ C), 128.2, 128.2, 139.0, 139.1, 144.6. **HRMS–ESI** (*m/z*): [*M*+Na]⁺ calcd for C₂₄H₃₀O₂Na, 373.21380; found, 373.21396. [α]_D²⁴ –14.09 (*c* 0.96, CHCl₃). The ee value (91% ee) was determined by chiral HPLC analysis of **3a** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm/OD-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane, 0.7 mL/min, 40 °C, 220 nm UV detector, retention time = 29.9 min for *S* isomer and 31.8 min for *R* isomer]. The absolute configuration of **3a** was assigned by consideration of the stereochemical pathway.

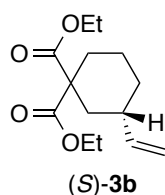
(*R*)-({[(3-Vinylcyclohexane-1,1-diyl)bis(methylene)]bis(oxy)}bis(methylene))dibenzene (**3a**)



The product **3a** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (24.5 mg, 0.07 mmol, 70% isolated yield from (*E*)-**1a**). Pale Yellow Oil. [α]_D²⁴ +13.51 (*c* 0.90, CHCl₃). The ee value (87% ee) was determined by chiral HPLC analysis of **3a** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm/OD-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane, 0.7 mL/min, 40 °C, 220 nm UV detector, retention time = 30.2 min for *S* isomer and 31.5 min for

R isomer]. The absolute configuration of **3a** was assigned by consideration of the stereochemical pathway.

(S)-Diethyl-3-vinylcyclohexane-1,1-dicarboxylate (3b)

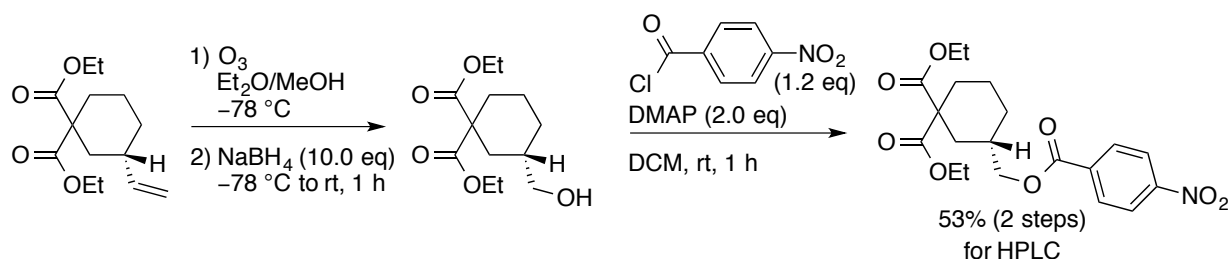


The product **3b** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) and GPC (13.2 mg, 0.05 mmol, 50% isolated yield from (*Z*)-**1b**). Pale Yellow Oil. **IR** (neat) 698, 911, 1066, 1096, 1141, 1242, 1310, 1451, 1640, 1728, 2857, 2935 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.21–1.29 (m, 6H), 1.38–1.48 (m, 2H), 1.53–1.62 (m, 2H), 1.71–1.77 (m, 2H), 2.16 (m, 1H), 2.32–2.43 (m, 2H), 4.15–4.22 (m, 4H), 4.94 (d, $J = 10.0$ Hz, 1H), 5.00 (d, $J = 17.6$ Hz, 1H), 5.74 (ddd, $J = 17.6, 10.0, 6.4$ Hz, 1H). **^{13}C NMR** (100 MHz, CDCl_3) δ 14.0, 14.1, 22.3, 30.8, 31.1, 36.6, 37.6, 55.0, 61.1, 61.3, 112.8, 143.1, 171.1, 172.4. **HRMS–EI** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{22}\text{O}_4$, 254.15181; found, 254.15236. $[\alpha]_{\text{D}}^{25}$ -1.92 (c 0.35, CHCl_3). The ee value (85% ee) was determined by chiral HPLC analysis of *p*-nitrobenzoate derivative obtained by the ozonolysis, reduction with NaBH_4 followed by benzoylation from **3b** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm/OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.8 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 46.8 min for *S* isomer and 49.2 min for *R* isomer]. The absolute configuration of **3b** was assigned by consideration of the stereochemical pathway.

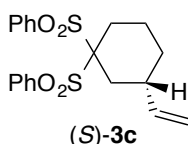
Derivatization of 3b.

Ozone was bubbled into a solution of **3b** (7.6 mg, 0.03 mmol) in MeOH/diethyl ether (1:10, 5.0 mL) at -78 $^\circ\text{C}$. After the starting material was completely disappeared (monitored by TLC), NaBH_4 (11.3 mg, 0.3 mmol) was added and the mixture was allowed to warm to room temperature and it was further stirred at the room temperature for 1 h. The mixture was quenched with water. The aqueous layer was extracted with EtOAc (three times). The combined organic layer was washed with water and brine, and then was dried and concentrated. The crude alcohol was used for next step without further purification.

To a solution of the corresponding alcohol in 300 μL of dry DCM were successively added DMAP (6.7 mg, 0.06 mmol) and 4-nitrobenzoyl chloride (6.7 mg, 0.036 mmol). After being stirred for 1 h at room temperature, the mixture was filtered through a short plug of silica gel, which was then washed with diethyl ether. The solvent was removed and the resulting residue was purified by flash chromatography on silica gel (2–5% EtOAc/hexane) provided *p*-nitrobenzoate derivative (6.5 mg, 0.016 mmol) in 53% yield (2 steps).

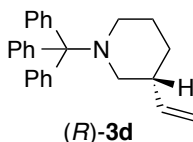


(*S*)-(3-Vinylcyclohexane-1,1-disulfonyl)dibenzene (**3c**)



The product **3c** was purified by flash chromatography on silica gel (3–7% EtOAc/hexane) and GPC (16.6 mg, 0.04 mmol, 40% isolated yield from (*Z*)-**1c**). Pale Yellow Oil. **IR** (neat) 685, 726, 921, 1075, 1142, 1305, 1446, 1583, 1640, 2921 cm^{-1} . **¹H NMR** (400 MHz, CDCl_3) δ 1.09 (m, 1H), 1.77–1.88 (m, 2H), 2.05 (m, 1H), 2.02–2.32 (m, 4H), 2.91 (m, 1H), 4.98 (d, J = 10.4 Hz, 1H), 5.03 (d, J = 16.8 Hz, 1H), 5.67 (ddd, J = 16.8, 10.4, 6.8 Hz, 1H), 7.56–7.61 (m, 4H), 7.67–7.73 (m, 2H), 8.01 (d, J = 7.2 Hz, 2H), 8.09 (d, J = 7.2 Hz, 2H). **¹³C NMR** (100 MHz, CDCl_3) δ 21.2, 26.0, 29.9, 31.5, 36.3, 88.3, 114.1, 128.5, 128.5, 131.1, 131.6, 134.3, 134.5, 136.2, 136.7, 142.1. **HRMS–ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{22}\text{O}_4\text{NaS}_2$, 413.08518; found, 413.08517. $[\alpha]_{\text{D}}^{25}$ –16.67 (c 0.31, CHCl_3). The ee value (89% ee) was determined by chiral HPLC analysis of **3c** [CHIRALCEL® OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 90:10, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 17.9 min for *R* isomer and 19.1 min for *S* isomer]. The absolute configuration of **3c** was assigned by consideration of the stereochemical pathway.

(*R*)-1-Trityl-3-vinylpiperidine (**3d**)



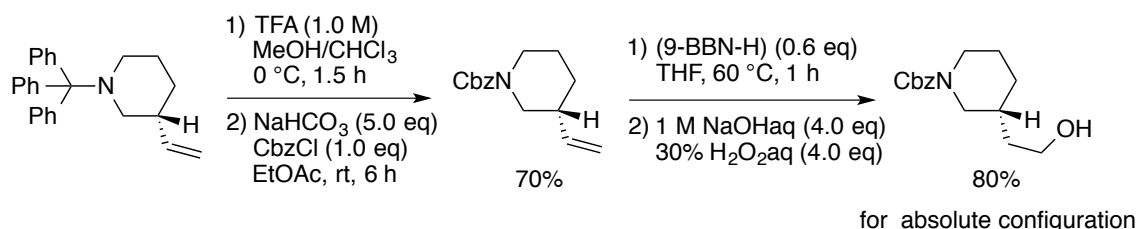
The product **3d** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (21.2 mg, 0.06 mmol, 60% isolated yield from (*Z*)-**1d**). White solid. **M.p.** 74.2–75.8 °C. **IR** (neat) 697, 758, 1018, 1215, 1447, 1586, 1639, 1735, 2852, 2924, 3059 cm^{-1} . **¹H NMR** (400 MHz, CDCl_3) δ 0.86–1.41 (br, 3H), 1.66–1.80 (br, 3H), 2.52 (br, 1H), 3.03–3.10 (br, 2H), 4.87–4.98 (br, 2H), 5.64 (br, 1H), 7.13–7.45 (br, 15H). **¹³C NMR** (100 MHz, CDCl_3) δ 30.7, 41.1, 48.9, 54.3 ($\times 2\text{C}$), 77.5, 113.3, 125.8, 127.3, 129.3 (br, $\times 2\text{C}$), 141.8. **HRMS–EI** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{26}\text{H}_{27}\text{N}$, 353.21435; found, 353.21356. $[\alpha]_{\text{D}}^{26}$ –21.89 (c 1.21, CHCl_3). The ee value (90% ee) was determined by chiral

HPLC analysis of **3e** [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm/ OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane, 0.3 mL/min, 40 °C, 250 nm UV detector, retention time = 56.0 min for *R* isomer and 59.4 min for *S* isomer]. The absolute configuration of **3d** was determined by optical rotation of the alcohol derivative. $[\alpha]_D^{24} +17.77$ (*c* 0.98, CHCl₃). {lit²¹, (*S*) isomer, >99% ee, $[\alpha]_D^{32} -16.2$ (*c* 0.9, CHCl₃)}.}

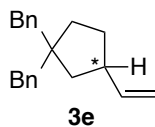
Derivatization of **3d**.

3d (42.4 mg, 0.12 mmol) was dissolved in a mixture of chloroform (120 μL) and methanol (120 μL) and cooled to 0 °C in an ice-bath. TFA (120 μL) was added dropwise and the reaction mixture was stirred at 0 °C 1 h. The solvents were removed under reduced pressure at 0 °C and the resulting solid residue was azeotroped five times with diethyl ether (three times) at 0 °C and partitioned between diethyl ether (1 mL) and water (2 mL). The organic layer was washed with water (two times) and the combined aqueous fractions were basified with NaHCO₃ (50.4 mg, 0.6 mmol). The aqueous fractions were diluted with ethyl acetate (3 mL) and the mixture was cooled to 0 °C. Benzyl chloroformate (14.7 μL, 0.12 mmol) was added and the reaction mixture was stirred vigorously at room temperature for 6 h. The layers were separated and the aqueous layer was washed with ethyl acetate (3 mL). The combined organic fractions were washed with brine, then dried over Na₂SO₄. After evaporation of the solvents, the resulting residue was purified by flash chromatography on silica gel (2–5% EtOAc/hexane) to give the corresponding *N*-benzyloxycarbonyl piperidine derivative (20.6 mg, 0.084 mmol) in 70% yield.

N-benzyloxycarbonyl piperidine (19.6 mg, 0.080 mmol) was added to a solution of 9-BBN dimer (11.7 mg, 0.048 mmol) in THF (170 μL). The reaction mixture was stirred at 60 °C for 1 h. The mixture was cooled to 0 °C and treated cautiously with a mixture of THF (100 μL), 30 % hydrogen peroxide (32.6 μL) and aqueous sodium hydroxide (320 μL of a 1 M solution), stirred at room temperature for 1 h. Na₂S₂O₃ aq was added, the layers were separated, and the aqueous phase was extracted with CH₂Cl₂ (three times). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give a colorless oil that was purified by GPC to provide alcohol derivative (16.9 mg, 0.064 mmol) in 80% yield.



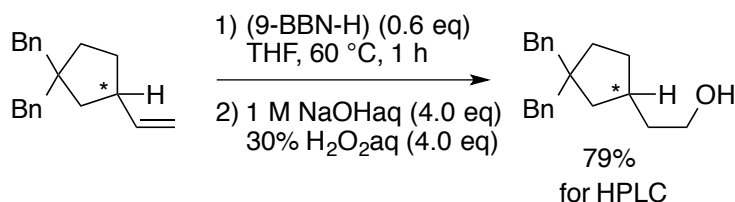
[(3-Vinylcyclopentane-1,1-diyl)bis(methylene)]dibenzene (3e)



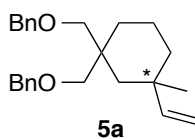
The product **3e** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (9.4 mg, 0.034 mmol, 34% isolated yield from (Z)-**1e**). Pale Yellow Oil. **IR** (neat) 700, 907, 1031, 1453, 1494, 1602, 1638, 2854, 2933, 3027 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.15–1.83 (m, 6H), 2.41 (m, 1H), 2.67–2.68 (m, 4H), 4.79 (d, J = 10.0 Hz, 1H), 4.87 (d, J = 17.6 Hz, 1H), 5.64 (ddd, J = 17.6, 10.0, 7.6 Hz, 1H), 7.13–7.30 (m, 10H). **^{13}C NMR** (100 MHz, CDCl_3) δ 31.3, 34.6, 41.8, 42.7, 45.5, 45.7, 47.3, 112.1, 125.9, 126.0, 127.8, 127.9, 130.7, 130.9, 139.2, 139.4, 143.7. **HRMS–EI** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{21}\text{H}_{24}$, 276.18780; found, 276.18653. $[\alpha]_{\text{D}}^{26}$ –17.86 (c 0.85, CHCl_3). The ee value (33% ee) was determined by chiral HPLC analysis of alcohol derivative obtained by the hydroboration followed by oxidation from **3d** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 96:4, 0.5 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 22.7 min for minor isomer and 25.2 min for major isomer].

Derivatization of 3e.

3e (5.5 mg, 0.020 mmol) was added to a solution of 9-BBN dimer (2.9 mg, 0.012 mmol) in THF (100 μL). The reaction mixture was stirred at 60 $^\circ\text{C}$ for 1 h. The mixture was cooled to 0 $^\circ\text{C}$ and treated cautiously with a mixture of THF (50 μL), 30 % hydrogen peroxide (8.1 μL) and aqueous sodium hydroxide (80 μL of a 1 M solution), stirred at room temperature for 1 h. $\text{Na}_2\text{S}_2\text{O}_3$ aq was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (three times). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo to give a colorless oil that was purified by GPC to provide alcohol derivative (4.7 mg, 0.016 mmol) in 79% yield.



[(3-Methyl-3-vinylcyclohexane-1,1-diyl)bis(methylene)]bis(oxy)}bis(methylene)]dibenzene (5a)



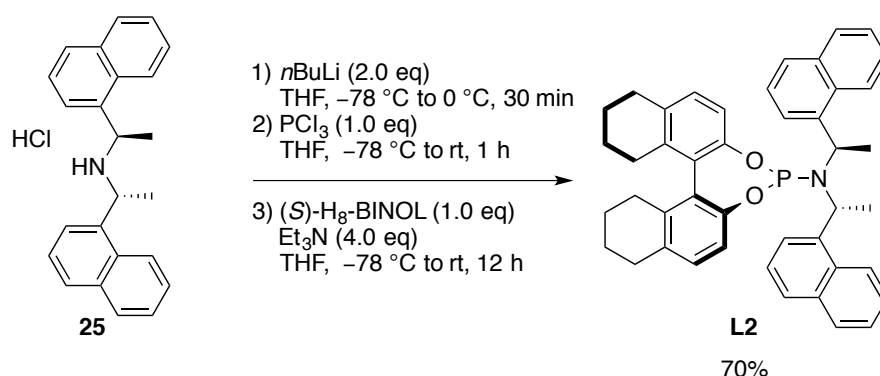
The product **5a** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (20.0

mg, 0.055 mmol, 55% isolated yield from (*E*)-**4a**). Pale Yellow Oil. **IR** (neat) 695, 732, 906, 1001, 1096, 1206, 1364, 1453, 1635, 2853, 2923, 3029 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 0.92 (s, 3H), 1.12–1.22 (m, 3H), 1.40–1.57 (m, 3H), 1.71 (d, $J = 13.2$ Hz, 1H), 1.79 (d, $J = 13.2$ Hz, 1H), 3.28 (s, 2H), 3.40 (d, $J = 7.2$ Hz, 1H), 3.44 (d, $J = 7.2$ Hz, 1H), 4.39–4.49 (m, 4H), 4.82 (dd, $J = 10.8, 1.6$ Hz, 1H), 4.92 (dd, $J = 17.6, 1.6$ Hz, 1H), 5.79 (dd, $J = 17.6, 10.6$, 1H), 7.23–7.34 (m, 10H). **^{13}C NMR** (100 MHz, CDCl_3) δ 18.4, 30.3, 32.5, 35.5, 36.1, 39.6, 41.8, 71.6, 72.9 ($\times 2\text{C}$), 73.2, 109.9, 127.2 ($\times 2\text{C}$), 127.3 ($\times 2\text{C}$), 127.4, 128.2, 128.2, 139.1, 148.6. **HRMS–EI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{25}\text{H}_{32}\text{O}_2\text{Na}$, 387.22945; found, 387.22964. $[\alpha]_{\text{D}}^{25} -7.87$ (c 0.71, CHCl_3). The ee value (83% ee) was determined by chiral HPLC analysis of **5a** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm/ OD-3 column, 4.6 mm $\times$ 250 mm/ OD-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane, 0.3 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 94.2 min for minor isomer and 97.1 min for major isomer].

Synthesis of **L2** (Scheme 9).

L2 was prepared according to the reported procedure.²² To a Schlenk tube containing a solution of bis[(*S*)-(–)-(1-naphthyl)ethyl]amine hydrochloride **25** (391.9 mg, 1 mmol) in THF (3.0 mL) was added 1.55 M solution of *n*BuLi in hexane (1.3 mL, 2 mmol, 2.0 equiv) at -78 $^\circ\text{C}$. The reaction mixture was slowly warmed to 0 $^\circ\text{C}$ over 30 min and transferred to a second Schlenk tube at -78 $^\circ\text{C}$ containing a solution of PCl_3 (89 μL , 1.0 mmol, 1.0 equiv) in THF (2.0 mL) at -78 $^\circ\text{C}$. The reaction mixture was slowly warmed to 0 $^\circ\text{C}$ over 1 h. To this flask was added Et_3N (556 μL , 4.0 mmol, 4.0 equiv) followed by (*R*)-**H₈-BINOL** (294.4 mg, 1.0 mmol) at 0 $^\circ\text{C}$. The reaction was allowed to warm to room temperature 12 h and was passed through a pad of Celite. The solution was concentrated, and the crude mixture was purified by column chromatography on silica gel (1–3% EtOAc/hexane) to afford **L2** as a white solid (453.5 mg, 70%). White solid. **M.p.** 114.2–115.3 $^\circ\text{C}$. **IR** (neat) 756, 786, 827, 850, 911, 1007, 1073, 1180, 1277, 1341, 1364, 1445, 1490, 1568, 1586, 1948, 3031 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.57–1.87 (m, 14H), 2.29 (m, 1H), 2.45 (m, 1H), 2.65–2.93 (m, 6H), 5.47 (quint, $J = 6.8$ Hz, 2H), 6.69 (t, $J = 7.2$ Hz, 2H), 7.09–7.22 (m, 6H), 7.28–7.34 (m, 6H), 7.57–7.59 (m, 2H), 7.87–7.89 (m, 2H). **^{13}C NMR** (100 MHz, CDCl_3) Due to the complexity of the spectrum, complete signal assignment based on P–C coupling is not shown here. δ 14.1, 22.5, 22.7, 22.8, 22.8, 27.6, 28.0, 29.0, 29.2, 31.5, 49.1, 49.2, 119.0, 123.2, 124.2, 124.3, 124.3, 124.7, 125.2, 126.7, 127.6, 128.3, 128.9, 129.3, 129.4, 129.5, 130.5, 132.7, 133.0, 134.2, 137.7, 138.1, 138.6, 148.7, 148.8, 148.8. **^{31}P NMR** (168 MHz, CDCl_3) δ 144.4. **HRMS–ESI** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{44}\text{H}_{43}\text{O}_2\text{NP}$, 648.30341; found, 648.30259. $[\alpha]_{\text{D}}^{25} -78.03$ (c 0.64, CHCl_3).

Scheme 9. Synthesis of L2



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- (16) The intermolecular coupling product was not observed.

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- (18) An attempt to form a seven-membered ring failed. No cyclization product was observed in a crude mixture by ¹H NMR spectroscopy.
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Chapter 3

Synthesis of α -Quaternary Formimides and Aldehydes through Copper-Catalyzed Asymmetric Three-Component Coupling Reaction of Isocyanides, Hydrosilanes, and Allylic Electrophile

A highly regio- and enantioselective Cu-catalyzed three-component coupling of isocyanides, hydrosilanes, and γ,γ -disubstituted allylic electrophiles was enabled by a combined use of chiral naphthol-carbene ligand, which was developed by Sawamura and Ohmiya group, as a functional Cu-supporting ligand and LiOtBu as a stoichiometric Lewis base for Si. This protocol provides simple, rapid, versatile, and reliable access to α -quaternary formimides and aldehydes.

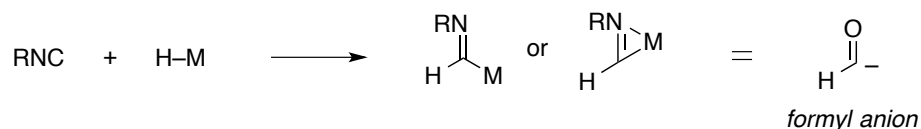
Introduction

Isocyanides, also called isonitriles, are chemical species isoelectronic with carbon monoxide, and their utilities in organic synthesis are remarkably diverse, having a rich history since the early 1900s (Figure 1a). Most typically, isocyanides have been employed as one-carbon reagents through their 1,1-insertion reactions into metal–element (M–E) bonds to form imidoymetal species $[M-C(=NR)-E]$, which exhibit characteristic reactivities in various catalytic transformations.¹ Specifically, formimidoymetal species $[M-C(=NR)-H]$, which can be produced through isocyanide 1,1-insertion into metal–H bonds, are expected to be “formyl anion (HCO^-)” equivalents (Figure 1b). In fact, about fifty years ago, Saegusa, Ito, and co-workers reported the copper-catalyzed 1,1-hydrosilylation of cyclohexyl isocyanide with trimethylsilane to yield (*N*-cyclohexylformimidoymethyl)trimethylsilane (Figure 1c). This reaction should involve silylation of catalytically generated formimidoymethylcopper(I) species. In this regard, Saegusa, Ito, and co-workers showed for the first time the high synthetic potential of isocyanide 1,1-insertion into a metal–H bond as a means of generating reactive “formyl anion” equivalents.² Surprisingly, however, for a period of about a half century after this discovery, catalytic reactions involving 1,1-insertion of isocyanides into metal–H bonds were not explored except for the copper-catalyzed indole-forming reductive cyclization of a 2-alkenylaryl isocyanide reported by Chatani and co-workers in 2010 (Figure 1d),³ while it was well documented that various hydride complexes of early or middle transition metals (groups 3–5 transition metals and lanthanides) reacted with isocyanides in a stoichiometric manner to form η^1 - or η^2 -formimidoymetal complexes.¹ As for copper, Sadighi and co-workers recently reported the synthesis of an η^1 -formimidoymethylcopper(I) complex through the stoichiometric reaction of benzyl isocyanide with isolated copper(I) hydride dimers coordinated with *N*-heterocyclic carbene ligands, but its reactivity was not revealed (Figure 1d).⁴

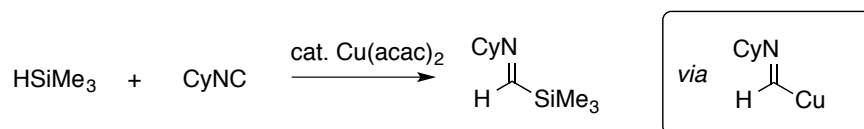
a) Isocyanide and carbon monoxide



b) Formation of formimidoylmatal species

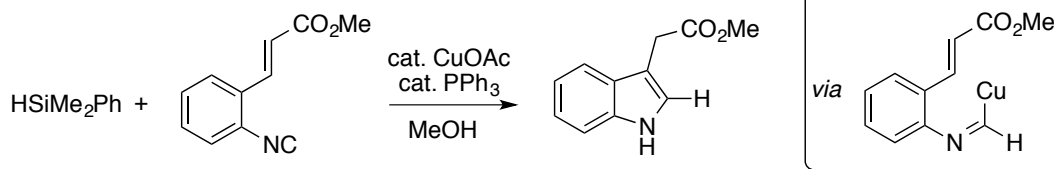


c) Cu-catalyzed 1,1-hydrosilylation reported by Saegusa and Ito (1967, ref 2)

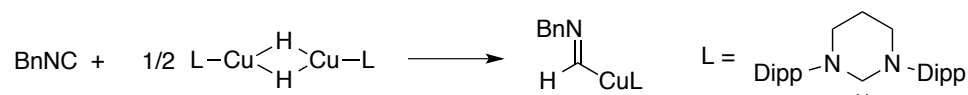


d) Formimidoylcopper(I) species in catalytic and stoichiometric reactions

Chatani's work (2010, ref 3)



Sadighi's work (2016, ref 4)



e) This work

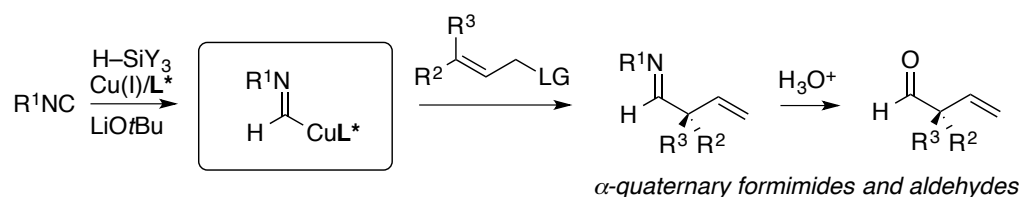


Figure 1. Isocyanides and their utilities as reagents for umpolung C1 synthons and as precursors for formyl anion equivalents. a) Isocyanide and carbon monoxide. b) Formation of formimidoyl metal species through isocyanide 1,1-insertion into metal hydride. M, transition metals and lanthanides. c) Copper-catalyzed 1,1-hydrosilylation of isocyanides. Cy, cyclohexyl. d) Formimidoylcopper(I) species in catalytic and stoichiometric reactions. Bn, benzyl. Dipp, 2,6-diisopropylphenyl. e) This work. *t*Bu, *tert*-butyl. L*, chiral ligand. LG, leaving group.

This chapter describes a highly regio- and enantioselective copper-catalyzed asymmetric three-component coupling reaction of isocyanides, hydrosilanes, and γ,γ -disubstituted primary

allylic phosphates (or chlorides) yielding chiral α -quaternary formimides, which were readily converted to the corresponding α -quaternary aldehydes.^{5,6} This enantioselective copper catalysis was enabled by a combined use of authors' original chiral naphthol-carbene ligand⁷⁻⁹ as a functional supporting ligand for Cu and LiOtBu as a stoichiometric Lewis basic activator for Si (Figure 1e). The author propose the possible participation of the ionized ligand naphtholic hydroxy group for generating lithium aryloxo(formimidoyl)cuprate species.

Due to the importance of acyl anion equivalents as umpolung reagents in organic synthesis,¹⁰ numerous efforts have been made in developing metal-catalyzed enantioselective allylic alkylation reactions using this type of nucleophile. For instance, stabilized carbanions prepared from acetoxy Meldrum's acid or malononitrile under basic conditions were employed as alkoxy carbonyl anion equivalents in the palladium and iridium catalyst systems.^{11,12} The palladium-catalyzed enantioselective allylic substitution with a sodium salt of 1-phenylsulfonyl-1-nitroethane as an acyl anion equivalent was developed and applied to the synthesis of hygromycin analogues.¹³ More recently, formaldehyde *N,N*-dialkylhydrazones were introduced as formyl anion equivalents in the iridium-catalyzed enantioselective kinetic resolution of racemic secondary allylic carbonates.¹⁴ However, these protocols constructed only tertiary carbon stereogenic centers. The enantioselective construction of all-carbon quaternary stereogenic centers remains highly challenging, in part due to the increased steric hindrance caused by the non-hydrogen substituents of a prochiral carbon.¹⁵⁻¹⁷ Given the synthetic versatility of enantioenriched chiral α -quaternary carbonyl compounds and their derivatives with transformable functional groups and the difficulty of preparing them, the development of such reactions is highly desirable.^{18,19} The enantioselective copper catalysis with isocyanides presented here provides simple, rapid, versatile, and reliable access to all-carbon quaternary stereogenic centers substituted with formimidoyl (or formyl) and vinyl groups, both of which can be used as handles for further transformations. It is to be noted that various α -quaternary formimides or aldehydes asymmetrically branched with various alkyl and aryl groups with very high enantiomeric excesses (96–99% ee) were obtained.

Results and discussion

Discovery of the reaction and screening of conditions

In previous reports from Sawamura and Ohmiya group on the copper-catalyzed enantioselective allylic substitution reactions of prochiral primary allylic phosphates with terminal alkyne or azole pronucleophiles, they synthesized some phenol-carbene chiral ligands and found them particularly efficient for enantioselective catalysis owing to the functional roles of the phenolic hydroxyl groups.^{7,8} The phenol-carbene chiral ligands were also useful for copper-

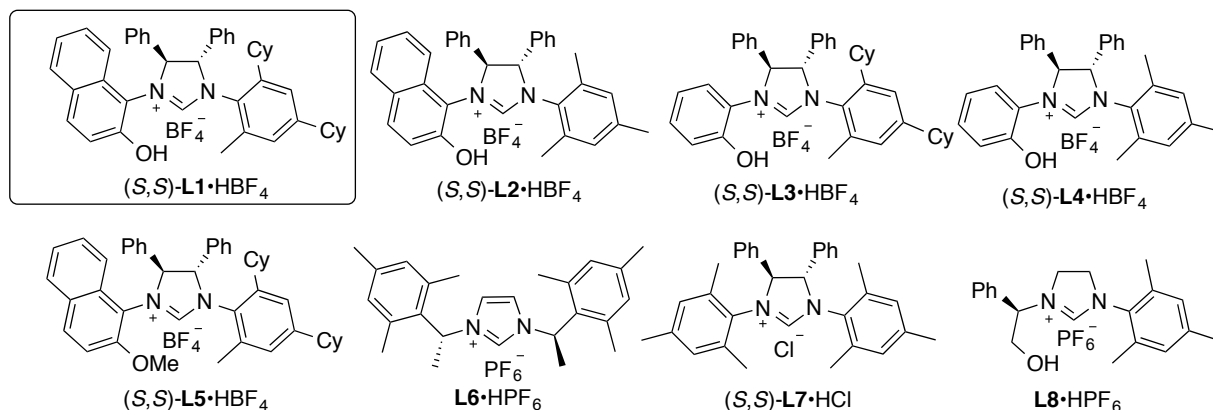
catalyzed enantioselective allylic substitution with allylboronate reagents.⁹ Based on this knowledge, the author proposed that the formation of formimidoylcopper(I) species from isocyanides might cooperate in a catalytic manner with the enantioselective allylic substitution to provide a new entry to enantioenriched α -branched formimides or aldehydes (Figure 1e).

Table 1. Screening of conditions for three-component coupling of **1**, **2a**, and **3a**.^a

Reaction scheme: HSiY_3 (**1**, 1.2 equiv) + CyNC (**2a**, 1.1 equiv) + $\text{Ph-CH=CH-CH}_2\text{-OP(OEt)}_2$ (**Z-3a**) $\xrightarrow[\text{THF, temp, 24 h}]{\text{CuCl (10 mol \%), L (10 mol \%), LiOtBu}}$ $\text{H-C(=N-Cy)-CH(Ph)-CH=CH}_2$ (**(S)-4aa**) $\xrightarrow{\text{silica gel}}$ $\text{H-C(=O)-CH(Ph)-CH=CH}_2$ (**(S)-5a**)

Entry	Ligand	Hydrosilane 1	Additive	Temp. (°C)	Yield (%) of 5a	ee (%) of 5a
1	L1 ·HBF ₄	Me ₂ PhSiH (1a)	LiOtBu	25	93	96
2	L1 ·HBF ₄	1a	LiOtBu	0	88	97
3	L1 ·HBF ₄	1a	LiOtBu (20 mol%)	25	0	–
4	L2 ·HBF ₄	1a	LiOtBu	25	89	72
5	L3 ·HBF ₄	1a	LiOtBu	25	90	81
6	L4 ·HBF ₄	1a	LiOtBu	25	22	32
7	L5 ·HBF ₄	1a	LiOtBu	25	0	–
8	L6 ·HBF ₄	1a	LiOtBu	25	25	4
9	L7 ·HBF ₄	1a	LiOtBu	25	0	–
10	L8 ·HBF ₄	1a	LiOtBu	25	0	–
11	None	1a	LiOtBu	25	0	–
12	Phen	1a	LiOtBu	25	0	–
13	Ph ₃ P	1a	LiOtBu	25	0	–
14	DPPE	1a	LiOtBu	25	0	–
15	IMes·HCl	1a	LiOtBu	25	25	–
16	SIMes·HBF ₄	1a	LiOtBu	25	0	–
17	L1 ·HBF ₄	(Me ₂ HSi) ₂ O (1b)	LiOtBu	0	84	97
18	L1 ·HBF ₄	PMHS (1c)	LiOtBu	0	42	95
19	L1 ·HBF ₄	EtMe ₂ SiH (1d)	LiOtBu	0	86	97
20	L1 ·HBF ₄	Et ₃ SiH (1e)	LiOtBu	0	0	–
21	L1 ·HBF ₄	<i>t</i> BuMe ₂ SiH (1f)	LiOtBu	0	0	–

22	L1 ·HBF ₄	1a	NaOtBu	0	20	93
23	L1 ·HBF ₄	1a	KOtBu	0	22	92
24	L1 ·HBF ₄	1a	LiOMe	0	6	—
25	L1 ·HBF ₄	1a	Li ₂ CO ₃	0	0	—



^aReaction conditions: **1** (0.18 mmol), **2a** (0.165 mmol), (*Z*)-**3a** (0.15 mmol), CuCl/**L** (10 mol %), LiOtBu (entries 1, 2, 4–6, 10, 17–25, 0.195 mmol; entry 3, 0.03 mmol; entries 7–9, 15, 16, 0.18 mmol; entries 11–14, 0.165 mmol), THF (0.6 mL), 24 h. THF, tetrahydrofuran. Phen, 1,10-phenanthroline. DPPE, 1,2-bis(diphenylphosphino)ethane. IMes·HCl, 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride. SIMes·HBF₄, 1,3-bis(2,4,6-trimethylphenyl)imidazolium tetrafluoroborate. PMHS, poly(methylhydrosiloxane). Yield of isolated product. Constitutional isomer ratio branched/linear >99:1 (determined by ¹H NMR analysis of the crude product). **4aa** was hydrolyzed with silica gel. The enantiomeric excess was determined by HPLC analysis.

In fact, the three-component coupling reaction of Me₂PhSiH (**1a**) (0.18 mmol), cyclohexyl isocyanide (**2a**) (0.165 mmol) and (*Z*)-3-phenyl-2-buten-1-ol derivative **3a** (0.15 mmol) occurred efficiently and cleanly in the presence of a stoichiometric amount of LiOtBu (0.18 mmol) and a catalytic amount of CuCl (10 mol%) and a chiral imidazolium salt (**L1**·HBF₄, 10 mol%) in THF at 25 °C to produce α-quaternary *N*-cyclohexylformimide (*S*)-**4aa**. This hydrolytically unstable compound was transformed to the corresponding α-quaternary aldehyde (*S*)-**5a** upon purification by silica gel chromatography. The yield of the purified (*S*)-**5a** was 93% based on **3a**, and its enantiomeric excess was as high as 96% (Table 1, entry 1). The γ-regioselectivity giving the γ,γ-double-branched product (**4aa**) over the achiral linear product (structure not shown) was exclusive (branched/linear >99:1). The enantioselectivity was further increased to 97% ee by lowering the reaction temperature to 0 °C (entry 2). The reaction in the presence of only 0.2 equiv of LiOtBu (relative to **3a**), which should be consumed as a Brønsted base to form an oxy anion form of the **L1** ligand (**L1**-H) (10 mol%), under otherwise identical conditions resulted in no reaction (entry 3). The stoichiometric amount of LiOtBu (1.0 eq to **3a**) seems to act as a Lewis basic activator for Si species in the copper catalysis (see Fig. 2). As for the allylic substrate, the corresponding (*Z*)-

allylic chloride and carbonates were not suitable due to their instability.

Other chiral carbene ligands bearing a naphthol or phenol group were less effective (Table 1, entries 4–6).^{7–9} Thus, replacing the *N*-2,4-dicyclohexyl-6-methylphenyl of **L1** with a *N*-mesityl group [(*S,S*)-**L2**] decreased the enantioselectivity to a moderate level (72% ee) (entry 4). The change of the naphthol group of **L1** to a phenol group [(*S,S*)-**L3**] also reduced the enantioselectivity (81%) (entry 5). The combination of phenol and *N*-mesityl groups [(*S,S*)-**L4**] resulted in significant reductions in product yield (22%) and enantioselectivity (32%) (entry 6).

The use of phenol- or naphthol-carbenes was essential not only for the enantiocontrol but also for the catalytic activity (Table 1, entries 7–10). No reaction occurred with *O*-methyl-protected ligand **L5** (entry 7). Thus, the OH group in **L1** was essential. The ring-unsaturated *C*₂-symmetric carbene ligand (**L6**) having 1-(mesityl)ethyl groups at both nitrogen atoms gave nearly racemic product with low yield (25%), whereas the branch regioselectivity was exclusive (entry 8).²⁰ The ring-saturated *C*₂-symmetric carbene ligand [(*S,S*)-**L7**], which has two stereogenic carbon centers in the imidazolidine ring and two mesityl groups at both nitrogen atoms, induced virtually no reaction (entry 9).²¹ The *N*-hydroxyalkyl-substituted carbene ligand (**L8**) having a stereogenic center in the *N*-alkyl side arm promoted no reaction (entry 10).²² Thus, having the alkanol in place of the arenol was not suitable.

Results with achiral catalyst systems are also listed in Table 1 (entries 11–16). The reaction did not occur at all without a ligand or with 1,10-phenanthroline, Ph₃P or DPPE ligands (entries 11–14). However, a copper-carbene complex prepared *in situ* from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl), CuCl and LiOtBu gave **4aa** in low yield (25%) with exclusive γ -regioselectivity (entry 15). The use of 1,3-bis(2,4,6-trimethylphenyl)imidazolinium tetrafluoroborate (SIMes·HBF₄) resulted in virtually no reaction (entry 16).

Results of the reaction conducted with other hydrosilane reagents (**L1**-Cu, 0 °C) are shown in Table 1, entries 17–21. Siloxane-type hydrosilane (Me₂HSi)₂O (**1b**) was as effective as Me₂PhSiH (**1a**) (entry 17), but poly(methylhydrosiloxane) (**1c**) gave a low product yield (42%) albeit a high level of enantioselectivity (entry 18). Relatively small trialkylsilane EtMe₂SiH (**1d**) was as effective as Me₂PhSiH (**1a**), but sterically more demanding trialkylsilanes such as Et₃SiH (**1e**) or *t*BuMe₂SiH (**1f**) did not participate in the reaction (entries 19–21).

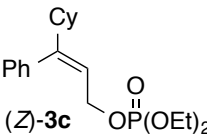
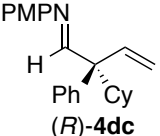
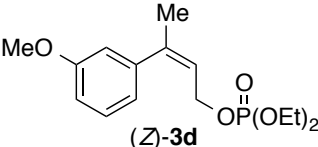
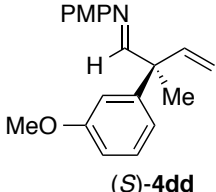
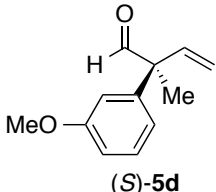
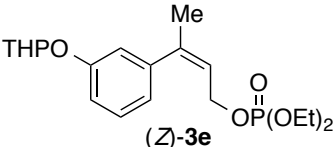
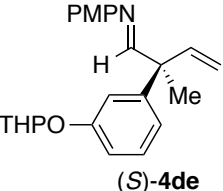
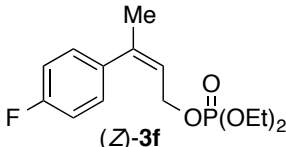
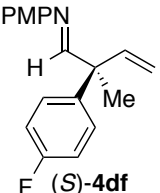
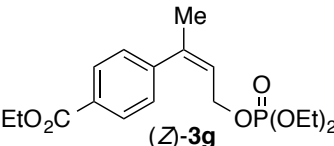
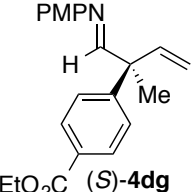
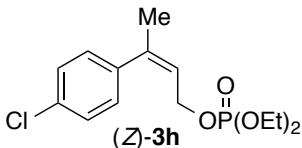
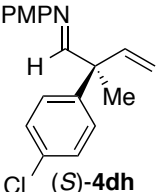
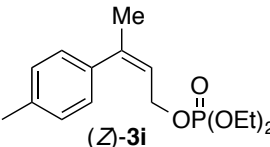
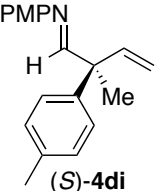
The nature of the Lewis base additives had a significant impact on the reaction efficiency and enantioselectivity (Table 1, entries 22–25). When the cation of LiOtBu was changed to K⁺ (KOtBu) or Na⁺ (NaOtBu) under the optimized conditions, the product yields were low and the enantioselectivity decreased slightly (entries 22 and 23). The additive with a smaller alkoxide, LiOMe, induced virtually no reaction (entry 24). Li₂CO₃ caused no reaction (entry 25).

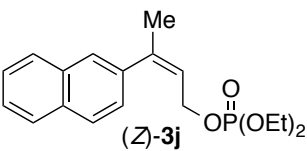
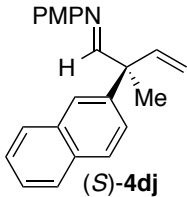
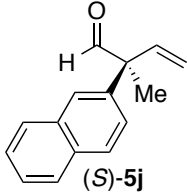
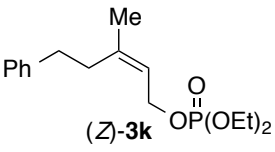
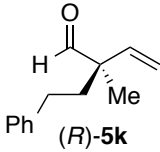
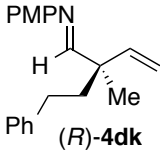
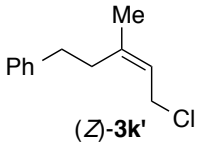
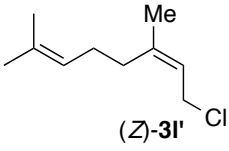
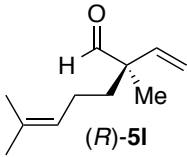
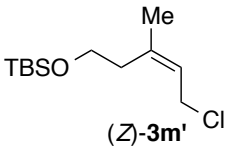
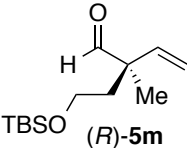
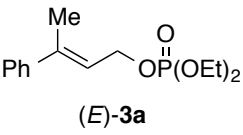
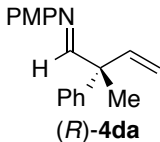
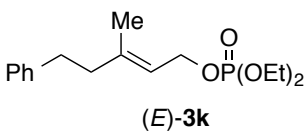
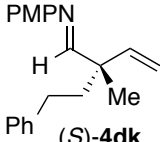
Substrates

Other isocyanides also participated in the enantioselective reaction with PhMe₂SiH (**1a**) and allylic phosphate **3a** under identical conditions (Table 2). The reaction of benzyl isocyanide (**2b**) occurred with excellent enantioselectivity, affording, after hydrolysis, aldehyde (*S*)-**5a** with 99% ee in 89% yield (entry 1). The reaction of *t*-butyl isocyanide (**2c**) also occurred with high enantioselectivity (93% ee), but the yield of (*S*)-**5a** was only moderate (50%) due to slower copper catalysis accompanied by decomposition of the allylic phosphate (entry 2). The reaction of 4-methoxyphenyl isocyanide (**2d**) gave the corresponding *N*-arylformimide [(*S*)-**4da**] with 99% ee in 94% yield (entry 3).

Table 2. Scope of isocyanides and allylic phosphates/chlorides.^a

entry	isocyanide	allylic substrate	formimide or aldehyde	yield (%)	ee (%)
1	BnNC 2b	 (<i>Z</i>)- 3a	 (<i>S</i>)- 5a	89	99
2	<i>t</i> BuNC 2c	(<i>Z</i>)- 3a	(<i>S</i>)- 5a	50	93
3	 2d	(<i>Z</i>)- 3a	 (<i>S</i>)- 4da	94	99
4	2d	(<i>Z</i>)- 3a	(<i>S</i>)- 5a	94	99
5	2d	(<i>Z</i>)- 3a (2 g, 7.04 mmol)	(<i>S</i>)- 4da	81	99
6 (5 mol %) ^c	2d	(<i>Z</i>)- 3a	(<i>S</i>)- 4da	90	99
7 (2.5 mol %) ^d	2d	(<i>Z</i>)- 3a	(<i>S</i>)- 4da	84	98
8	2d	 (<i>Z</i>)- 3b	 (<i>S</i>)- 4db	90	96

9	2d	 (<i>Z</i>)- 3c	 (<i>R</i>)- 4dc	89	97
10	2d	 (<i>Z</i>)- 3d	 (<i>S</i>)- 4dd	93	98
11	2d	(<i>Z</i>)- 3d	 (<i>S</i>)- 5d	93	98
12	2d	 (<i>Z</i>)- 3e	 (<i>S</i>)- 4de	90	99
13	2d	 (<i>Z</i>)- 3f	 (<i>S</i>)- 4df	90	96
14	2d	 (<i>Z</i>)- 3g	 (<i>S</i>)- 4dg	92	97
15	2d	 (<i>Z</i>)- 3h	 (<i>S</i>)- 4dh	88	95
16	2d	 (<i>Z</i>)- 3i	 (<i>S</i>)- 4di	95	98

17	2d	 (<i>Z</i>)- 3j	 (<i>S</i>)- 4dj	90	97
18	2d	(<i>Z</i>)- 3j	 (<i>S</i>)- 5j	90	97
19	2a	 (<i>Z</i>)- 3k	 (<i>R</i>)- 5k	89	83
20	2d	(<i>Z</i>)- 3k	 (<i>R</i>)- 4dk	90	84
21	2d	(<i>Z</i>)- 3k	(<i>R</i>)- 5k	90	84
22 ^e	2a	 (<i>Z</i>)- 3k'	(<i>R</i>)- 5k	60	86
23 ^e	2a	 (<i>Z</i>)- 3l'	 (<i>R</i>)- 5l	60	86
24 ^e	2a	 (<i>Z</i>)- 3m'	 (<i>R</i>)- 5m	46	84
25	2d	 (<i>E</i>)- 3a	 (<i>R</i>)- 4da	86	66
26	2d	 (<i>E</i>)- 3k	 (<i>S</i>)- 4dk	92	70

^aReaction conditions: **1a** (0.18 mmol), **2** (0.165 mmol), **3** (0.15 mmol), CuCl/**L1** (10 mol %), LiOtBu (0.195 mmol), THF (0.6 mL), 0 °C, 24 h. X, OP(O)(OEt)₂ or Cl. Bn, benzyl. PMP, *p*-methoxyphenyl. THP, 2-tetrahydropyranyl. TBS, *tert*-butyldimethylsilyl. Yield of isolated product. Constitutional isomer ratio branched/linear >99:1 (determined by ¹H NMR analysis of the crude product). The enantiomeric excess was determined by HPLC analysis.

^cEntries 3, 9, 17: **4** was hydrolyzed with 2 M HCl aq. Entries 1, 2, 16, 18–20: **4** was hydrolyzed with silica gel. ^d5 mol % of CuCl/**L1** was used. Reaction for 48 h. ^e2.5 mol % of CuCl/**L1** was used. Reaction for 72 h. ^fPoly(methylhydrosiloxane) (**1c**) was used.

The potential for scaling up the copper-catalyzed reaction was examined on a preparative scale. Thus, the reaction of **1a** (1.19 g, 8.44 mmol), **2d** (1.06 g, 7.74 mmol), and **3a** (2.0 g, 7.04 mmol) yielded 1.51 g (81%) of (*S*)-**4da** with 99% ee (Table 2, entry 5). The Cu loading could be reduced to 5 or 2.5 mol% with the enantioselectivity retained (entries 6 and 7).

Table 2 also summarizes the results of the reactions of various (*Z*)- γ,γ -disubstituted allylic phosphates having aryl and alkyl substituents at the γ -position under the CuCl-**L1** catalyst system 4-methoxyphenyl isocyanide (**2d**) was used as an isocyanide reagent because *N*-(4-methoxyphenyl)formimide products are generally more hydrolytically stable than *N*-alkylformimides. The former could be isolated by chromatography on silica gel. The *N*-(4-methoxyphenyl)formimides were readily converted to the corresponding aldehydes upon acidic hydrolysis (2 M HCl aq). The methyl group of **3a** could be replaced with an ethyl group with virtually no deviation in enantioselectivity (entry 8). Remarkably, the allylic phosphate [(*Z*)-**3c**], with a sterically more demanding cyclohexyl group at the γ -position, also participated in the reaction to produce a significantly sterically congested quaternary stereogenic center with excellent enantioselectivity (entry 9). Various functional groups such as methoxy, THP ether, fluoro, ethoxy carbonyl and chloro substituents were tolerated at the *meta*- or *para*-positions of the aromatic γ -substituent of the allylic phosphate (entries 10–15). The *p*-tolyl- and 2-naphthyl-substituted allylic substrates were also suitable (entries 16 and 17).

Furthermore, the copper catalyst system was applicable for the reaction of allylic substrates having two alkyl substituents at the γ -position albeit with somewhat decreased enantioselectivities. Thus, the reactions of allylic phosphate **3k** having methyl and phenylethyl groups at the γ -position with **2a** or **2d** occurred under the optimal reaction conditions with exclusive branch selectivities, affording the corresponding products [(*R*)-**5k** and (*R*)-**4dk**] with 83% ee in aldehyde or imine forms, respectively (entries 19 and 20). The combination of chloride as a leaving group and poly(methylhydrosiloxane) as a hydrosilane caused an increase in enantioselectivity (86% ee) (entry 22). Alkene [(*Z*)-**3l'**] and silyl ether [(*Z*)-**3m'**] moieties in the aliphatic γ -substituent of the allylic chloride were compatible with the reaction (entries 23 and 24). The reaction of γ -monosubstituted allylic substrates did not give the corresponding formimide products with tertiary stereogenic centers, but gave trisubstituted alkenes and conjugate dienes, which were produced through isomerization of the three-component coupling products and elimination reaction of the allylic substrates, respectively.

In all entries in Table 2, the copper catalysis afforded neither simple hydride reduction products²³ nor isocyanide 1,1-hydrosilylation products.² In addition, the two-component reaction between hydrosilane **1a** and allylic phosphate (*Z*)-**3a** (1.1/1) in the presence of a stoichiometric amount of LiOtBu (1.3 eq) and a catalytic amount of the CuCl-**L1** system (10 mol%) in THF at 0 °C over 24 h gave only a trace amount of simple reduction product 3-phenylbutene (3% yield). In the absence of the allylic phosphate (**3a**), the two-component reaction between **1a** and isocyanide **2d** (1.2/1) under otherwise identical conditions did not afford the isocyanide 1,1-hydrosilylation product with complete recovery of the two substrates. These results imply that a copper(I) hydride (Cu–H) species might not be a reactive intermediate in the three-component coupling reaction catalyzed by the Cu-naphthol-carbene system, but a mechanism involving such a species is not ruled out by these results.

The reaction of (*E*)-**3a** or (*E*)-**3k** with *E*-configuration under the optimized conditions provided the antipode of the product derived from the corresponding (*Z*)-isomer in excellent product yield and with excellent branch selectivity (> 99:1) (Table 2, entries 25 and 26). This result suggests that *Z* alkenes are more favorable substrates than *E* alkenes and that the substitution pattern at the β carbon is more important than that at the γ carbon for enantioselection by the catalyst.

Considerations for reaction pathways

This copper-catalyzed three-component coupling presumably goes through the formation of a lithium aryloxo(formimidoyl)cuprate species (**E**) followed by its formal S_N2' reaction with allylic substrate **3** (Figure 2a and 2b). For the formation of the formimidoylcopper(I) species (**E**), two types of reaction pathways are conceivable. One involves isocyanide 1,1-insertion into a Cu–H bond (copper hydride pathway, Figure 2a), and the other is direct reaction of hydrosilane, isocyanide-Cu(I) complex (**A**) and LiOtBu (hydrosilicate pathway, Figure 2b).

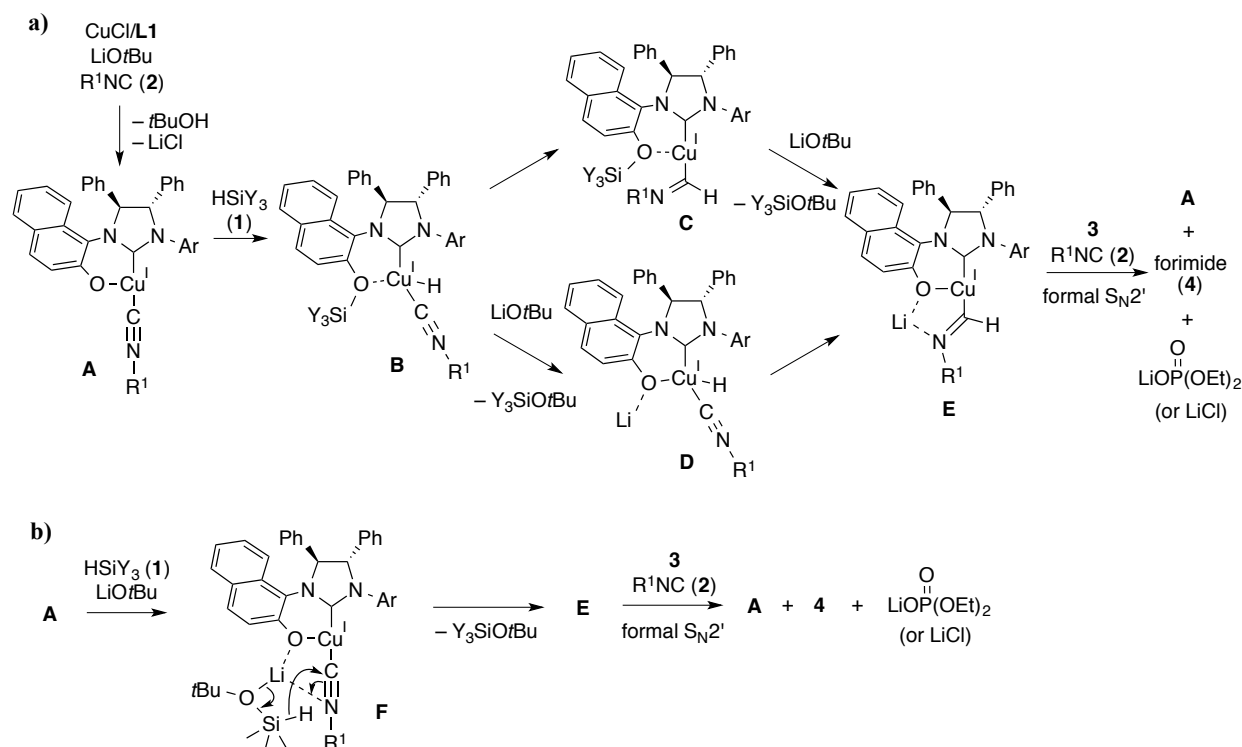


Figure 2. Possible reaction pathways for the formation of formimidoylcopper(I) species. a) Copper hydride pathway. b) Hydrosilicate pathway. Ar, 2,4-Cy₂-6-Me-C₆H₂.

In the copper hydride pathway (Figure 2a), the reaction of CuCl, **L1**, LiOtBu, and isocyanide **2** forms (**L1**-H)-Cu(I)-isocyanide complex **A**, in which the chiral carbene ligand coordinates to Cu as an anionic C,O-bidentate ligand (**L1**-H). Transmetalation between **A** and a hydrosilane (**1**) produces a copper(I) hydride species (**B**).²⁴ Next, isocyanide insertion into the Cu-H bond may form a η^1 -formimidoylcopper species (**C**), which undergoes transmetalation between its aryloxysilane moiety and LiOtBu to form a lithium aryloxo(formimidoyl)cuprate (**E**). Alternatively, formation of aryloxo(formimidoyl)cuprate **E** may proceed through prior activation of the silyl ether moiety of **B** by LiOtBu to form a cuprate species (**D**) followed by isocyanide 1,1-insertion to the Cu-H bond.

On the other hand, the hydrosilicate pathway (Figure 2b) does not form a Cu-H bond. Thus, the aryloxo(copper(I) isocyanide complex **A** recruits LiOtBu Lewis base through an $\text{O}\cdots\text{Li}^+\cdots\text{O}$ ionic bridge to activate the hydrosilane reagent (**1**), forming a hydrosilicate species **F**. The nucleophilic hydrosilicate moiety attacks the positively charged isocyanide terminal carbon that is in close proximity, producing lithium aryloxo(formimidoyl)cuprate **E**.

Although we do not rule out either reaction pathway at present, the hydrosilicate pathway (Figure 2b) better explains the critical roles of the ligand hydroxyl group (Table 1, entry 1 with **L1** vs. entry 7 with **L7**) for the promotion of the reaction because the naphthoxo group directly

participate in the formation of the formimidoylcopper structure only in the hydrosilicate pathway. In addition, preliminary NMR or FTIR studies on stoichiometric reactions with CuCl, **L1**, LiO*t*Bu, hydrosilane **1a**, and benzyl isocyanide (**2b**) (1/1/3/1/1) in THF-*d*₈ (for NMR) or THF (for FTIR) at room temperature indicated coordination of the isocyanide (**2b**) to Cu in an asymmetric environment, interaction of LiO*t*Bu with the Cu-isocyanide complex, and the formation of a formimidoylcopper species upon addition of the hydrosilane (**1a**) (See below). During these NMR or FTIR experiments, no evidence of the formation of Cu–H species was obtained. These spectroscopic results are also in support of the hydrosilicate pathway.

When the arenol group was absent in the carbene ligand, the *t*BuO ion derived from the added Lewis base may have taken place the role of the ligand naphthoxo group, forming a lithium *t*-butoxo(formimidoyl)cuprate (Table 1, entries 8 and 15). The lower reaction efficiencies with these systems can be deduced to unfavorable steric and entropy effects in the intermolecular participation of the bulky alkoxide anion for the formation of the (alkoxo)formimidoylcuprate. The increased steric demand of the cuprate would also be unfavorable for the subsequent formal S_N2' reaction with the allylic substrate.

NMR Studies for the Stoichiometric Reaction

CuCl (3.0 mg, 0.03 mmol), **L1**·HBF₄ (21.2 mg, 0.03 mmol), LiOtBu (5.0 mg, 0.06 mmol) and THF-*d*₈ (0.75 mL) were placed in an NMR tube. The tube was sealed, evacuated, and filled with argon. After shaking the mixture for 15 min at 25 °C and measuring a ¹H NMR spectrum (Figure 3), benzyl isocyanide (**2b**) (3.7 μL, 0.03 mmol) was added (See also Figure 8 for ¹H NMR spectrum for **2b**), and the mixture was shaken for 15 min at 25 °C: a ¹H NMR signal for the benzyl protons of the isocyanide (**2b**) appeared as an AB quartet (δ4.59 and 4.67 ppm, *J* = 17.2 Hz), indicating coordination of the isocyanide (**2b**) to Cu in an asymmetric environment (Figure 4). Next, LiOtBu (2.5 mg, 0.03 mmol) was added, and the resulting mixture was shaken for 15 min at 25 °C: the signal for the benzyl protons shifted from δ4.59 and 4.67 ppm (*J* = 17.2 Hz) to δ4.48 and 4.60 ppm (*J* = 17.2 Hz), suggesting interaction of LiOtBu with the Cu-isocyanide complex (Figure 5). Subsequently, PhMe₂SiH (4.8 μL, 0.03 mmol) was added to the mixture (See also Figure 9 for ¹H NMR spectrum for PhMe₂SiH), and the mixture was shaken for 1.5 h at 25 °C, the ¹H NMR spectrum showed a new characteristic peak at δ9.98 ppm, consistent with the formation of a formimidoylcopper species [Cu-C(=NBn)-H] (Figure 6).⁴ The signal for the benzyl protons shifted from δ4.48 and 4.60 ppm (*J* = 17.2 Hz) to δ4.61 and 4.71 ppm (*J* = 17.2 Hz). The prolonged reaction time (48 h) resulted in further increase of this signal and decrease of the signals for the PhMe₂SiH (Figure 7). This spectrum change was accompanied by gradual down-field shift of the benzyl protons and disappearance of the ²*J*_{H-H} coupling (s, δ4.87 ppm), suggesting dynamic nature of the reaction mixture and dissociation of imidoyl moieties from chirally modified metal complex fragments. Finally, one equiv of the allylic phosphate was added to the mixture. However, the formation of three-component coupling product **4ba** was not detected.

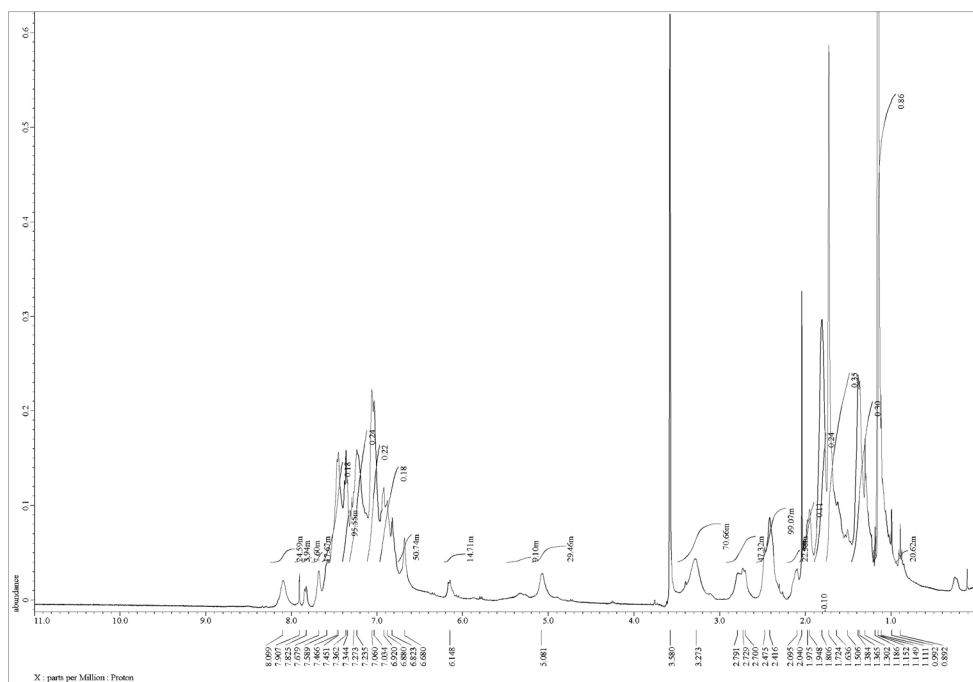


Figure 3. ¹H NMR spectrum for the reaction of CuCl, **L1**·HBF₄ and LiOtBu (1/1/2) (400 MHz, THF-*d*₈)

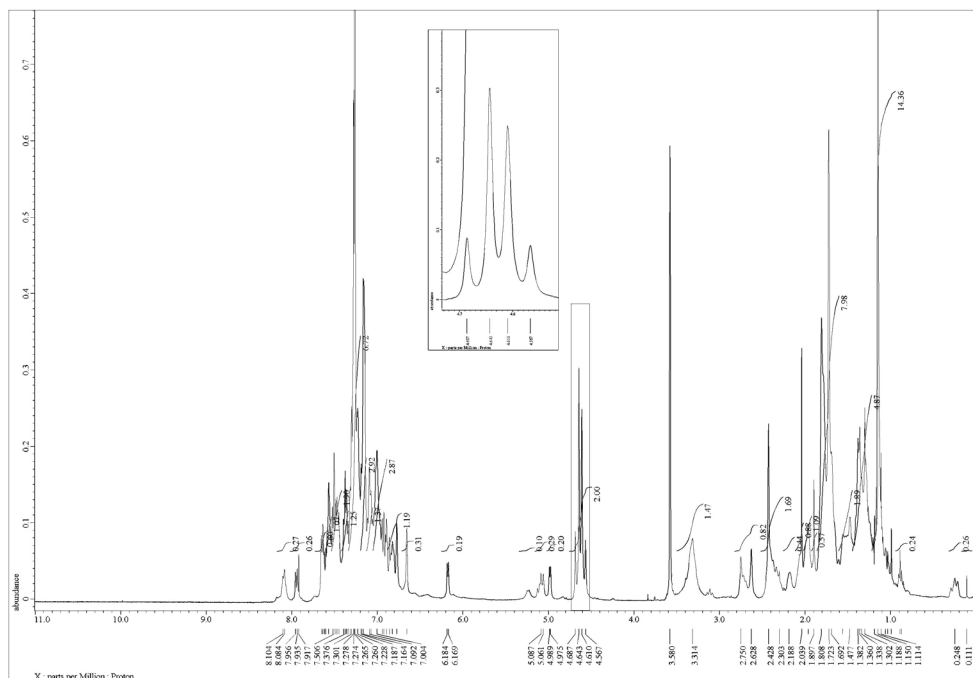


Figure 4. ^1H NMR spectrum for the reaction of CuCl , $\text{L1}\cdot\text{HBF}_4$, LiOtBu and benzyl isocyanide (**2b**) (1/1/2/1) (400 MHz, $\text{THF-}d_8$)

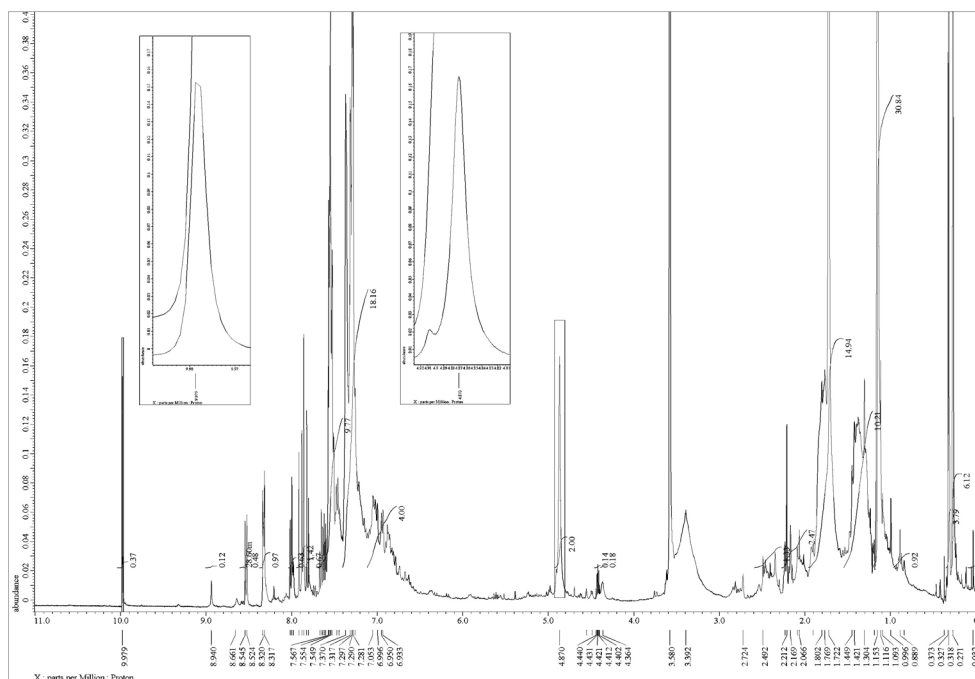


Figure 7. ^1H NMR spectrum for the reaction of CuCl , $\text{L1}\cdot\text{HBF}_4$, LiOtBu , benzyl isocyanide (**2b**) and PhMe_2SiH (1/1/3/1/1) (48 h) (400 MHz, $\text{THF-}d_8$)

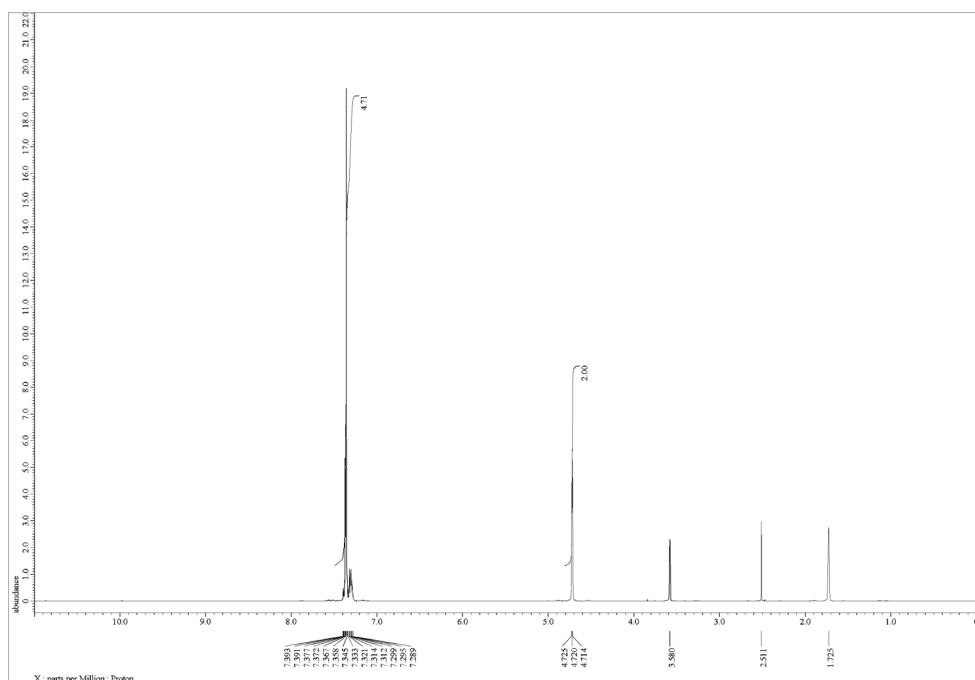


Figure 8. ^1H NMR spectrum for benzyl isocyanide (**2b**) (400 MHz, $\text{THF-}d_8$)

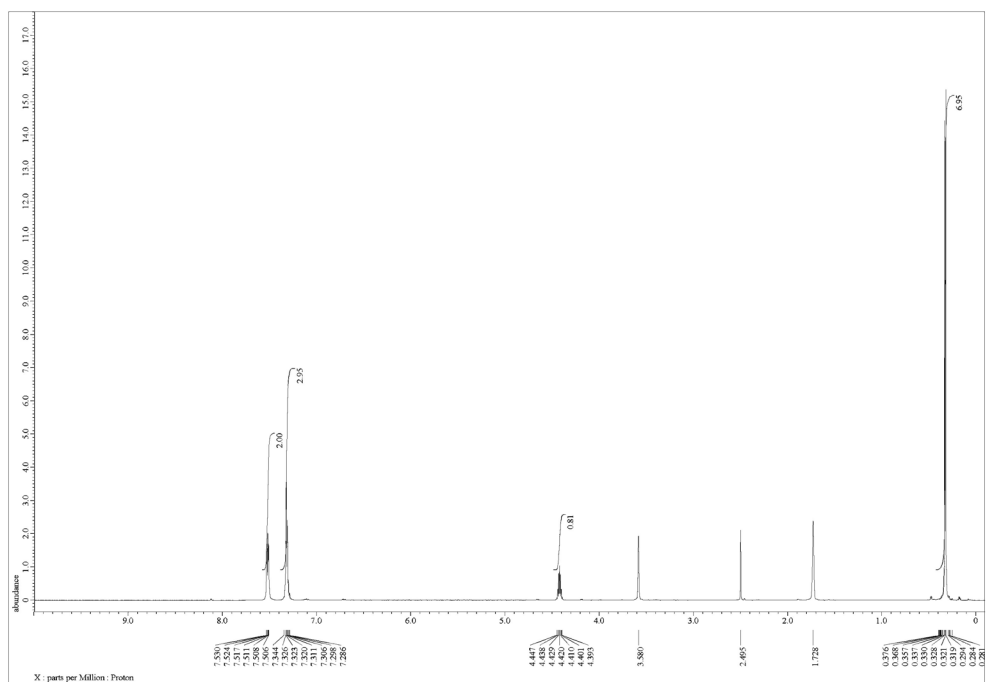


Figure 9. ^1H NMR spectrum for PhMe_2SiH (400 MHz, $\text{THF-}d_8$)

FTIR Studies for the Stoichiometric Reaction

CuCl (1.5 mg, 0.015 mmol), **L1**·HBF₄ (10.6 mg, 0.015 mmol), LiOtBu (2.5 mg, 0.03 mmol) and THF (1.0 mL) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon[®]-coated silicon rubber septum, and then the vial was evacuated and filled with argon. After stirring for 15 min at 25 °C (Figure 10), benzyl isocyanide (**2b**) (1.8 μL, 0.015 mmol) was added (See also Figure 14 for FTIR spectrum for **2b**). The mixture was stirred for 15 min at 25 °C, and transferred to a NaCl cell (0.1 mm path length cell) under argon atmosphere: the FTIR spectrum showed an intense absorption of the isocyanide NC stretching at 2171 cm⁻¹. This wave number is larger than that of free **2b** (2149 cm⁻¹), indicating Cu coordination of **2b** (Figure 11). Next, LiOtBu (1.2 mg, 0.015 mmol) was added (See also Figure 15 for FTIR spectrum for LiOtBu), and the resulting mixture was stirred for 15 min at 25 °C: the absorption band in the isocyanide did not change (Figure 12). Subsequently, PhMe₂SiH (2.4 μL, 0.015 mmol) was added to the mixture (See also Figure 16 for FTIR spectrum for PhMe₂SiH), and the mixture was stirred for 48 h at 25 °C: the FTIR spectrum showed an absorption at 1680 cm⁻¹, consistent with the formation of imido species (Figure 13).

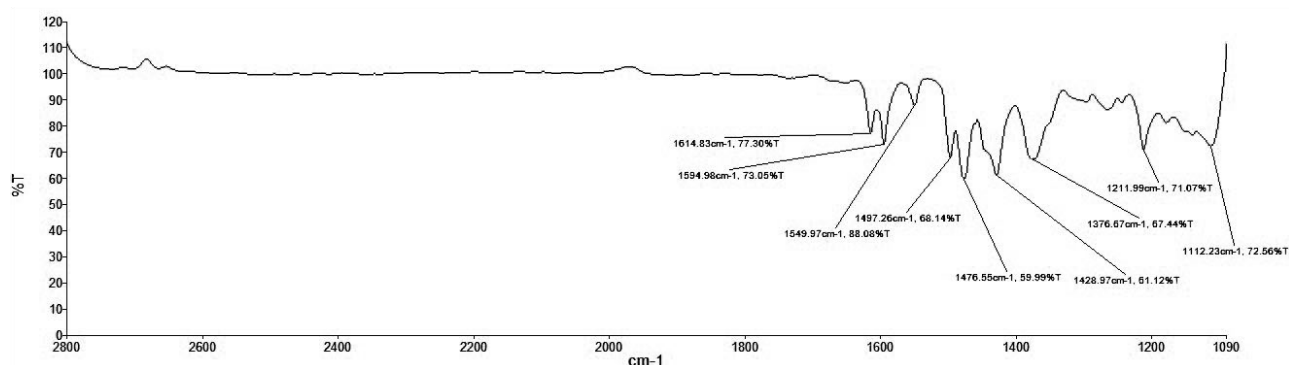


Figure 10. FTIR spectrum for the reaction of CuCl, **L1**·HBF₄ and LiOtBu (1/1/2)

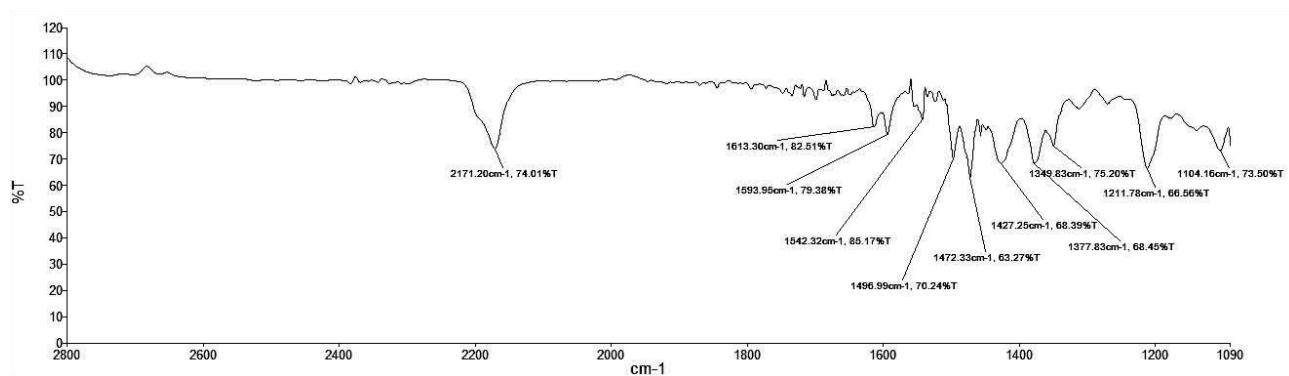


Figure 11. FTIR spectrum for the reaction of CuCl, **L1**·HBF₄, LiOtBu and benzyl isocyanide (**2b**) (1/1/2/1)

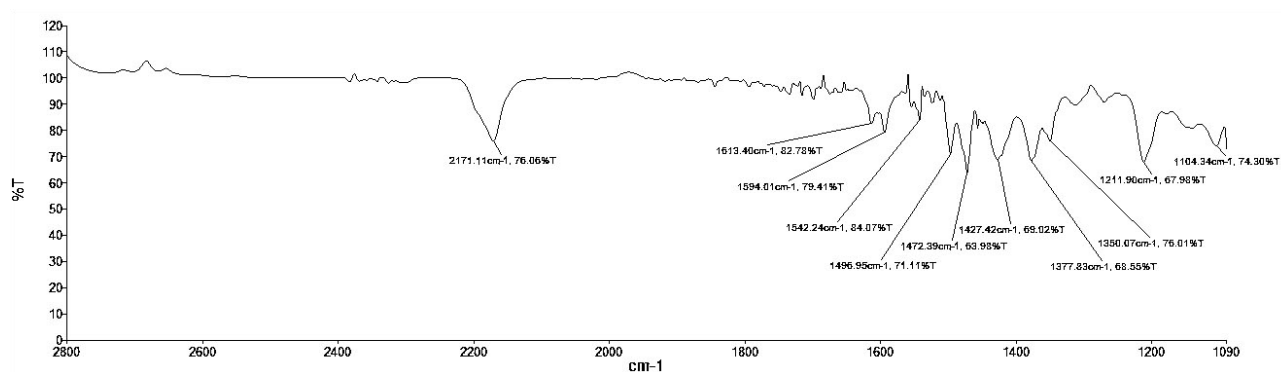


Figure 12. FTIR spectrum for the reaction of CuCl, **L1**·HBF₄, LiOtBu and benzyl isocyanide (**2b**) (1/1/3/1)

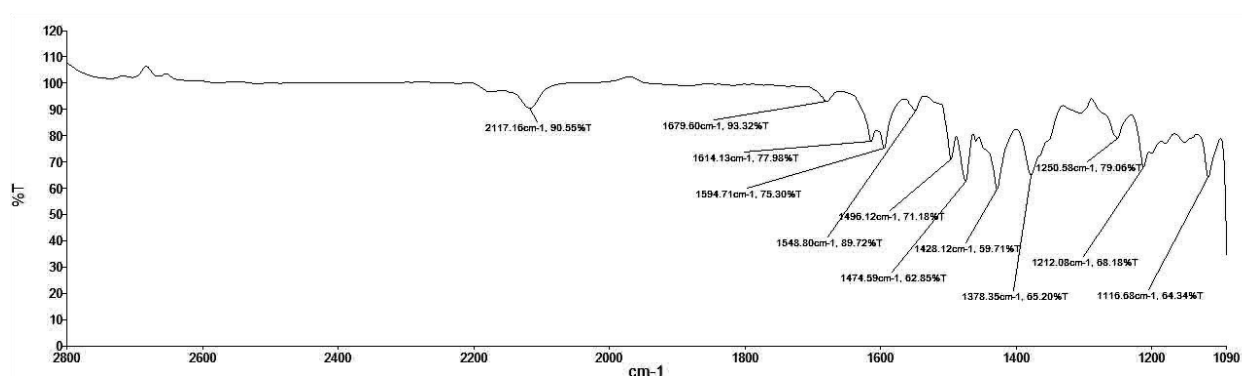


Figure 13. FTIR spectrum for the reaction of CuCl, **L1**·HBF₄, LiOtBu, benzyl isocyanide (**2b**) and PhMe₂SiH (1/1/3/1/1)

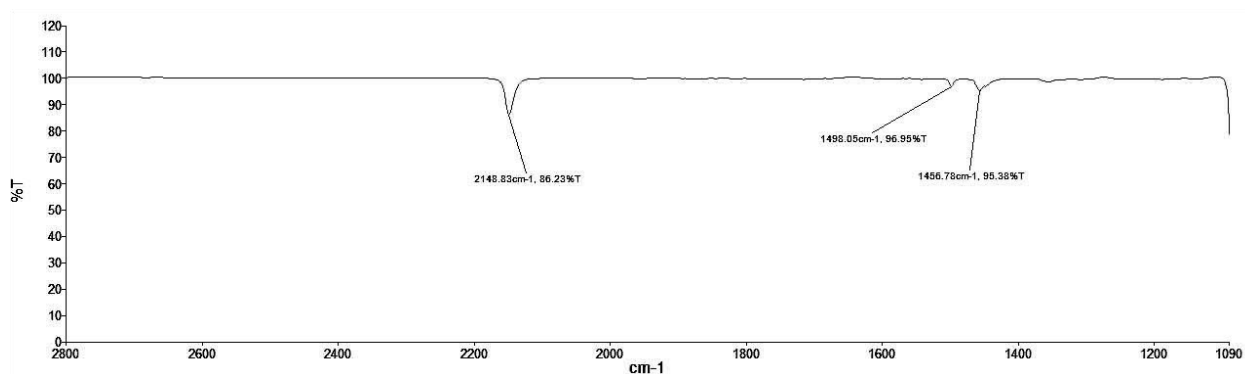


Figure 14. FTIR spectrum for benzyl isocyanide (**2b**)

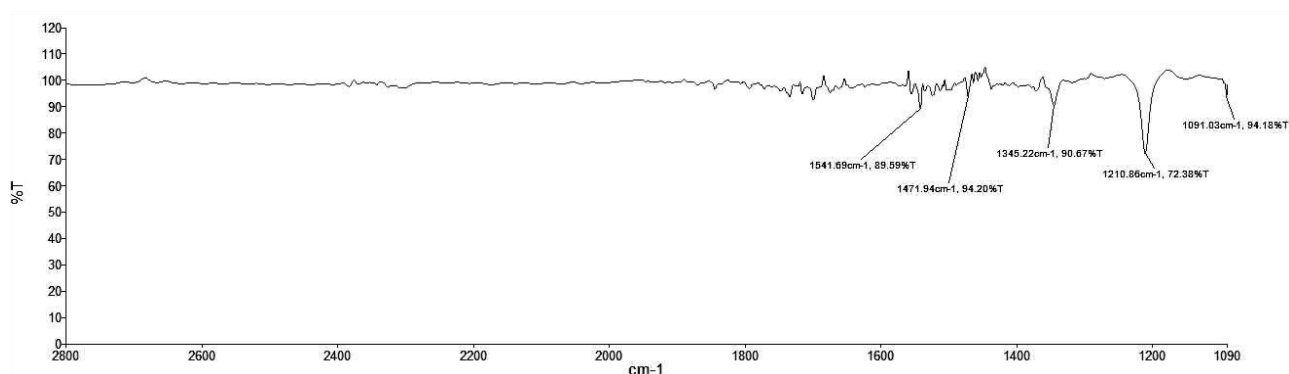


Figure 15. FTIR spectrum for LiOtBu

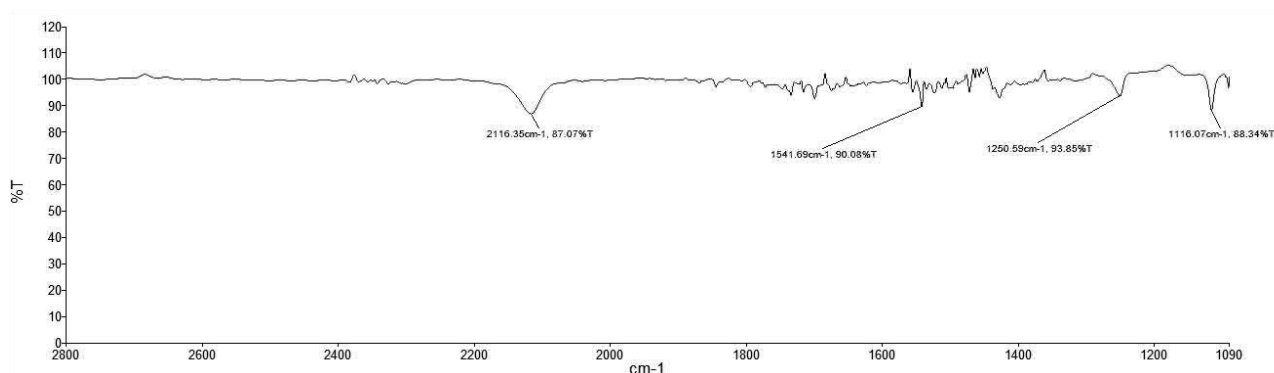


Figure 16. FTIR spectrum for PhMe₂SiH

Considerations for Enantioselection Mechanism

When the lithium aryloxo(formimidoyl)cuprate intermediate (**E**) assumed above reacts with the prochiral allylic substrate (**3**) in a formal S_N2' manner, either the Cu atom or the imidoyl C(sp²) atoms may attack the γ carbon of **3**. Furthermore, the possibility for the intervention of bond formation between the aryloxo O atom of **L1** and the α or γ carbon atoms of **3** should not be ruled out. This complicated situation hampers the development of a model to explain the highly efficient enantioselection by the Cu-**L1** catalyst at present. However, it is likely that the Li⁺ ion, bridging the isocyanide N and aryloxo O atoms in **E**, plays an essential role in the enantioselection. Thus, a Li⁺ ion located at a well-defined position in a chiral environment would fix the rotation of the formimidoyl ligand around the Cu–C(imidoyl, sp²) axis and assist the reaction of **E** with **3** in a cooperative manner through binding to the leaving group, limiting possible enantioselectivity-determining transition state conformers. Based on these considerations, the decreased efficiency of NaOtBu and KOtBu may reflect lower Lewis acidities of Na and K cations or lower solubility of species involving these cations (Table 1, entries 2, 22, and 23).

Product Derivatization

The enantioenriched α-quaternary formimide (*S*)-**4da** and aldehyde (*S*)-**5a** obtained by the

enantioselective copper catalysis were used to demonstrate the synthetic utility of this methodology (Figure 15). Formimide (*S*)-**4da** was readily converted to primary alcohol (*S*)-**6a** through acidic hydrolysis followed by NaBH₄ reduction (Figure 15a). Reduction of (*S*)-**4da** with NaBH₄ followed by removal of the PMP group through treatment with cerium ammonium nitrate afforded secondary amine (*S*)-**7a** (Figure 15a). The NaBH₄ reduction of (*S*)-**4da** and *N*-allylation followed by ring-closing alkene metathesis produced the *N*-heterocyclic six-membered ring compound (*S*)-**8a** (Figure 15a). The α -quaternary aldehyde could be transformed to 2,2-disubstituted 3-butenonitrile [(*S*)-**9j**] or 2,5-dienoate [(*S*)-**10a**] via Horner-Wadsworth-Emmons reaction (Figures 15b and c).

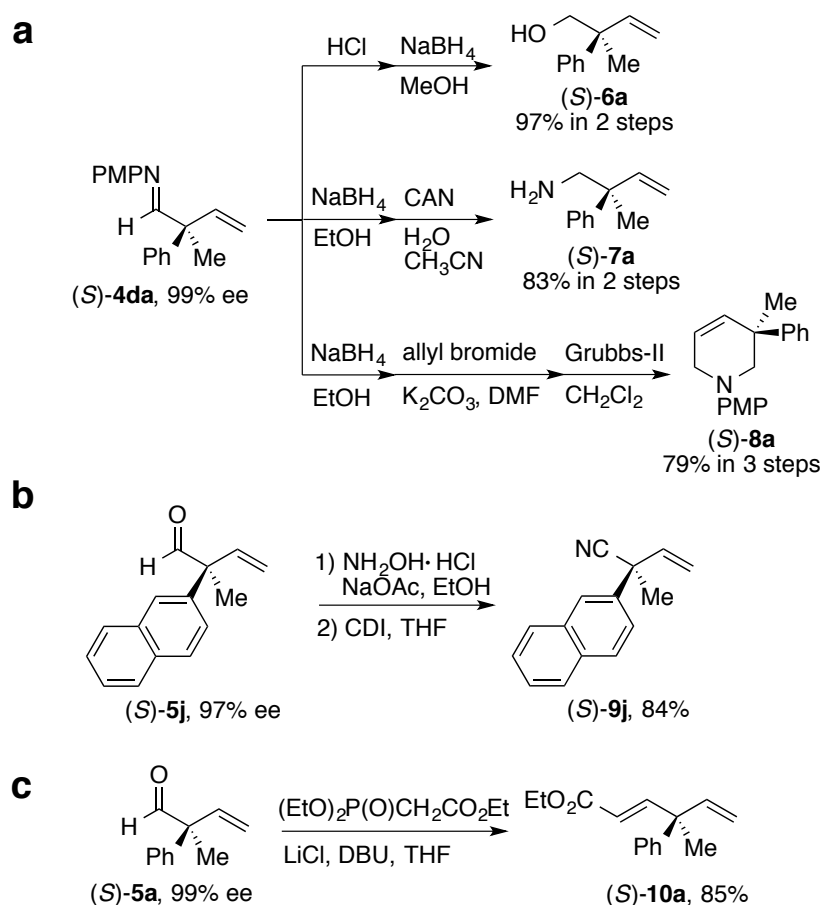


Figure 15. Derivatizations of α -quaternary formimide and aldehyde. a) Synthesis of primary alcohol, primary amine and *N*-heterocyclic six-membered ring compound. CAN, ceric ammonium nitrate. b) Synthesis of allylic nitrile. Ac, acetyl. CDI, carbonyldiimidazole. c) Horner-Wadsworth-Emmons reaction.

Conclusion

A copper-catalyzed asymmetric three-component coupling reaction of isocyanides, hydrosilanes, and γ,γ -disubstituted primary allylic phosphates or chlorides occurred with exclusive regioselectivity and with high enantioselectivities to yield chiral α -quaternary formimides, which were readily converted to the corresponding aldehydes. This enantioselective copper catalysis was enabled by a combined use of original chiral naphthol-carbene ligand of Sawamura and Ohmiya group as a functional supporting ligand for Cu and LiOtBu as a stoichiometric Lewis basic activator for Si. Owing to the mildness of the reaction conditions, various functional groups were tolerated in the substrates. The formimidoyl group and vinyl group in the three-component coupling products can be used as handles for further transformations. This copper catalysis presumably goes through a lithium aryloxo(formimidoyl)cuprate intermediate, which was previously undescribed in the literature. Possible participation of the ionized ligand naphtholic hydroxy group in the formation of the formimidoylcuprate species is proposed (hydrosilicate pathway). Mechanistic studies by intermediate analysis and theoretical calculations are underway. The enantioselective copper catalysis presented here provides a new strategy for asymmetric synthesis using isocyanides as reagents for umpolung C1 synthons.

Experimental Section

Instrumentation and Chemicals

NMR spectra were recorded on a JEOL ECX-400, operating at 400 MHz for ^1H NMR and 100.5 MHz for ^{13}C NMR. Chemical shift values for ^1H and ^{13}C are referenced to Me_4Si and the residual solvent resonances, respectively. Chemical shifts are reported in δ ppm. Mass spectra were obtained with Thermo Fisher Scientific Exactive, JEOL JMS-T100LP or JEOL JMS-700TZ at the Instrumental Analysis Division, Global Facility Center, Creative Research Institution, Hokkaido University. HPLC analyses were conducted on a HITACHI ELITE LaChrom system with a HITACHI L-2455 diode array detector or a HITACHI Chromaster with a HITACHI 5430 diode array detector. Optical rotations were measured on a JASCO P-2200. TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel 60F₂₅₄ or commercial glass plates bearing 0.25-mm layer of diol-modified silica gel (Fuji Silysia Chemical Ltd., Chromatorex). Silica gel (Kanto Chemical Co., Silica gel 60 N, spherical, neutral), diol-modified silica gel (Fuji Silysia Chemical Ltd., Chromatorex, Diol MB100-40/75) or aluminum oxide (Nacalai Tesuque, Alumina Activated 200) were used for column chromatography. IR spectra were measured with a Perkin-Elmer Spectrum One. Gel permeation chromatography (GPC) was performed by LaboACE LC-5060 (Japan Analytical Industry Ltd., two in-line JAIGEL-HR, ethyl acetate, 10 mL/min, UV and RI detectors).

All reactions were carried out under nitrogen or argon atmosphere. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. CuCl, and LiOtBu were purchased from Aldrich Chemical Co., stored under nitrogen, and used as received. THF was purchased from Kanto Chemical Co., and purified by passage through activated alumina under positive argon pressure as described by Grubbs *et al.* Isocyanides **2a, b** were purchased from TCI Chemical Co., stored under nitrogen, and used as received. **2c** was purchased from Aldrich Chemical Co., stored under nitrogen, and used as received. PhMe₂SiH, (Me₂HSi)₂O, Et₃SiH and *t*BuMe₂SiH were purchased from TCI Chemical Co., stored under nitrogen, and used as received. poly(methylhydrosiloxane) was purchased from Sant Cruz Biotechnology Inc., stored under nitrogen, and used as received. Carbene Ligands **L6–8** are found in the literature.^{25–27}

Preparation of Allylic Substrates

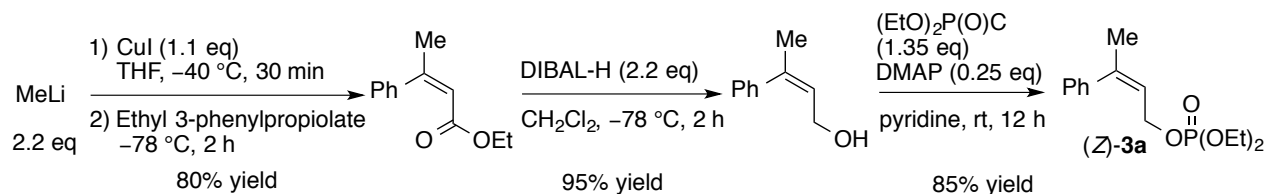
Preparation of (Z)-3a, (Z)-3b, (Z)-3d–f and (Z)-3i, (Z)-3j. Allylic phosphates were prepared through carbocupration of alkynoate, DIBAL-H reduction followed by phosphorylation. The preparation of (Z)-**3a** is representative (Scheme 1). To a solution of CuI (3.14 g, 16.5 mmol) in THF (44.0 mL) was added methyllithium (1.1 M in Et₂O, 30.0 mL, 33.0 mmol) at –40 °C, and the resulting mixture was stirred at –40 °C for 30 min. To the mixture was added ethyl 3-phenylpropiolate (2.61 g, 15.0 mmol) dropwise at –78 °C, and the mixture was stirred at –78 °C for 2 h. Saturated NH₄Cl aq was added and the mixture was allowed to warm to room temperature. The resulting slurry was diluted with EtOAc (60.0 mL) and washed with NH₄Cl aq and brine. The organic layer was separated and dried over MgSO₄. Then, the drying agent was removed by filtration, and the resulting solution was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) provided alkenoate (2.28 g, 12.0 mmol) in 80% yield.

To a stirred solution of alkenoate (1.90 g, 10.0 mmol) in CH₂Cl₂ was dropped DIBAL-H (21.6 mL in 1.02 M hexane solution, 22.0 mmol) at –78 °C and the reaction was stirred for 2 h at the same temperature. Sat. NH₄Cl was added and the mixture was vigorously stirred at room temperature for 10 min. Solid was filtered through a pad of celite and the filtrate was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (5–20% EtOAc/hexane) to give allylic alcohol (1.41 g, 9.5 mmol) in 95% yield.

To a solution of (Z)-3-phenyl-2-buten-1-ol (296.4 mg, 2.0 mmol) and DMAP (61.1 mg, 0.5 mmol) in pyridine (2.7 mL), (EtO)₂P(O)Cl (406 μL, 2.7 mmol) was added at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was diluted with EtOAc (20.0 mL) and was treated with water (5.0 mL). The resulting mixture was washed with saturated CuSO₄ aq.

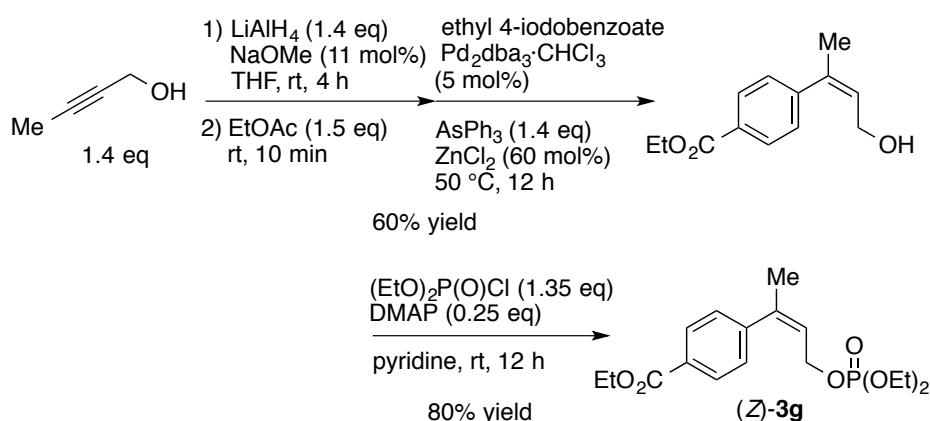
(10.0 mL $\times$ 3) and was dried over anhydrous MgSO_4 , filtered, and evaporated under reduced pressure. The residue was purified by GPC to provide (Z)-**3a** (483 mg, 1.7 mmol) in 85% yield.

Scheme 1. Preparation of (Z)-**3a**, (Z)-**3b**, (Z)-**3d–f** and (Z)-**3i**, (Z)-**3j**



Preparation of (Z)-3g**.** Allylic phosphate was prepared through the phosphorylation of the corresponding allylic alcohol obtained by the reported palladium catalyzed reaction of 2-butyne-1-ol and ethyl 4-iodobenzoate (Scheme 2).²⁸ To a solution of the allylic alcohol (220 mg, 1.0 mmol) and DMAP (30.6 mg, 0.25 mmol) in pyridine (1.4 mL), $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$ (194 μL , 1.35 mmol) was added at 0 °C. After being stirred at room temperature for 12 h, the reaction mixture was diluted with EtOAc (5 mL) and was treated with water (2.5 mL). The resulting mixture was washed with saturated CuSO_4 aq. (5.0 mL $\times$ 3) and brine, and was dried over anhydrous MgSO_4 , filtered, and evaporated under reduced pressure. The residue was purified by GPC to provide (Z)-**3g** (285 mg, 0.8 mmol) in 80% yield.

Scheme 2. Preparation of (Z)-**3g**



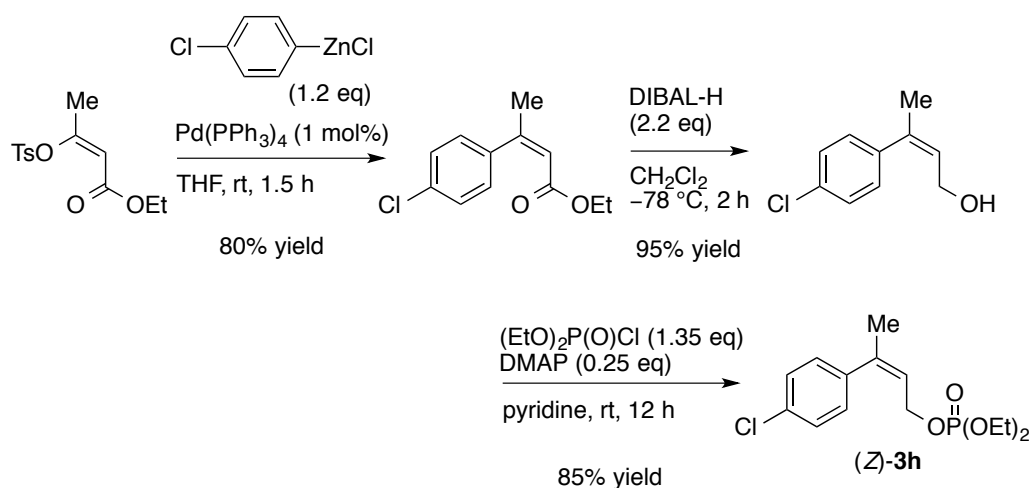
Preparation of (Z)-3h**.** Allylic phosphate was prepared through Negishi cross-coupling, DIBAL-H reduction followed by phosphorylation (Scheme 3). To a stirred solution of 1-bromo-4-chlorobenzene (957 mg, 5.0 mmol) in THF (4.7 mL) was dropped *n*BuLi (3.1 mL in 1.65 M hexane solution, 5.0 mmol) at -78 °C and the reaction was continued for 10 min at the same temperature. Next, ZnCl_2 (682 mg, 5.0 mmol) in THF (2.0 mL) was added to the mixture at -78

°C. The reaction mixture was allowed to warm to room temperature, stirred for another 45 min to prepare arylzinc reagent. To a suspension of $\text{Pd}(\text{PPh}_3)_4$ (46.2 mg, 40.0 μmol) and alkenyltosylate (1.1 g, 4.0 mmol) in THF (4.0 mL) was added the arylzinc reagent at room temperature. After being stirred at room temperature for 1.5 h, the reaction mixture was quenched with saturated NH_4Cl aq. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with brine. The mixture was dried over anhydrous MgSO_4 , filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0–3% EtOAc/hexane) to give alkenoate (719 mg, 3.2 mmol) in 80% yield.

To a stirred solution of alkenoate (382 mg, 1.7 mmol) in CH_2Cl_2 was dropped DIBAL-H (3.6 mL in 1.02 M hexane solution, 3.7 mmol) at -78°C and the reaction was stirred for 2 h at the same temperature. Sat. NH_4Cl was added and the mixture was vigorously stirred at room temperature for 10 min. Solid was filtered through celite pad and the filtrate was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (5–20% EtOAc/hexane) to give allylic alcohol (292 mg, 1.6 mmol) in 95% yield.

To a solution of the allylic alcohol (182 mg, 1.0 mmol) and DMAP (30.6 mg, 0.3 mmol) in pyridine (1.4 mL), $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$ (194 μL , 1.4 mmol) was added at 0°C . After being stirred at room temperature for 12 h, the reaction mixture was diluted with EtOAc (5.0 mL) and was treated with water (2.5 mL). The resulting mixture was washed with saturated CuSO_4 aq. (5.0 mL $\times$ 3) and brine, and was dried over anhydrous MgSO_4 , filtered, and evaporated under reduced pressure. The residue was purified by GPC to provide (*Z*)-**3h** in 85% yield (271 mg, 0.85 mmol).

Scheme 3. Preparation of (*Z*)-2h



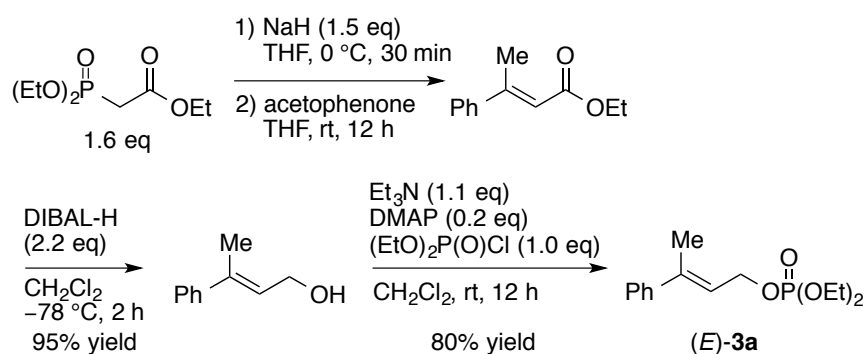
Preparation of (*Z*)-3c and (*E*)-3a. Allylic phosphates were prepared through Horner-Wadsworth-Emmons reaction of acetophenone, DIBAL-H reduction followed by phosphorylation. The preparation of (*E*)-**3a** is representative (Scheme 4). To a solution of NaH (982 mg, 22.5 mmol)

in THF (40.0 mL) was added triethyl phosphonoacetate (4.76 mL, 24.0 mmol) dropwise at 0 °C, and the resulting mixture was stirred at 0 °C for 30 min. To the mixture was added acetophenone (1.80 g, 15.0 mmol) at room temperature and the mixture was stirred at the same temperature for 12 h. Saturated NH₄Cl aq was added. The resulting slurry was diluted with EtOAc (50.0 mL) and washed with water and brine. The organic layer was separated and dried over MgSO₄. Then, the drying agent was removed by filtration, and the resulting solution was evaporated. The residue was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) provided alkenoate (20.0 g, 10.5 mmol) in 70% yield.

To a stirred solution of alkenoate (20.0 g, 10.5 mmol) in CH₂Cl₂ was dropped DIBAL-H (22.7 mL in 1.02 M hexane solution, 23.2 mmol) at –78 °C and the reaction was continued for 2 h at the same temperature. Sat. NH₄Cl was added and the mixture was vigorously stirred for 10 min. Solid was filtered through celite pad and the filtrate was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (10–50% EtOAc/hexane) to give allylic alcohol (1.48 g, 10.0 mmol) in 95% yield.

To a solution of allylic alcohol (296 mg, 2.0 mmol) and Et₃N (307 μL, 2.2 mmol) in CH₂Cl₂ (10 mL), (EtO)₂P(O)Cl (301 μL, 2.0 mmol) and DMAP (48.9 mg, 0.4 mmol) were sequentially added at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for another 12 h, diluted with EtOAc (20 mL) and was treated with water (5 mL). The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with water and brine. The organic layer was separated and dried over MgSO₄. Then, the drying agent was removed by filtration, and the resulting solution was evaporated under reduced pressure. The residue was purified by GPC to provide (*E*)-**3a** (455 mg, 1.6 mmol) in 80% yield.

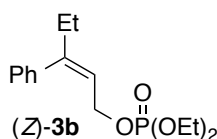
Scheme 4. Preparation of (*Z*)-2c and (*E*)-3a



Characterization Data for Allylic Substrates

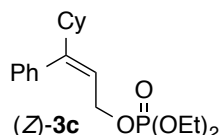
(*Z*)-**3a** and (*E*)-**3a** are found in the literature.⁵

(Z)-Diethyl(3-phenyl-2-penten-1-yl)phosphate (3b)



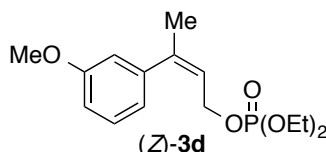
Colorless Oil. **IR** (neat) 702, 824, 963, 996, 1095, 1263, 1443, 1655, 2934, 2979 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.00 (t, $J = 7.2$, 3H), 1.30 (t, $J = 7.2$ Hz, 6H), 2.41 (q, $J = 7.2$ Hz, 2H), 4.07 (quintet, $J = 7.2$ Hz, 4H), 4.44 (t, $J = 7.2$ Hz, 2H), 5.67 (t, $J = 7.2$ Hz, 1H), 7.12–7.14 (m, 2H), 7.27–7.36 (m, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 12.5, 16.1 (d, $J = 6.7$ Hz), 31.7, 63.6 (d, $J = 5.7$ Hz), 65.0 (d, $J = 5.7$ Hz), 120.0 (d, $J = 7.6$ Hz), 127.3, 128.0, 128.2, 139.5, 148.8. **HRMS–ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{23}\text{O}_4\text{NaP}$, 321.12262; found, 321.12234.

(Z)-3-Cyclohexyl-3-phenylallyl Diethyl Phosphate (3c)



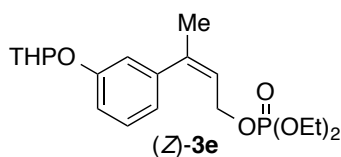
Colorless Oil. **IR** (neat) 703, 820, 978, 1009, 1166, 1263, 1443, 1653, 2927, 2983 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.07–1.30 (m, 11H), 1.66 (m, 1H), 1.73–1.78 (m, 4H), 2.20 (t, $J = 11.2$ Hz, 1H), 4.05 (quintet, $J = 7.2$ Hz, 4H), 4.36 (t, $J = 7.2$ Hz, 2H), 5.61 (t, $J = 7.2$ Hz, 1H), 7.05–7.08 (m, 2H), 7.25–7.34 (m, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 16.1 (d, $J = 7.7$ Hz), 26.2, 26.5, 31.9, 45.7, 63.5 (d, $J = 5.7$ Hz), 65.2, 119.3 (d, $J = 6.7$ Hz), 127.1, 128.0, 128.3, 139.7, 152.4. **HRMS–ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{29}\text{O}_4\text{NaP}$, 375.16957; found, 375.16936.

(Z)-Diethyl[3-(3-methoxyphenyl)-2-buten-1-yl]phosphate (3d)



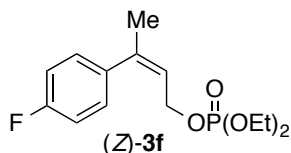
Colorless Oil. **IR** (neat) 704, 789, 978, 1025, 1167, 1252, 1429, 1487, 1577, 2982 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.30 (t, $J = 7.2$ Hz, 6H), 2.10 (d, $J = 1.2$ Hz, 3H), 3.81 (s, 3H), 4.08 (quintet, $J = 7.2$ Hz, 4H), 4.47 (t, $J = 7.2$ Hz, 2H), 5.70 (td, $J = 7.2, 1.2$ Hz, 1H), 6.72–6.77 (m, 2H), 6.83 (dd, $J = 8.0, 2.4$ Hz, 1H), 7.26 (t, $J = 8.0$ Hz, 1H). **^{13}C NMR** (100 MHz, CDCl_3) δ 16.1 (d, $J = 6.7$ Hz), 25.3, 55.1, 63.6 (d, $J = 5.7$ Hz), 64.9 (d, $J = 4.8$ Hz), 112.7, 113.4, 120.0, 121.7 (d, $J = 7.7$ Hz), 129.3, 141.5, 142.7, 159.4. **HRMS–ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{23}\text{O}_5\text{NaP}$, 337.11753; found, 337.11717.

(Z)-Diethyl(3-{3-[(tetrahydro-2H-pyran-2-yl)oxy]phenyl}-2-buten-1-yl)phosphate (3e)



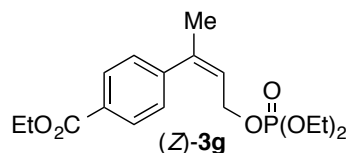
Colorless Oil. **IR** (neat) 732, 820, 1026, 1166, 1261, 1394, 1490, 1656, 2910, 2982 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.30 (t, $J = 7.2$ Hz, 6H), 1.59–1.74 (m, 3H), 1.84–1.88 (m, 2H), 1.96–2.09 (m, 4H), 3.62 (m, 1H), 3.91 (m, 1H), 4.08 (quintet, $J = 7.2$ Hz, 4H), 4.49 (t, $J = 7.2$ Hz, 2H), 5.42 (t, $J = 3.2$ Hz, 1H), 5.68 (t, $J = 7.2$ Hz, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.86 (m, 1H), 7.00 (m, 1H), 7.25 (t, $J = 8.0$ Hz, 1H). **^{13}C NMR** (100 MHz, CDCl_3) δ 16.0 (d, $J = 6.7$ Hz), 18.8, 25.1, 25.2, 30.3, 62.1, 63.6 (d, $J = 5.7$ Hz), 64.9 (d, $J = 4.8$ Hz), 96.3, 115.2, 115.9, 120.9, 121.7 (d, $J = 7.7$ Hz), 129.2, 141.3, 142.5, 156.9. **HRMS–ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{29}\text{O}_6\text{NaP}$, 407.15940; found, 407.15939.

(Z)-Diethyl[3-(4-fluorophenyl)-2-buten-1-yl]phosphate (3f)



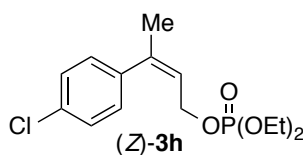
Colorless Oil. **IR** (neat) 726, 818, 979, 1025, 1162, 1223, 1261, 1508, 1603, 2983 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.31 (t, $J = 7.2$ Hz, 6H), 2.09 (d, $J = 1.2$ Hz, 3H), 4.09 (quintet, $J = 7.2$ Hz, 4H), 4.44 (t, $J = 7.2$ Hz, 2H), 5.72 (td, $J = 7.2, 1.2$ Hz, 1H), 7.04 (dd, $J = 8.8, 8.8$ Hz, 2H), 7.16 (dd, $J = 8.8, 5.2$ Hz, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 16.1 (d, $J = 6.7$ Hz), 25.4, 63.6 (d, $J = 5.7$ Hz), 64.8 (d, $J = 4.8$ Hz), 115.2 (d, $J = 20.9$ Hz), 121.9 (d, $J = 6.7$ Hz), 129.3 (d, $J = 8.5$ Hz), 135.9 (d, $J = 2.9$ Hz), 141.9, 162.1 (d, $J = 245.0$ Hz). **HRMS–ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{O}_4\text{FNaP}$, 325.09755; found, 325.09775.

(Z)-Ethyl 4-{4-[(Diethoxyphosphoryl)oxy]-2-buten-2-yl}benzoate (3g)



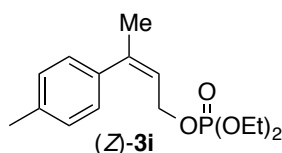
Pale Yellow Oil. **IR** (neat) 710, 864, 995, 1025, 1103, 1271, 1394, 1609, 1716, 2983 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.31 (t, $J = 7.2$ Hz, 6H), 1.40 (t, $J = 7.2$ Hz, 3H), 2.12 (s, 3H), 4.08 (quintet, $J = 7.2$ Hz, 4H), 4.36–4.45 (m, 4H), 5.78 (t, $J = 7.2$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 2H), 8.03 (d, $J = 8.0$ Hz, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 14.3, 16.1 (d, $J = 6.7$ Hz), 25.0, 61.0, 63.6 (d, $J = 4.7$ Hz), 64.6 (d, $J = 4.7$ Hz), 122.7 (d, $J = 6.7$ Hz), 127.7, 129.5, 141.9 ($\times 2\text{C}$), 144.7, 166.2. **HRMS–ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{25}\text{O}_6\text{NaP}$, 379.12810; found, 379.12784.

(Z)-3-(4-Chlorophenyl)-2-buten-1-yl Diethyl Phosphate (3h)



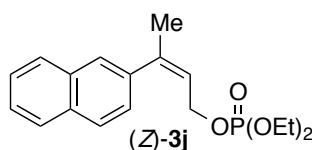
Colorless Oil. **IR** (neat) 704, 818, 1000, 1028, 1182, 1261, 1434, 1576, 2944 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.31 (t, $J = 7.2$ Hz, 6H), 2.09 (s, 3H), 4.09 (quintet, $J = 7.2$ Hz, 4H), 4.43 (t, $J = 7.2$ Hz, 2H), 5.73 (t, $J = 7.2$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 2H), 7.32 (d, $J = 8.0$ Hz, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 16.1 (d, $J = 6.7$ Hz), 25.2, 63.6 (d, $J = 5.7$ Hz), 64.7 (d, $J = 4.8$ Hz), 122.2 (d, $J = 7.6$ Hz), 128.4, 129.0, 133.3, 138.4, 141.7. **HRMS-ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{O}_4\text{ClNaP}$, 341.06799; found, 341.06781.

(Z)-Diethyl [3-(*p*-tolyl)-2-buten-1-yl]phosphate (3i)



Colorless Oil. **IR** (neat) 747, 816, 978, 1026, 1166, 1261, 1445, 1512, 1654, 2982 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.30 (t, $J = 7.2$ Hz, 6H), 2.09 (s, 3H), 2.35 (s, 3H), 4.08 (quintet, $J = 7.2$ Hz, 4H), 4.48 (t, $J = 7.2$ Hz, 2H), 5.69 (t, $J = 7.2$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 2H), 7.15 (d, $J = 8.0$ Hz, 2H). **^{13}C NMR** (100 MHz, CDCl_3) δ 16.1 (d, $J = 6.7$ Hz), 21.1, 25.3, 63.6 (d, $J = 5.7$ Hz), 65.1 (d, $J = 5.7$ Hz), 121.3 (d, $J = 7.6$ Hz), 127.6, 128.9, 137.0, 137.2, 142.8. **HRMS-ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{23}\text{O}_4\text{NaP}$, 321.12262; found, 321.12251.

(Z)-Diethyl[3-(naphthalen-2-yl)-2-buten-1-yl]phosphate (3j)



Colorless Oil. **IR** (neat) 748, 819, 978, 1025, 1260, 1393, 1443, 1504, 1599, 2981 cm^{-1} . **^1H NMR** (400 MHz, CDCl_3) δ 1.27 (t, $J = 7.2$ Hz, 6H), 2.19 (s, 3H), 4.07 (quintet, $J = 7.2$ Hz, 4H), 4.52 (t, $J = 7.2$ Hz, 2H), 5.81 (t, $J = 7.2$ Hz, 1H), 7.32 (d, $J = 8.0$ Hz, 1H), 7.45–7.51 (m, 2H), 7.62 (s, 1H), 7.81–7.84 (m, 3H). **^{13}C NMR** (100 MHz, CDCl_3) δ 16.0 (d, $J = 6.7$ Hz), 25.3, 63.6 (d, $J = 5.7$ Hz), 65.0 (d, $J = 5.7$ Hz), 122.0 (d, $J = 7.6$ Hz), 125.7, 126.0, 126.2, 126.5, 127.6, 127.9, 127.9, 132.6, 133.0, 137.5, 142.8. **HRMS-ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{23}\text{O}_4\text{NaP}$, 357.12262; found, 357.12240.

Procedure for Asymmetric Three-Component Coupling

The reaction in Table 1, entry 2 is representative. CuCl (1.5 mg, 0.015 mmol), $\text{L1}\cdot\text{HBF}_4$

(10.6 mg, 0.015 mmol) and LiOtBu (16.1 mg, 0.195 mmol) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon[®]-coated silicon rubber septum, and then the vial was evacuated and filled with argon. THF (0.6 mL) was added to the vial, and then the mixture was stirred at room temperature for 10 min. Next, PhMe₂SiH (27.9 μ L, 0.18 mmol) and cyclohexyl isocyanide (**2a**) (18.0 mg, 0.20 mmol) were added. Finally, allylic phosphate **3a** (42.6 mg, 0.15 mmol) was added at 0 °C. After 24 h stirring at 0 °C, the reaction mixture was diluted with hexane (2.0 mL). The reaction mixture was filtered through a short plug of aluminum oxide (1.0 g) with diethyl ether as an eluent. The resulting solution was evaporated under reduced pressure, and the residue was filtered through a short plug of silica gel (3.0 g) [(*S*)-**4aa** was hydrolyzed]. After volatiles were removed under reduced pressure, flash column chromatography on silica gel (0–1% EtOAc/hexane) gave (*S*)-**5a** (21.1 mg, 0.132 mmol) in 88% yield.

The reaction in Table 2, entry 3 is representative. CuCl (1.5 mg, 0.015 mmol), **L1**•HBF₄ (10.6 mg, 0.015 mmol) and LiOtBu (16.1 mg, 0.195 mmol) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon[®]-coated silicon rubber septum, and then the vial was evacuated and filled with argon. THF (0.6 mL) was added to the vial, and then the mixture was stirred at room temperature for 10 min. Next, PhMe₂SiH (27.9 μ L, 0.18 mmol) and 4-methoxyphenyl isocyanide (**2c**) (22.6 mg, 0.165 mmol) were added. Finally, allylic phosphate **3a** (42.6 mg, 0.15 mmol) was added at 0 °C. After 24 h stirring at 0 °C, the reaction mixture was diluted with hexane (2.0 mL). The reaction mixture was filtered through a short plug of aluminum oxide (1.0 g) with diethyl ether as an eluent. The filtrate was evaporated under reduced pressure, flash column chromatography on diol-modified silica gel (hexane) gave (*S*)-**4ca** (37.4 mg, 0.141 mmol) in 94% yield.

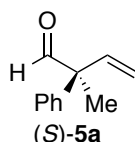
To a solution of the formimide (*S*)-**4ca** in diethyl ether (0.56 mL) was added 2M HCl aq. (0.21 mL) at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was diluted with diethyl ether and extracted with diethyl ether (2.0 mL $\times$ 3). The combined organic layer was washed with saturated NaHCO₃ aq., water and brine, and was dried over anhydrous MgSO₄, filtered, and evaporated under reduced pressure to give (*S*)-**5a** as a colorless oil (22.6 mg, 0.141 mmol, quant.).

A gram scale reaction (Table 2, entry 5). The reaction in Table 2, entry 5 is representative. CuCl (69.7 mg, 0.70 mmol), **L1**•HBF₄ (498 mg, 0.70 mmol) and LiOtBu (755 mg, 9.15 mmol) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon[®]-coated silicon rubber septum, and then the vial was evacuated and filled with argon. THF (28.2 mL) was added to the vial, and then the mixture was stirred at room temperature for 10 min. Next, PhMe₂SiH (1.19 g, 8.44 mmol) and 4-methoxyphenyl isocyanide (**2c**) (1.06 g, 7.74 mmol) were added. Finally, allylic phosphate **3a** (2.0 g, 7.04 mmol) was added at 0 °C. After 24 h stirring at 0

°C, the reaction mixture was diluted with hexane (60.0 mL). The reaction mixture was filtered through a short plug of aluminum oxide (10.0 g) with diethyl ether as an eluent. After volatiles were removed under reduced pressure, flash column chromatography on diol-modified silica gel (0–1% EtOAc/hexane) gave (*S*)-**4da** (1.51 g, 5.69 mmol) in 81% yield.

Characterization Data for α -Quaternary Formimides and Aldehydes

(*S*)-2-Methyl-2-phenyl-3-butenal (**5a**)

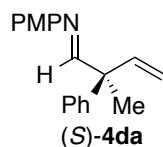


The product **5a** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (Table 1, entry 2; 21.1 mg, 0.132 mmol, 88% isolated yield from (*Z*)-**3a**, Table 2, entry 1; 21.4 mg, 0.134 mmol, 89% isolated yield from (*Z*)-**3a**, Table 2, entry 2; 12.0 mg, 0.075 mmol, 50% isolated yield from (*Z*)-**3a**, Table 2, entry 3; 22.6 mg, 0.141 mmol, 94% isolated yield from (*Z*)-**3a**. Colorless Oil. **IR** (neat) 761, 922, 1029, 1078, 1387, 1446, 1492, 1724, 2713, 2814, 2982 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 1.54 (s, 3H), 5.19 (d, *J* = 17.6 Hz, 1H), 5.42 (d, *J* = 10.0 Hz, 1H), 6.22 (dd, *J* = 17.6, 10.0 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 2H), 9.58 (s, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 20.1, 57.8, 117.4, 127.4 ($\times$ 2C), 128.9, 138.2, 140.0, 199.4. **HRMS–APCI** (*m/z*): [*M*+*H*]⁺ calcd for C₁₁H₁₃O, 161.09609; found, 161.09618. [α]_D²⁴ –43.16 (*c* 0.93, CHCl₃). The absolute configuration of **5a** was determined to be *S* by the optical rotation of **5a** obtained by reduction with NaBH₄ from **5a**. (*S*)-2-Methyl-2-phenyl-3-buten-1-ol (**6a**); [α]_D²⁶ +29.29 (99% ee, *c* 0.72, ethanol). {lit³⁰, (*R*) isomer, 81% ee, [α]_D²⁰ –18.1 (1.9, ethanol)}.

Table 1, entry 2; the ee value (97% ee) was determined by chiral HPLC analysis of **6a** obtained by reduction with NaBH₄ from **5a** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 97:3, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 15.1 min for *R* isomer and 16.0 min for *S* isomer].

Table 2, entry 1; the ee value (99% ee) was determined by chiral HPLC analysis of **6a** obtained by reduction with NaBH₄ from **5a** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 97:3, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 15.1 min for *R* isomer and 16.0 min for *S* isomer].

(*S,E*)-*N*-(4-Methoxyphenyl)-2-methyl-2-phenyl-3-buten-1-imine (4da)

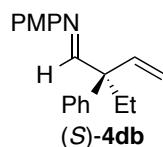


The product **4da** was purified by flash chromatography on diol-modified silica gel (hexane) (Table 2, entry 3; 37.4 mg, 0.141 mmol, 94% isolated yield from (*Z*)-**3a**, Table 2, entry 5; 801 mg, 3.02 mmol, 86% isolated yield from (*Z*)-**3a**). Pale Yellow Oil. **IR** (neat) 761, 827, 1243, 1293, 1444, 1504, 1602, 1647, 2835, 2979 cm^{-1} . **¹H NMR** (400 MHz, CDCl_3) δ 1.68 (s, 3H), 3.80 (s, 3H), 5.14 (d, $J = 17.6$ Hz, 1H), 5.31 (d, $J = 10.8$ Hz, 1H), 6.33 (dd, $J = 17.6, 10.8$ Hz, 1H), 6.87 (d, $J = 8.8$ Hz, 2H), 7.06 (d, $J = 8.8$ Hz, 2H), 7.25 (m, 1H), 7.33–7.38 (m, 4H), 7.90 (s, 1H). **¹³C NMR** (100 MHz, CDCl_3) δ 23.0, 51.2, 55.5, 114.2, 114.8, 121.9, 126.8, 127.2, 128.6, 142.0, 143.8, 145.1, 157.8, 166.8. **HRMS–ESI** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{20}\text{ON}$, 266.15394; found, 266.15397. $[\alpha]_{\text{D}}^{27} -25.97$ (99% ee, c 0.95, CHCl_3). The absolute configuration of **4da** was determined to be *S* by the optical rotation of the corresponding aldehyde **5a**. The geometry of formimidoyl moiety was determined by NOESY experiment.

Table 2, entry 3; the ee value (99% ee) was determined by chiral HPLC analysis of **4da** [CHIRALCEL® AD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 97:3, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 11.3 min for *R* isomer and 11.8 min for *S* isomer].

Table 2, entry 5; the ee value (99% ee) was determined by chiral HPLC analysis of **4da** [CHIRALCEL® AD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 97:3, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 10.6 min for *R* isomer and 11.3 min for *S* isomer].

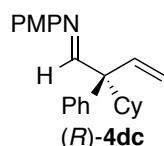
(*S,E*)-2-Ethyl-*N*-(4-methoxyphenyl)-2-phenyl-3-buten-1-imine (4db)



The product **4db** was purified by flash chromatography on diol-modified silica gel (hexane) (37.7 mg, 0.135 mmol, 90% isolated yield from (*Z*)-**3b**). Pale Yellow Oil. **IR** (neat) 757, 828, 919, 1034, 1242, 1293, 1505, 1580, 1645, 2878, 2935, 2969 cm^{-1} . **¹H NMR** (400 MHz, CDCl_3) δ 0.90 (t, $J = 7.2$ Hz, 3H), 2.15–2.29 (m, 2H), 3.79 (s, 3H), 5.05 (dd, $J = 18.0, 1.2$ Hz, 1H), 5.35 (dd, $J = 10.8, 1.2$ Hz, 1H), 6.37 (dd, $J = 18.0, 10.8$ Hz, 1H), 6.87 (d, $J = 9.2$ Hz, 2H), 7.05 (d, $J = 9.2$ Hz, 2H), 7.25 (m, 1H), 7.31–7.38 (m, 4H), 7.87 (s, 1H). **¹³C NMR** (100 MHz, CDCl_3)

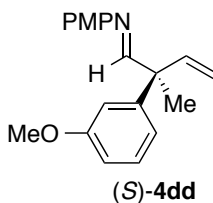
δ 9.1, 29.3, 54.7, 55.4, 114.1, 116.1, 121.8, 126.7, 128.0, 128.4, 140.8, 142.2, 145.3, 157.8, 166. 7. **HRMS–ESI** (m/z): $[M+H]^+$ calcd for $C_{19}H_{22}ON$, 280.16959; found, 280.16946. $[\alpha]_D^{23}$ –15.58 (c 1.30, $CHCl_3$). The ee value (96% ee) was determined by chiral HPLC analysis of **4db** [CHIRALCEL® AD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 97:3, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 11.9 min for *R* isomer and 12.7 min for *S* isomer]. The absolute configuration of **4db** was assigned by consideration of the stereochemical pathway.

(*R,E*)-2-Cyclohexyl-*N*-(4-methoxyphenyl)-2-phenyl-3-buten-1-imine (4dc**)**



The product **4dc** was purified by flash chromatography on diol-modified silica gel (hexane) (44.7 mg, 0.134 mmol, 89% isolated yield from (*Z*)-**3c**). Pale Yellow Oil. **IR** (neat) 731, 828, 910, 1036, 1242, 1293, 1446, 1504, 1643, 2853, 2927 cm^{-1} . **¹H NMR** (400 MHz, $CDCl_3$) δ 0.84–1.12 (m, 3H), 1.22–1.40 (m, 2H), 1.64–1.76 (m, 4H), 1.93 (d, J = 11.2 Hz, 1H), 2.44 (tt, J = 12.0, 2.8 Hz, 1H), 3.79 (s, 3H), 5.02 (dd, J = 18.0, 1.2 Hz, 1H), 5.40 (dd, J = 10.8, 1.2 Hz, 1H), 6.39 (dd, J = 18.0, 10.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.24 (m, 1H), 7.30–7.36 (m, 4H), 7.87 (s, 1H). **¹³C NMR** (100 MHz, $CDCl_3$) δ 26.7, 26.9 ($\times$ 2C), 28.4, 29.0, 43.5, 55.5, 58.0, 114.1, 116.8, 121.7, 126.5, 128.1, 128.8, 139.8, 141.2, 145.6, 157.7, 166.5. **HRMS–ESI** (m/z): $[M+H]^+$ calcd for $C_{23}H_{28}ON$, 334.21654; found, 334.21631. $[\alpha]_D^{23}$ +24.07 (c 1.09, $CHCl_3$). The ee value (97% ee) was determined by chiral HPLC analysis of **4dc** [CHIRALCEL® OD-3 column, 4.6 mm $\times$ 250 mm/OD-3 column, 4.6 mm $\times$ 220 mm/OD-H column, 4.6 mm $\times$ 220 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 26.0 min for *S* isomer and 26.7 min for *R* isomer]. The absolute configuration of **4dc** was assigned by consideration of the stereochemical pathway.

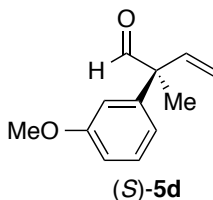
(*S,E*)-2-(3-Methoxyphenyl)-*N*-(4-methoxyphenyl)-2-methyl-3-buten-1-imine (4dd**)**



The product **4dd** was purified by flash chromatography on diol-modified silica gel (hexane) (41.3 mg, 0.140 mmol, 93% isolated yield from (*Z*)-**3d**). Pale Yellow Oil. **IR** (neat) 773, 830, 1035, 1242, 1290, 1504, 1580, 1599, 1647, 2835, 2935 cm^{-1} . **¹H NMR** (400 MHz, $CDCl_3$) δ 1.67

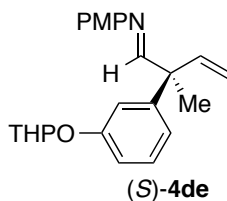
(s, 3H), 3.80 (s, 6H), 5.15 (dd, $J = 17.2, 1.2$ Hz, 1H), 5.31 (dd, $J = 10.8, 1.2$ Hz, 1H), 6.32 (dd, $J = 17.2, 10.8$ Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 1H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.90 (t, $J = 2.0$ Hz, 1H), 6.93 (m, 1H), 7.05 (d, $J = 8.8$ Hz, 2H), 7.28 (t, $J = 8.4$ Hz, 1H), 7.88 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.9, 51.1, 55.2, 55.4, 111.6, 113.5, 114.1, 114.9, 119.6, 121.9, 129.5, 141.8, 145.1, 145.5, 157.8, 159.7, 166.6. **HRMS-ESI** (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{O}_2\text{N}$, 296.16451; found, 296.16448. $[\alpha]_{\text{D}}^{26} -17.32$ (c 1.13, CHCl_3). The ee value (98% ee) was determined by chiral HPLC analysis of **4dd** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99.5:0.5, 0.5 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 13.5 min for *R* isomer and 15.3 min for *S* isomer]. The absolute configuration of **4dd** was assigned by consideration of the stereochemical pathway.

(*S*)-2-(3-Methoxyphenyl)-2-methyl-3-butenal (5d**)**



Colorless Oil. **IR** (neat) 779, 924, 1045, 1257, 1485, 1582, 1599, 1725, 2713, 2836, 2981 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.53 (s, 3H), 3.81 (s, 3H), 5.19 (d, $J = 18.0$ Hz, 1H), 5.41 (d, $J = 10.8$ Hz, 1H), 6.21 (dd, $J = 18.0, 10.8$ Hz, 1H), 6.79–6.86 (m, 3H), 7.31 (t, $J = 8.0$ Hz, 1H), 9.57 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 20.0, 55.2, 57.8, 112.4, 113.6, 117.5, 119.7, 129.9, 138.1, 141.6, 160.0, 199.2. **HRMS-ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{O}_2\text{Na}$, 213.08860; found, 213.08905. $[\alpha]_{\text{D}}^{25} -43.45$ (c 0.90, CHCl_3). The absolute configuration of **5d** was assigned by consideration of the stereochemical pathway.

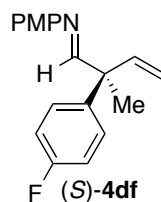
(*S,E*)-*N*-(4-Methoxyphenyl)-2-methyl-2-{3-[(tetrahydro-2*H*-pyran-2-yl)oxy]phenyl}-3-buten-1-imine (4de**) (Diastereomeric ratio 1:1)**



The product **4de** was purified by flash chromatography on diol-modified silica gel (0–1% EtOAc/hexane) (49.3 mg, 0.135 mmol, 90% isolated yield from (*Z*)-**3e**). Pale Yellow Oil. **IR** (neat) 773, 872, 968, 1036, 1109, 1243, 1505, 1579, 1647, 2873, 2944 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.58–1.71 (m, 0.5 $\times$ 6H, 0.5 $\times$ 6H), 1.83–1.87 (m, 0.5 $\times$ 2H, 0.5 $\times$ 2H), 1.96–2.06 (m, 0.5 $\times$ 1H, 0.5 $\times$ 1H), 3.56–3.62 (m, 0.5 $\times$ 1H, 0.5 $\times$ 1H), 3.80 (0.5 $\times$ 3H, 0.5 $\times$ 3H), 3.88–3.94 (m,

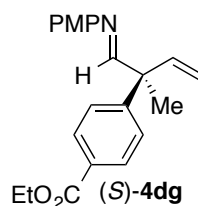
0.5 × 1H, 0.5 × 1H), 5.12–5.18 (dd, $J = 17.2, 1.2$ Hz, 0.5 × 1H, 0.5 × 1H), 5.29–5.32 (dd, $J = 11.2, 1.2$ Hz, 0.5 × 1H, 0.5 × 1H), 5.39–5.41 (t, $J = 3.2$ Hz, 0.5 × 1H, 0.5 × 1H), 6.28–6.36 (dd, $J = 17.2, 11.2$ Hz, 0.5 × 1H, 0.5 × 1H), 6.86–6.88 (d, $J = 8.8$ Hz, 0.5 × 2H, 0.5 × 2H), 6.95–6.99 (m, 0.5 × 2H, 0.5 × 2H), 7.02–7.03 (t, $J = 2.0$ Hz, 0.5 × 1H, 0.5 × 1H), 7.04–7.07 (d, $J = 8.8$ Hz, 0.5 × 2H, 0.5 × 2H), 7.25–7.28 (t, $J = 8.0$ Hz, 0.5 × 1H, 0.5 × 1H), 7.88 (s, 0.5 × 1H, 0.5 × 1H). ¹³C NMR (100 MHz, CDCl₃) δ 18.9, 18.9, 22.9, 22.9, 25.2, 25.2, 30.4, 30.4, 51.1, 51.1, 55.5, 55.5, 62.1, 62.1, 96.4, 96.4, 114.1, 114.1, 114.3, 114.3, 114.8, 114.8, 115.9, 116.0, 120.5, 120.5, 121.9, 121.9, 129.4, 129.4, 141.8, 141.9, 145.1, 145.1, 145.3, 145.4, 157.3, 157.3, 157.8, 157.8, 166.7, 166.7. **HRMS–ESI** (m/z): [M+H]⁺ calcd for C₂₃H₂₈O₃N, 366.20637; found, 366.20648. [α]_D²⁴ –14.58 (c 0.99, CHCl₃). The ee value (99% ee) was determined by chiral HPLC analysis of **4de** [CHIRALCEL[®] OD-3 column, 4.6 mm × 250 mm/OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99.5:0.5, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 46.2 min and 67.2 min for *S* isomer and 49.1 min and 64.9 min for *R* isomer]. The absolute configuration of **4de** was assigned by consideration of the stereochemical pathway.

(*S,E*)-2-(4-Fluorophenyl)-*N*-(4-methoxyphenyl)-2-methyl-3-buten-1-imine (4df**)**



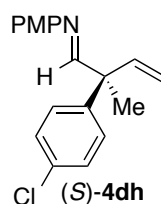
The product **4df** was purified by flash chromatography on diol-modified silica gel (hexane) (3.83 mg, 0.135 mmol, 90% isolated yield from (*Z*)-**3f**). Pale Yellow Oil. **IR** (neat) 774, 828, 1034, 1162, 1243, 1394, 1504, 1602, 1646, 2836, 2979 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 1.66 (s, 3H), 3.80 (s, 3H), 5.13 (dd, $J = 17.6, 1.2$ Hz, 1H), 5.31 (dd, $J = 10.4, 1.2$ Hz, 1H), 6.30 (dd, $J = 17.6, 10.4$ Hz, 1H), 6.87 (d, $J = 9.2$ Hz, 2H), 7.01–7.07 (m, 4H), 7.30 (dd, $J = 9.2, 5.2$ Hz, 2H), 7.86 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 23.3, 50.7, 55.5, 114.2, 115.0, 115.3 (d, $J = 21.9$ Hz), 121.9, 128.9 (d, $J = 7.6$ Hz), 139.4 (d, $J = 2.8$ Hz), 141.9, 144.9, 157.9, 161.7 (d, $J = 244.0$ Hz), 166.3. **HRMS–ESI** (m/z): [M+H]⁺ calcd for C₁₈H₁₉ONF, 284.14452; found, 284.14435. [α]_D²⁷ –30.81 (c 1.20, CHCl₃). The ee value (96% ee) was determined by chiral HPLC analysis of **4df** [CHIRALCEL[®] OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 21.1 min for *R* isomer and 22.0 min for *S* isomer]. The absolute configuration of **4df** was assigned by consideration of the stereochemical pathway.

Ethyl (*S,E*)-4-{1-[(4-Methoxyphenyl)imino]-2-methyl-3-buten-2-yl}benzoate (4dg**)**



The product **4dg** was purified by flash chromatography on diol-modified silica gel (0–2% EtOAc/hexane) (46.6 mg, 0.138 mmol, 92% isolated yield from (*Z*)-**3g**). Pale Yellow Oil. **IR** (neat) 770, 1019, 1102, 1243, 1272, 1504, 1607, 1647, 1713, 2836, 2980 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 1.39 (t, *J* = 6.8 Hz, 3H), 1.69 (s, 3H), 3.80 (s, 3H), 4.37 (q, *J* = 6.8 Hz, 2H), 5.15 (d, *J* = 17.2 Hz, 1H), 5.34 (d, *J* = 10.8 Hz, 1H), 6.32 (dd, *J* = 17.2, 10.8 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.89 (s, 1H), 8.03 (d, *J* = 8.8 Hz, 2H). **¹³C NMR** (100 MHz, CDCl₃) δ 14.3, 23.1, 51.4, 55.5, 60.9, 114.2, 115.4, 121.9, 127.3, 129.0, 129.8, 141.4, 144.8, 148.9, 158.0, 165.8, 166.4. **HRMS–ESI** (*m/z*): [M+H]⁺ calcd for C₂₁H₂₄O₃N, 338.17507; found, 338.17523. [α]_D²⁴ –6.34 (*c* 1.15, CHCl₃). The ee value (97% ee) was determined by chiral HPLC analysis of **4dg** [CHIRALCEL® AD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 95:5, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 20.0 min for *R* isomer and 21.6 min for *S* isomer]. The absolute configuration of **4dg** was assigned by consideration of the stereochemical pathway.

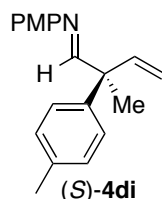
(*S,E*)-2-(4-Chlorophenyl)-*N*-(4-methoxyphenyl)-2-methyl-3-buten-1-imine (4dh**)**



The product **4dh** was purified by flash chromatography on diol-modified silica gel (hexane) (39.6 mg, 0.132 mmol, 88% isolated yield from (*Z*)-**3h**). Pale Yellow Oil. **IR** (neat) 777, 824, 922, 1012, 1095, 1293, 1243, 1505, 1647, 2835, 2980 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 1.66 (s, 3H), 3.80 (s, 3H), 5.13 (d, *J* = 17.6 Hz, 1H), 5.32 (d, *J* = 10.8 Hz, 1H), 6.29 (dd, *J* = 17.6, 10.8 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.26–7.34 (m, 4H), 7.86 (s, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 23.1, 50.8, 55.5, 114.2, 115.2, 121.9, 128.6, 128.7, 132.7, 141.6, 142.2, 144.8, 158.0, 166.0. **HRMS–ESI** (*m/z*): [M+H]⁺ calcd for C₁₈H₁₉ONCl, 300.11497; found, 300.11509. [α]_D²⁴ –15.62 (*c* 1.21, CHCl₃). The ee value (95% ee) was determined by chiral HPLC analysis of **4dh** [CHIRALCEL® AD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-

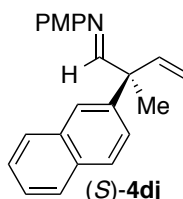
propanol = 97:3, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 11.1 min for *R* isomer and 12.1 min for *S* isomer]. The absolute configuration of **4dh** was assigned by consideration of the stereochemical pathway.

(*S,E*)-*N*-(4-Methoxyphenyl)-2-methyl-2-(*p*-tolyl)-3-buten-1-imine (4di**)**



The product **4di** was purified by flash chromatography on diol-modified silica gel (hexane) (39.8 mg, 0.143 mmol, 95% isolated yield from (*Z*)-**3i**). Pale Yellow Oil. **IR** (neat) 721, 816, 828, 919, 1035, 1243, 1504, 1580, 1646, 2835, 2978 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 1.66 (s, 3H), 2.34 (s, 3H), 3.80 (s, 3H), 5.13 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.29 (dd, *J* = 10.4, 1.2 Hz, 1H), 6.32 (dd, *J* = 17.6, 10.4 Hz, 1H), 6.86 (d, *J* = 9.2 Hz, 2H), 7.05 (d, *J* = 9.2 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.87 (s, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 20.9, 23.0, 50.8, 55.4, 114.1, 114.6, 121.9, 127.1, 129.3, 136.4, 140.7, 142.2, 145.1, 157.8, 166.9. **HR MS–ESI** (*m/z*): [M+H]⁺ calcd for C₁₉H₂₂ON, 280.16959; found, 280.16971. [α]_D²⁸ +44.50 (*c* 1.08, CHCl₃). The ee value (98% ee) was determined by chiral HPLC analysis of **4di** [CHIRALCEL® AD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 97:3, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 11.1 min for *R* isomer and 12.8 min for *S* isomer]. The absolute configuration of **4di** was assigned by consideration of the stereochemical pathway.

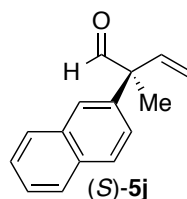
(*S,E*)-*N*-(4-Methoxyphenyl)-2-methyl-2-(naphthalen-2-yl)-3-buten-1-imine (4dj**)**



The product **4dj** was purified by flash chromatography on diol-modified silica gel (hexane) (42.6 mg, 0.135 mmol, 90% isolated yield from (*Z*)-**3j**). Pale Yellow Oil. **IR** (neat) 731, 747, 818, 1033, 1243, 1503, 1600, 1646, 3709, 2834, 2932, 2978, 2980, 3056 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 1.77 (s, 3H), 3.79 (s, 3H), 5.18 (d, *J* = 17.2 Hz, 1H), 5.36 (d, *J* = 10.8 Hz, 1H), 6.43 (dd, *J* = 17.2, 10.8 Hz, 1H), 6.87 (d, *J* = 9.2 Hz, 2H), 7.09 (d, *J* = 9.2 Hz, 2H), 7.45–7.49 (m, 3H), 7.78–7.84 (m, 4H), 7.97 (s, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 23.1, 51.3, 55.4, 114.2, 115.1, 121.9, 125.7, 125.8, 125.9, 126.1, 127.5, 128.0, 128.2, 132.2, 1

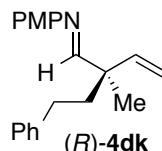
33.4, 141.1, 142.0, 145.0, 157.9, 166.6. **HRMS–ESI** (m/z): $[M+H]^+$ calcd for $C_{22}H_{22}ON$, 316.16959; found, 316.16971. $[\alpha]_D^{27} +8.92$ (c 1.07, $CHCl_3$). The ee value (97% ee) was determined by chiral HPLC analysis of **4dj** [CHIRALCEL® AD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 97:3, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 14.3 min for *R* isomer and 16.5 min for *S* isomer]. The absolute configuration of **4dj** was assigned by consideration of the stereochemical pathway.

(S)-2-Methyl-2-(naphthalen-2-yl)but-3-enal (5j)



Colorless Oil. **IR** (neat) 818, 924, 1131, 1370, 1505, 1724, 2812, 2929, 3057 cm^{-1} . **¹H NMR** (400 MHz, $CDCl_3$) δ 1.64 (s, 3H), 5.24 (d, J = 17.2 Hz, 1H), 5.48 (d, J = 11.2 Hz, 1H), 6.32 (dd, J = 17.2, 11.2 Hz, 1H), 7.35 (dd, J = 8.8, 1.6 Hz, 1H), 7.49–7.51 (m, 2H), 7.71 (d, J = 1.6 Hz, 1H), 7.81–7.87 (m, 3H), 9.66 (s, 1H). **¹³C NMR** (100 MHz, $CDCl_3$) δ 20.2, 58.0, 117.8, 125.4, 126.3, 126.4, 126.4, 127.6, 128.0, 128.6, 132.5, 133.4, 137.4, 138.2, 199.5. **HRMS–APCI** (m/z): $[M+H]^+$ calcd for $C_{15}H_{15}O$, 211.11174; found, 211.11191. $[\alpha]_D^{25} -35.11$ (c 1.01, $CHCl_3$). The absolute configuration of **5j** was assigned by consideration of the stereochemical pathway.

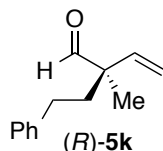
(R,E)-N-(4-Methoxyphenyl)-2-methyl-2-phenethyl-3-buten-1-imine (4dk)



The product **4dk** was purified by flash chromatography on diol-modified silica gel (hexane) (39.6 mg, 0.135 mmol, 90% isolated yield from (*Z*)-**3k**). Pale Yellow Oil. **IR** (neat) 731, 828, 1035, 1210, 1242, 1455, 1505, 1604, 1648, 2835, 2932 cm^{-1} . **¹H NMR** (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.93–2.00 (m, 2H), 2.57–2.69 (m, 2H), 3.80 (s, 3H), 5.14 (dd, J = 18.0, 1.2 Hz, 1H), 5.22 (dd, J = 10.8, 1.2 Hz, 1H), 6.02 (dd, J = 18.0, 10.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 7.16–7.20 (m, 3H), 7.24–7.29 (m, 2H), 7.71 (s, 1H). **¹³C NMR** (100 MHz, $CDCl_3$) δ 21.0, 30.8, 40.5, 46.1, 55.4, 114.1, 114.2, 121.7, 125.8, 128.3, 128.4, 142.5, 142.6, 145.3, 157.7, 168.4. **HRMS–ESI** (m/z): $[M+H]^+$ calcd for $C_{20}H_{24}ON$, 294.18524; found, 294.18546. $[\alpha]_D^{24} -19.09$ (c 1.11, $CHCl_3$). The ee value (84% ee) was determined by chiral HPLC analysis of **4dk** [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm/OD-3 column, 4.6 mm × 220 mm, Daicel Chemical Industries, hexane/2-propanol = 98:2, 0.7 mL/min, 40 °C, 220 nm UV detector, retention time = 26.7 min for *S* isomer and 29.5 min for *R* isomer]. The absolute configuration of

4dk was determined to be *R* by the optical rotation of the corresponding formaldehyde **5k**. The geometry of formimidoyl moiety was determined by NOESY experiment.

(*R*)-2-Methyl-2-phenethyl-3-butenal (5k**)**

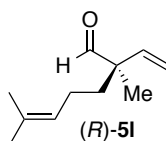


The product **5k** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (Table 2, entry 19; 25.3 mg, 0.134 mmol, 89% isolated yield from (*Z*)-**3k**, Table 2, entry 20; 25.4 mg, 0.135 mmol, 90% isolated yield from (*Z*)-**3k**, Table 2, entry 22; 16.9 mg, 0.09 mmol, 60% isolated yield from (*Z*)-**3k'**). **5k** was consistent with the literature data.³¹ $[\alpha]_D^{23} -19.89$ (86% ee, *c* 0.90, CH₂Cl₂) {lit³¹, (*S*) isomer, >99% ee, $[\alpha]_D^{25} +26.7$ (*c* 1.15, CH₂Cl₂)}.

Table 2, entry 19; the ee value (83% ee) was by chiral HPLC analysis was obtained by reduction with NaBH₄ from **5k** [CHIRALCEL[®] OD-3 column, 4.6 mm × 250 mm/ OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 95:5, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 38.6 min for *S* isomer and 40.4 min for *R* isomer].

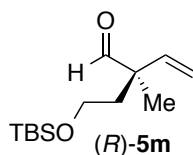
Table 2, entry 22; the ee values (86% ee) was determined by chiral HPLC analysis was obtained by reduction with NaBH₄ from **5k** [CHIRALCEL[®] OD-3 column, 4.6 mm × 250 mm/ OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, hexane/2-propanol = 95:5, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 39.1 min for *S* isomer and 40.9 min for *R* isomer].

(*R*)-2,6-Dimethyl-2-vinyl-5-heptenal (5l**)**



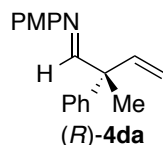
The product **5l** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (15.0 mg, 0.09 mmol, 60% isolated yield from (*Z*)-**3l'**). **5l** was consistent with the literature data.³² $[\alpha]_D^{25} -8.76$ (*c* 1.21, CHCl₃). The ee value (88% ee) was determined by chiral HPLC analysis of *N*-(4-methoxyphenyl)formimide derivative obtained by the reaction between **5l** and 4-methoxyphenylamine [CHIRALCEL[®] OD-3 column, 4.6 mm × 250 mm/OD-3 column, 4.6 mm × 220 mm, Daicel Chemical Industries, hexane/2-propanol = 99.5:0.5, 0.7 mL/min, 40 °C, 220 nm UV detector, retention time = 13.6 min for *R* isomer and 14.3 min for *S* isomer]. The absolute configuration of **5l** was assigned by consideration of the stereochemical pathway.

(*R*)-2-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-2-methyl-3-butenal (5m**)**



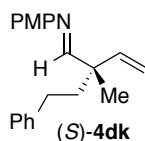
The product **5m** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (16.7 mg, 0.069 mmol, 46% isolated yield from (*Z*)-**3m'**). Pale Yellow Oil. **IR** (neat) 775, 834, 921, 1095, 1255, 1388, 1464, 1727, 2858, 2930, 2956 cm^{-1} . **¹H NMR** (400 MHz, CDCl_3) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 1.19 (s, 3H), 1.79 (ddd, $J = 14.0, 5.6, 5.6$ Hz, 1H), 2.00 (ddd, $J = 14.0, 7.2, 6.4$ Hz, 1H), 3.61–3.71 (m, 2H), 5.13 (d, $J = 18.0$ Hz, 1H), 5.25 (d, $J = 10.0$ Hz, 1H), 5.83 (dd, $J = 18.0, 10.0$ Hz, 1H), 9.40 (s, 1H). **¹³C NMR** (100 MHz, CDCl_3) δ –5.6, 18.1, 18.2, 25.8, 39.1, 51.2, 59.0, 116.2, 138.8, 202.0. **HRMS–ESI** (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{26}\text{O}_2\text{NaSi}$, 265.15943; found, 265.15980. $[\alpha]_D^{26} +18.34$ (c 1.11, CHCl_3). The ee value (84% ee) was determined by chiral HPLC analysis of *N*-(4-methoxyphenyl)formimide derivative obtained by the reaction between **5m** and 4-methoxyphenylamine [CHIRALCEL® OD-3 column, 4.6 mm $\times$ 250 mm/OD-3 column, 4.6 mm $\times$ 220 mm, Daicel Chemical Industries, hexane/2-propanol = 99.5:0.5, 0.7 mL/min, 40 °C, 220 nm UV detector, retention time = 12.4 min for *R* isomer and 13.3 min for *S* isomer]. The absolute configuration of **5m** was assigned by consideration of the stereochemical pathway.

(*R,E*)-*N*-(4-Methoxyphenyl)-2-methyl-2-phenyl-3-buten-1-imine (4da**)**



The product **4da** was purified by flash chromatography on diol-modified silica gel (hexane) (34.2 mg, 0.129 mmol, 86% isolated yield from (*E*)-**3a**). $[\alpha]_D^{23} +15.45$ (c 0.99, CHCl_3). The ee value (66% ee) was determined by chiral HPLC analysis of **4da**. [CHIRALCEL® AD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 97:3, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 10.1 min for *R* isomer and 11.0 min for *S* isomer].

(*S,E*)-*N*-(4-Methoxyphenyl)-2-methyl-2-phenethyl-3-buten-1-imine (4dk**)**



The product **4dk** was purified by flash chromatography on diol-modified silica gel (hexane) (40.5 mg, 0.138 mmol, 92% isolated yield from (*E*)-**3k**). $[\alpha]_D^{24} +13.63$ (c 1.32, CHCl_3). The ee

value (70% ee) was determined by chiral HPLC analysis of **4dk** [CHIRALCEL® OD-3 column, 4.6 mm × 250 mm/OD-3 column, 4.6 mm × 220 mm, Daicel Chemical Industries, hexane/2-propanol = 98:2, 0.7 mL/min, 40 °C, 220 nm UV detector, retention time = 26.8 min for *S* isomer and 29.8 min for *R* isomer].

Procedures for Product Derivatization (Figure 15)

Synthesis of primary alcohol (Figure 15a).

To a solution of (*S*)-**4da** (37.4 mg, 0.141 mmol) in diethyl ether (0.56 mL) was added 2 M HCl aq. (0.21 mL) at 0 °C. After stirring at rt for 2 h, the reaction mixture was diluted with diethyl ether and extracted with diethyl ether (2.0 mL × 3). The combined organic layer was washed with saturated NaHCO₃ aq., water and brine, and was dried over anhydrous MgSO₄, filtered, and evaporated under reduced pressure to give (*S*)-**5a** as a colorless oil (22.6 mg, 0.141 mmol, quant.).

To a solution of (*S*)-**5a** in MeOH (1.0 mL) was added NaBH₄ (11.3 mg, 0.3 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for another 30 min, water was added. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with water and brine. The mixture was dried and concentrated *in vacuo*. Purification by column chromatography (silica gel, 5–30% EtOAc/hexane) yielded (*S*)-**6a** (15.7 mg, 0.097 mmol) in 97% yield. Pale Yellow Oil. **5a** was consistent with the literature data.³⁰ [α]_D²⁶ +29.29 (*c* 0.72, ethanol).

Synthesis of primary amine (Figure 15a)

To a solution of (*S*)-**4da** (133 mg, 0.5 mmol) in EtOH (5.0 mL) was added NaBH₄ (189 mg, 5.0 mmol). The reaction mixture was stirred at 60 °C for 12 h, quenched with water. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with water and brine, and was dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give secondary amine as a pale yellow oil (131 mg, 0.49 mmol) in 98% yield.

To a solution of the secondary amine (53.5 mg, 0.2 mmol) in CH₃CN (2.0 mL) was added ceric ammonium nitrate (548 mg, 1.0 mmol) in water (2.0 mL) at room temperature. After being stirred at room temperature for 2 h, the reaction mixture was diluted with Et₂O (4.0 mL) and water (4.0 mL). The aqueous layer was extracted with Et₂O, and the combined organic layer was washed with water and brine, and was dried over anhydrous Na₂SO₄, filtered, and evaporated under reduced pressure to give (*S*)-**7a** as a red oil (27.1 mg, 0.168 mmol) in 84% yield. Pale Yellow Oil. **IR** (neat) 761, 812, 915, 1029, 1374, 1413, 1445, 1494, 1645, 2968 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 1.39 (s, 3H), 2.95 (dd, *J* = 13.2 Hz, 1H), 3.00 (dd, *J* = 13.2 Hz, 1H), 5.10 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.23 (dd, *J* = 10.8, 1.2 Hz, 1H), 6.07 (dd, *J* = 17.6, 10.8 Hz, 1H), 7.22 (m, 1H), 7.33–7.37 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 23.1, 46.7, 51.6, 113.7, 126.2, 126.8, 128.4, 144.6,

145.5. **HRMS–ESI** (m/z): $[M+H]^+$ calcd for $C_{11}H_{16}N$, 162.12773; found, 162.12815. $[\alpha]_D^{25} +13.84$ (c 0.81, $CHCl_3$).

Synthesis of *N*-heterocyclic six-membered ring compound (Figure 15a).

To a solution of (*S*)-**4da** (133 mg, 0.5 mmol) in EtOH (5.0 mL) was added $NaBH_4$ (189 mg, 5.0 mmol). The reaction mixture was stirred at 60 °C for 12 h, quenched with water. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with water and brine, and was dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give secondary amine as a pale yellow oil (131 mg, 0.49 mmol) in 98% yield.

To a solution of the secondary amine (53.5 mg, 0.2 mmol) in DMF (0.8 mL) was added allylbromide (41.2 μ L, 0.5 mmol) and K_2CO_3 (69.1 mg, 0.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 24 h, diluted with Et_2O and quenched with water. The aqueous layer was extracted with Et_2O , and the combined organic layer was washed with brine. The mixture was dried over anhydrous Na_2SO_4 , filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0–1% EtOAc/hexane) to give the allylamine (53.9 mg, 0.175 mmol) in 88% yield.

To a solution of the allylamine (23.6 mg, 76.0 μ mol) in CH_2Cl_2 (760 μ L) was added Grubbs-II catalyst (3.2 mg, 3.8 μ mol) at room temperature. After being stirred at room temperature for 2 h, the reaction mixture was diluted with Et_2O . The mixture was filtrated through a short plug of silica gel with Et_2O as an eluent. The mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0–1% EtOAc/hexane) to give (*S*)-**8a** (19.5 mg, 70.0 μ mol) in 92% yield. Pale Yellow Oil. **IR** (neat) 760, 818, 1038, 1242, 1509, 1458, 1581, 1601, 1663, 2965 cm^{-1} . **1H NMR** (400 MHz, $CDCl_3$) δ 1.52 (s, 3H), 3.19 (d, J = 12.4 Hz, 1H), 3.32 (d, J = 12.4 Hz, 1H), 3.62–3.64 (m, 2H), 3.74 (s, 3H), 5.87–5.96 (m, 2H), 6.74 (d, J = 9.2 Hz, 2H), 6.79 (d, J = 9.2 Hz, 2H), 7.20 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 9.2 Hz, 2H), 7.45 (t, J = 9.2 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 25.5, 41.4, 48.7, 55.6, 61.9, 114.4, 116.8, 124.0, 126.1, 126.6, 128.1, 134.1, 145.4, 146.9, 152.9. **HRMS–ESI** (m/z): $[M+H]^+$ calcd for $C_{19}H_{22}ON$, 280.16759; found, 280.17010. $[\alpha]_D^{25} -97.03$ (c 0.66, $CHCl_3$).

Synthesis of allylic nitrile (Figure 15b).

To a solution of (*S*)-**5j** (19.7 mg, 0.095 mmol) in EtOH (0.32 mL) was added $NH_2OH \cdot HCl$ (9.2 mg, 0.133 mmol) and NaOAc (11.7 mg, 0.143 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 h. After concentration of the reaction mixture *in vacuo*, Et_2O was added to the mixture. The organic layer was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure.

To a solution of the residue in THF (0.32 mL) was added 1,1'-carbonyldiimidazole (77.0 mg, 0.475 mmol). The reaction mixture was refluxed for 2 h and then cooled to 0 °C. The reaction

mixture was diluted with Et₂O and quenched with water at 0 °C. The aqueous layer was extracted with Et₂O, and the combined organic layer was washed with brine. The mixture was dried over anhydrous MgSO₄, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0–2% EtOAc/hexane) to give (*S*)-**9j** (16.6 mg, 0.08 mmol) in 84% yield. Pale Yellow Oil. **IR** (neat) 746, 930, 1131, 1410, 1456, 1600, 1637, 1724, 2236, 2986 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 1.92 (s, 3H), 5.38 (d, *J* = 10.8 Hz, 1H), 5.59 (d, *J* = 17.6, 1H), 6.04 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 7.49–7.55 (m, 3H), 7.83–7.92 (m, 4H). **¹³C NMR** (100 MHz, CDCl₃) δ 26.6, 44.6, 116.1, 121.8, 123.8, 124.7, 126.6, 126.7, 127.6, 128.1, 128.9, 132.7, 133.1, 136.6, 138.2. **HRMS–APCI** (*m/z*): [M+H]⁺ calcd for C₁₅H₁₄N, 208.11208; found, 208.11227. [α]_D²⁶ –44.79 (*c* 0.90, CHCl₃).

Horner-Wadworth-Emmons reaction (Figure 15c).

To a solution of (EtO)₂P(O)CH₂CO₂Et (40.5 μ L, 0.2 mmol) and LiCl (8.5 mg, 0.2 mmol) in CH₃CN (0.5 mL) was dropped DBU (30.0 μ L, 0.2 mmol) at room temperature and the reaction was stirred for 1 h at the same temperature. Next, (*S*)-**5a** (16.0 mg, 0.1 mmol) in CH₃CN (0.5 mL) was added dropwise over a period of 20 min at room temperature. After being stirred at room temperature for 4 h, the mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0–1% EtOAc/hexane) to give (*R*)-**10a** (19.5 mg, 0.85 mmol) in 85% yield. Pale Yellow Oil. **IR** (neat) 721, 764, 919, 990, 1030, 1165, 1277, 1649, 1717, 2979 cm⁻¹. **¹H NMR** (400 MHz, CDCl₃) δ 1.29 (t, *J* = 7.2 Hz, 3H), 1.56 (s, 3H), 4.20 (q, *J* = 7.2 Hz, 2H), 5.06 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.22 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.79 (d, *J* = 15.6 Hz, 1H), 6.06 (dd, *J* = 17.6, 10.4 Hz, 1H), 7.17–7.35 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 14.2, 24.8, 47.9, 60.4, 114.2, 119.8, 126.7, 127.0, 128.4, 143.3, 144.4, 154.2, 166.8. **HRMS–ESI** (*m/z*): [M+Na]⁺ calcd for C₁₅H₁₈O₂Na, 253.11990; found, 253.12027. [α]_D²³ –26.45 (*c* 0.98, CHCl₃).

Synthesis of Chiral Naphthol-Carbene Ligand

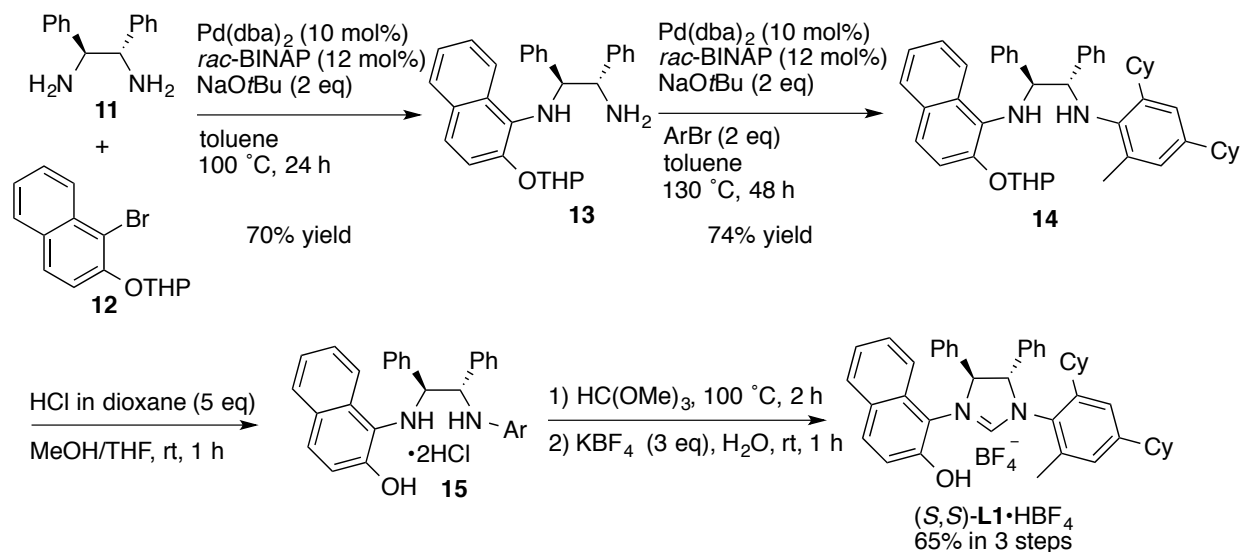
The phenol- or naphthol-carbene ligands **L1–5** were found in previous works of Sawamura and Ohmiya group and prepared according to the reported procedures.^{8,9} The synthesis of **L1•HBF₄** is representative (Scheme 5). To a solution of Pd(dba)₂ (575 mg, 1.0 mmol), *rac*-BINAP (770 mg, 1.2 mmol) and NaOtBu (1.98 g, 20.0 mmol) in toluene (30 mL) was added (1*S*,2*S*)-(–)-1,2-diphenylethylenediamine (**11**) (2.17 g, 10.0 mmol) and a solution of arylbromide **12** (3.69 g, 12.0 mmol) in toluene (20 mL). After being stirred at 100 °C for 24 h, the reaction mixture was filtered through a pad of celite, and the celite was washed with EtOAc. Solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel,

5–45% EtOAc/hexane) to yield the coupling product **13** (3.07 g, 70%) as a brown solid. **13** was consistent with the literature data.⁸

To a solution of Pd(dba)₂ (403 mg, 0.7 mmol), *rac*-BINAP (539 mg, 0.84 mmol) and NaOtBu (1.39 g, 14.0 mmol) in toluene (14 mL) was added amine **13** (3.07 g, 7.0 mmol) and a solution of 2-bromo-3,5-dicyclohexyltoluene³³ [5.52 g, 14.0 mmol, containing 4-bromo-3,5-dicyclohexyltoluene (15%)] in toluene (14.0 mL). After being stirred at 130 °C for 48 h, the reaction mixture was filtered through a pad of celite, and the celite was washed with EtOAc. Solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 0–1% EtOAc/hexane) to yield the coupling product **14** (3.6 g, 74%) as a white solid. **14** was consistent with the literature data.⁸

To a solution of **14** (3.6 g, 5.2 mmol) in MeOH/THF (11.1 mL/13.6 mL) was added HCl (4.0 M in dioxane, 6.5 mL, 26.0 mmol) at room temperature. After being stirred at room temperature for 1 h, the solvent was removed under reduced pressure, and the residue was triturated with hexane. The yellow solid was collected with a Kiriya-funnel, washed with hexane, and was dried in vacuum to give **15** (3.63 g) as a yellow powder. The solid was treated with trimethylorthoformate (8.9 mL, 80.0 mmol). After being stirred at 100 °C for 3 h, the reaction mixture was concentrated under reduced pressure. The crude imidazolium salt **L1**•HCl was triturated with hexane in an ultrasonic cleaning bath for ca. 20 min. During this time, the desired salt precipitated as a yellow solid, which was collected with a Kiriya-funnel, washed with hexane, and was concentrated. The residue (3.51 g) was purified by flush column chromatography (silica gel, 0–1.5% MeOH/CH₂Cl₂) and was triturated with hexane in an ultrasonic cleaning bath for ca. 10 min. The pale yellow solid was collected with a Kiriya-funnel, washed with hexane. The obtained solid was treated with NH₄BF₄ (1.33 g, 12.3 mmol) in water (13.7 mL) and the mixture was stirred at room temperature for 1 h. The water suspension was extracted with CH₂Cl₂ (three times). The combined CH₂Cl₂ extract was dried and concentrated, and was triturated with pentane in an ultrasonic cleaning bath for ca. 5 min. The pale yellow solid was collected with a Kiriya-funnel, washed with hexane, and was dried in vacuum at 60 °C for 12 h to give **L1**•HBF₄ (2.38 g, 3.37 mmol) in 65% yield in 3 steps. **L1**•HBF₄ was consistent with the literature data.^{7,9}

Scheme 4. The synthesis of **L1**•HBF₄



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Publication List

- 1) Construction of Quaternary Stereogenic Carbon Centers through Copper-Catalyzed Enantioselective Allylic Cross-Coupling with Alkylboranes.

Hojoh, K.; Shido, Y.; Ohmiya, H.; Sawamura, M.

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- 2) Copper-Catalyzed Enantioselective Allylic Cross-Coupling with Alkylboranes.

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- 3) Synthesis of α -Quaternary Formimides and Aldehydes through Umpolung Asymmetric Copper Catalysis with Isocyanides.

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