



Title	Development of Copper-Catalyzed Asymmetric Allylic Cross-Coupling Reactions
Author(s)	安田, 優人
Degree Grantor	北海道大学
Degree Name	博士(理学)
Dissertation Number	甲第13682号
Issue Date	2019-03-25
DOI	https://doi.org/10.14943/doctoral.k13682
Doc URL	https://hdl.handle.net/2115/80675
Type	doctoral thesis
File Information	Yuto_Yasuda.pdf



Development of Copper-Catalyzed Asymmetric Allylic Cross-Coupling Reactions

(銅触媒不斉アリル系クロスカップリング反応の開発)

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2019

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General Introduction

Transition-metal-catalyzed enantioselective allylic substitutions are important methods for a C–C bond formation to produce the products with a stereogenic center. Palladium-catalyzed Tsuji–Trost reaction is recognized as a pioneering and representative example of catalytic asymmetric allylic couplings. Due to the usefulness of the reaction, Tsuji–Trost reaction has been applied to total syntheses of various complex molecules.

In addition to palladium catalyst, other metals (copper, rhodium, iridium, molybdenum, etc.) have been employed for catalytic allylic coupling in recent years. In particular, copper is the most studied metal for the catalytic reactions compared to other rare metals, because “copper” has attractive features such as inexpensive, low-toxic, and earth-abundant.

1. Allylic Substitution with Copper Catalyst

Transition-metal-catalyzed allylic substitution reaction proceeds via a unique reaction pathway depending on the metal species (Figures 1 and 2). The metal-dependent reaction pathway greatly influences the regio- and/or stereoselectivities of allylic substitution when substituted allylic electrophiles are used. In a palladium-catalyzed reaction, a π -allyl palladium formation from an allylic electrophile via oxidative addition is the first step. Next, a “soft” nucleophile directly attacks the carbon of this electrophilic π -allyl palladium species from the opposite side to the palladium (Figure 1, left cycle), while transmetalation reaction proceeds on the palladium metal with “hard” nucleophile followed by reductive elimination to form C–C bond from the same side to the palladium (Figure 1, right cycle). The coupling product is obtained through either pathway in regioisomeric mixture. On the other hand, the reaction with metal catalysts such as rhodium, iridium, and molybdenum afford the branched product preferentially. Like palladium catalysis, the π -allyl metal species is formed first from an allylic electrophile, via the stereoinversion process. Then, the nucleophilic substitution from the opposite side to the metal occurs on the π -allyl metal species, delivering a branch coupling product as a major regioisomer (Figure 1, left cycle). As a result, the reaction proceeds with net retention for the configuration of the starting material.

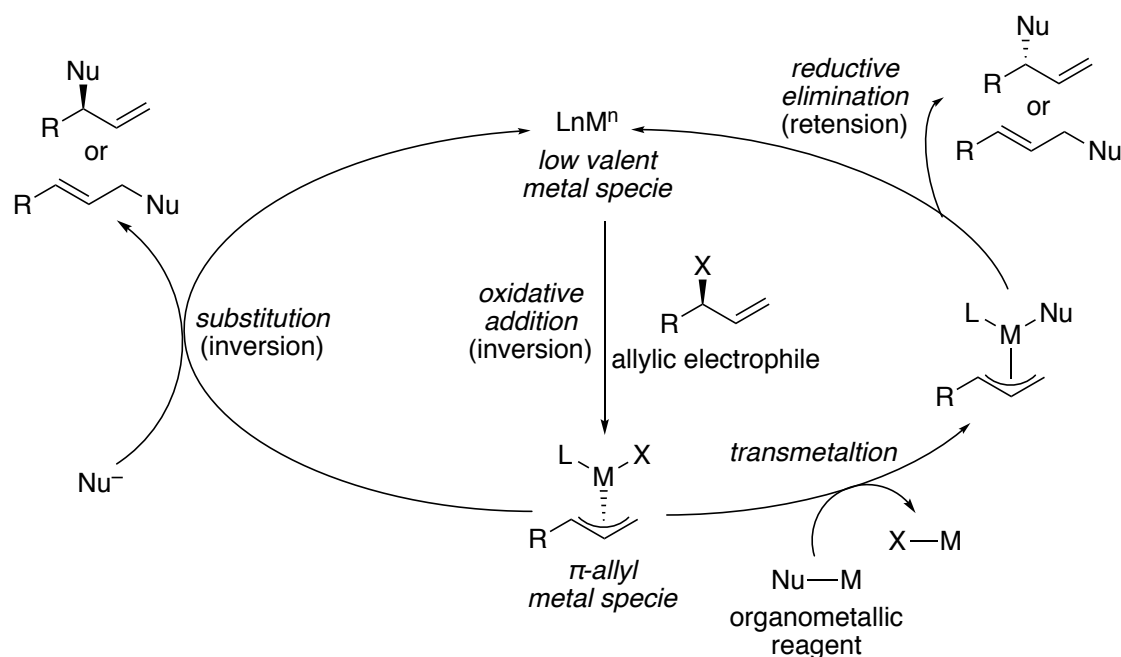


Figure 1. Plausible reaction pathway of allylic substitution in rare metal catalysis

The reaction pathway of a copper-catalyzed allylic substitution is not same as any pathways mentioned above (Figure 2). The transmetalation reaction between an organometallic reagent and a copper complex proceeds first to afford an active organocopper species in copper catalysis. Following substitution reaction between the organocopper and an allylic substrate proceeds in $\text{S}_{\text{N}}2'$ type reaction, along with the regeneration of copper catalyst. The new C–C bond formation generally occurs in $\text{S}_{\text{N}}2'$ type regioselectivity regardless of the size of the substituent on allylic electrophiles. In addition, the substitution reaction proceeds with *anti* stereochemistry to the leaving group. In this way, copper-catalyzed allylic substitution proceeds via a unique reaction pathway, forming the cross-coupling product with a new stereogenic center using a prochiral γ -substituted allylic electrophile (Scheme 1).

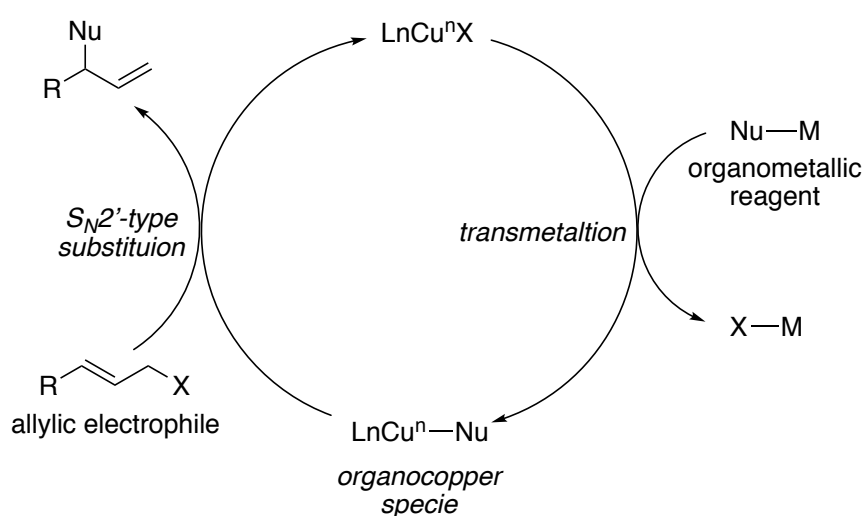
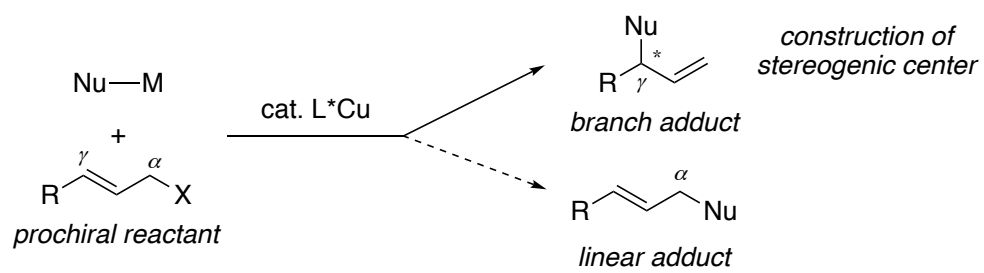


Figure 2. Plausible reaction pathway of allylic substitution in copper catalysis

Scheme 1. Construction of stereogenic center in chiral copper catalysis

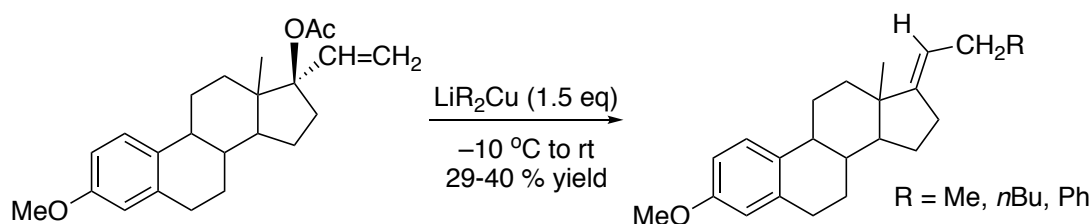


2. History of Copper-Catalyzed Asymmetric Allylic Substitution

2.1. Stoichiometric Reaction

In 1969, Crabbe and co-workers reported the first example of the use of organocuprates in the allylic substitution reaction (Scheme 2).¹ They demonstrated the reaction of allyl acetates with a stoichiometric organocopper(I) reagents (for example: LiMe_2Cu , $\text{Li}^i\text{Bu}_2\text{Cu}$, LiPh_2Cu) in ether at room temperature. The coupling proceeded exclusively via the γ -substitution manner to give internal olefins.

Scheme 2. Reaction of a stoichiometric amount of organocopper(I) reagent



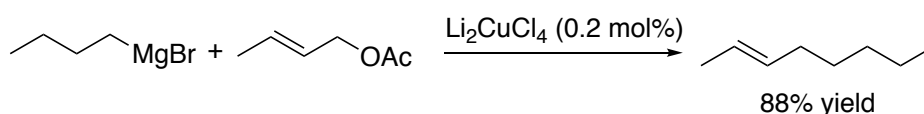
Since this report, the allylic substitution with organocopper reagents has been the important methods in organic synthesis. Following their pioneering work, a lot of researchers developed the related reactions and studied the reaction mechanisms. However, the details of copper catalysis have not been revealed, compared with the other catalysis.

2.2. Copper-Catalyzed Asymmetric Allylic Substitution

2.2.1. Copper-Catalyzed Asymmetric Allylic Substitution with Grignard Reagents

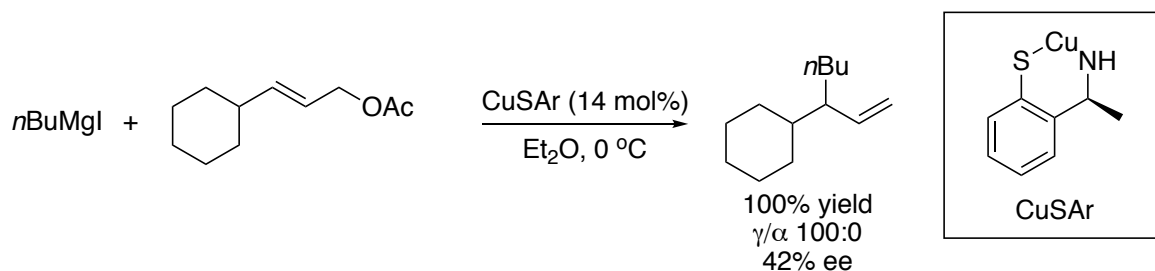
In 1974, Schlosser reported the allylic substitution with Grignard reagents under a catalytic amount of a copper salt (Scheme 3).² The reaction catalyzed by 0.2 mol% of Li_2CuCl_4 gave the coupling product from *trans*-crotylacetate and *n*-butyl magnesium bromide. This is the first example of copper-catalyzed allylic substitution.

Scheme 3. Allylic alkylation reaction with a catalytic amount of a copper salt



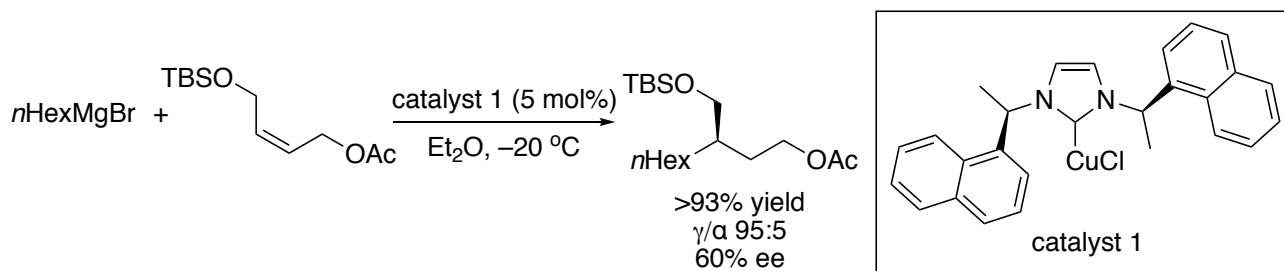
From this report, a lot of copper-catalyzed allylic substitution reactions have been developed. In addition, the chemistry was extended to the development of asymmetric reactions. In 1995, Bäckvall and van Koten found the allylic substitution proceeded enantioselectively under the chiral copper catalyst (Scheme 4).³ The chiral arenethiolatocopper(I)-catalyzed coupling reaction gave the products in exceptional γ -regioselectivity, producing a tertiary stereogenic center derived from prochiral allyl acetates, by using Grignard reagents as stoichiometric nucleophiles. The enantioselectivity, however, was moderate.

Scheme 4. First example of copper-catalyzed asymmetric allylic alkylation



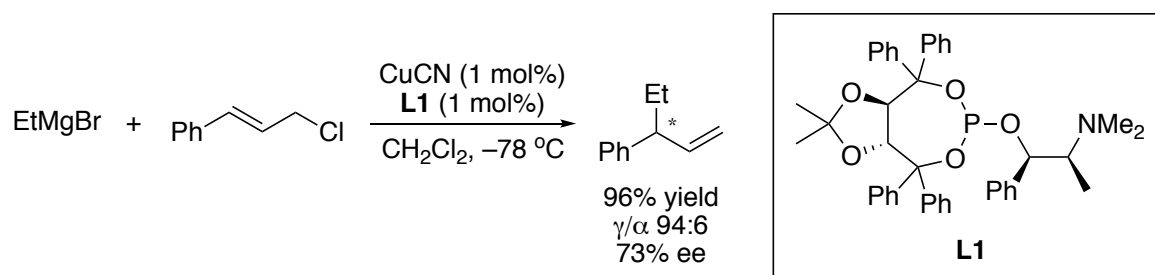
Based on Bäckvall's work, many research groups have explored the efficient chiral ligand in the copper-catalyzed enantioselective allylic substitution with Grignard reagents. Okamoto and co-workers applied the chiral *N*-heterocyclic carbene (NHC) ligand to the enantioselective allylic substitution in copper catalysis.⁴ The reaction afforded the alkylated products mainly at γ -position to the leaving group with good enantioselectivity (Scheme 5). However, the enantioselectivity was not a suitable level for practical syntheses.

Scheme 5. Copper-catalyzed allylic alkylation with chiral NHC ligand

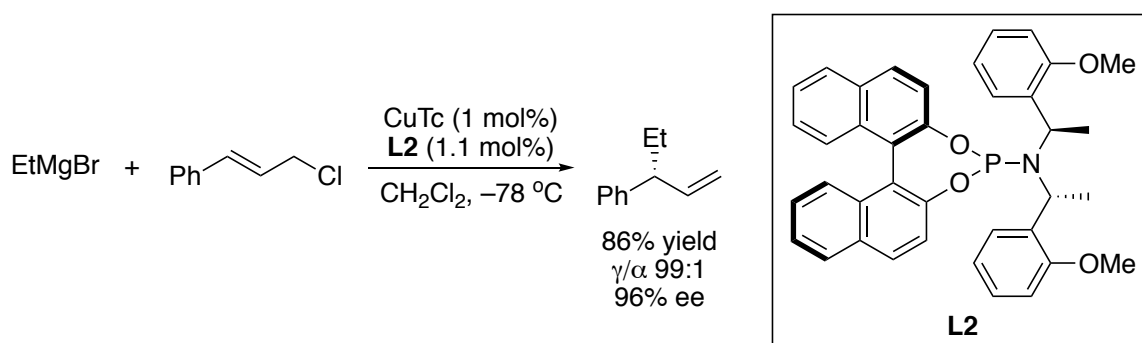


Compared to these ligands, more efficient chiral ligands were disclosed by Alexakis and Feringa groups. In the late 1990's, Alexakis and co-workers developed the chiral phosphoramidite ligand for the copper-catalyzed asymmetric conjugate addition of enones with diethyl zinc.⁵ In 2001, they applied it to the copper-catalyzed enantioselective allylic substitution reaction of Grignard reagents. The new chiral ligand derived from tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) afforded the coupling products with good enantioselectivity (up to 73% ee) (Scheme 6).⁶ More reactive chiral copper catalysts were developed by the same group, though the induction of enantioselectivity was similar level to previous ones.⁷ In 2004, they reported the new chiral phosphoramidite ligand that gave up to 96% ee in copper-catalyzed allylic substitutions (Scheme 7).⁸ Installation of *ortho*-methoxy group to the phenyl rings of known chiral ligand^{5g} were effective for regio- and enantioselectivities. The reaction of cinnamyl chloride with ethyl magnesium bromide afforded the corresponding product with high regioselectivity ($\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2$ 99:1) and excellent enantioselectivity (96% ee). Using other Grignard reagents and allylic substrates, the results were equally good. The chiral ligand-copper complex was applicable to not only Grignard reagents but also dialkylzinc reagents (Scheme 8).

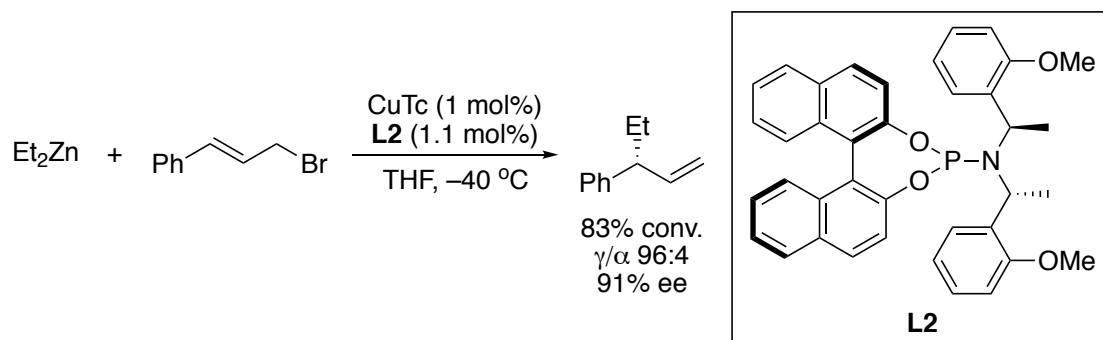
Scheme 6. Copper-catalyzed enantioselective allylic alkylation with TADDOL type ligand



Scheme 7. Copper-catalyzed highly enantioselective allylic substitution with chiral phosphoramidite ligand

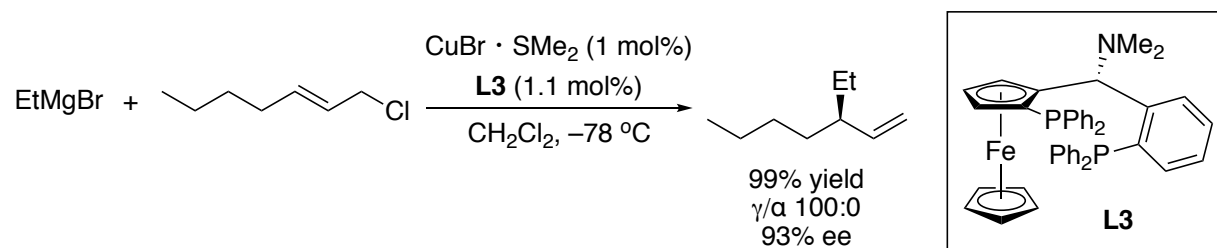


Scheme 8. Copper-catalyzed asymmetric allylic substitution of diethylzinc



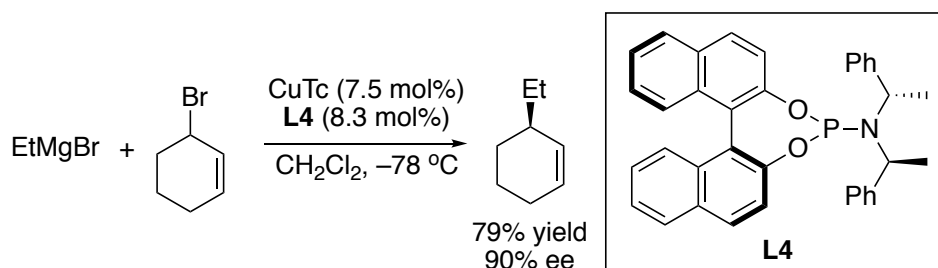
2 years later, Feringa group reported highly enantioselective copper-catalyzed allylic coupling using a chiral bisphosphine ligand (Scheme 9).⁹ The excellent enantioselectivities (up to 98% ee) and excellent regioselectivities could be achieved by the use of Taniaphos ligand. This is the first example which succeeded in the use of non-conjugated linear allyl halides for a highly enantioselective allylic alkylation with Grignard reagents.

Scheme 9. Copper-catalyzed enantioselective allylic alkylation with Taniaphos ligand



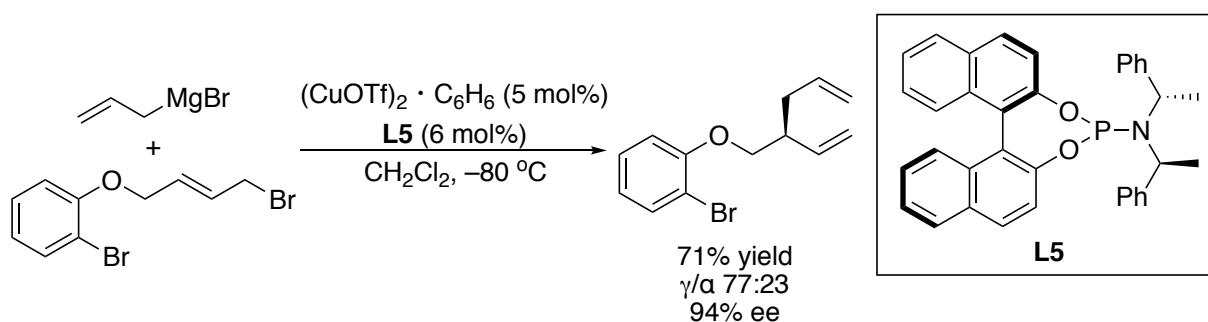
Alexakis and Feringa groups independently demonstrated the use of various allylic substrates in the copper-catalyzed enantioselective allylic substitution reactions, and the synthetic application of the products: 3-bromopropenyl esters derivatives,¹⁰ 1,4-dihalo-2-butenes,¹¹ β - and γ -disubstituted allyl halides,¹² δ -*N*-substituted allyl bromides,¹³ allylic gem-dichlorides,¹⁴ enyne chlorides¹⁵ and others¹⁶ were used as substrates. In addition, Alexakis and co-workers reported the application of the dynamic kinetic asymmetric transformation with racemic cyclic and acyclic substrates in copper-catalyzed asymmetric allylic alkylation (Scheme 10).¹⁷

Scheme 10. Dynamic kinetic asymmetric transformation in copper-catalyzed allylic alkylation



More recently, Feringa developed the first copper-catalyzed enantioselective allyl–allyl cross-coupling.¹⁸ The reactions between a commercially available allyl Grignard reagent and readily accessible allyl bromides were effectively catalyzed by a copper(I)-phosphoramidite complex (Scheme 11). This catalytic system affords the chiral 1,5-diene derivatives with high enantioselectivity. They demonstrated the application of this method for total synthesis.

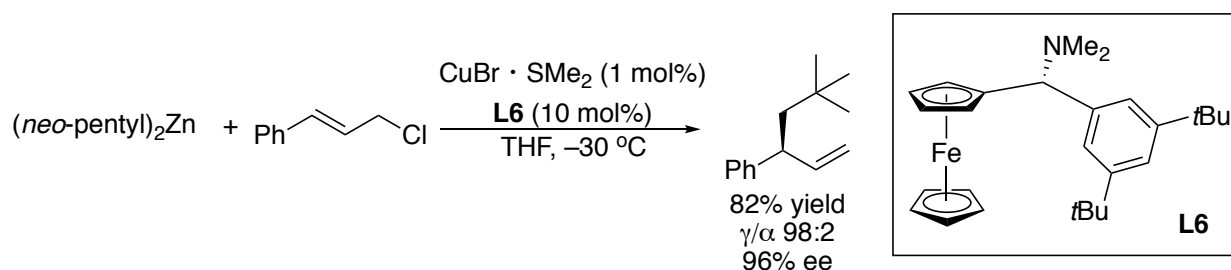
Scheme 11. Copper-catalyzed enantioselective allyl–allyl cross-coupling



2.2.2. Copper-Catalyzed Asymmetric Allylic Substitution with Organozinc Compounds

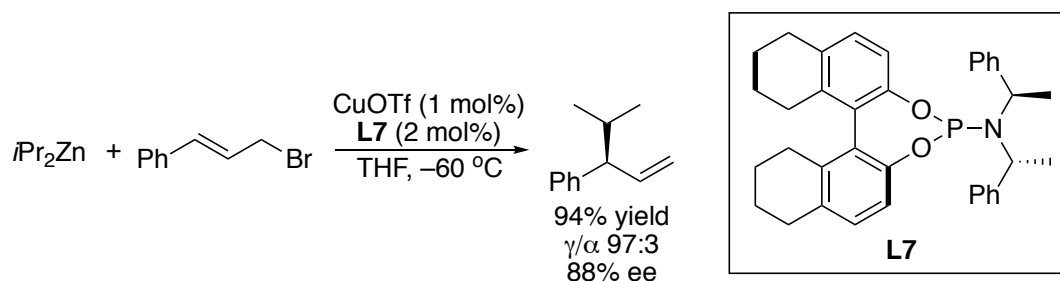
Since the first example of copper-catalyzed enantioselective allylic substitution using Grignard reagents reported by Bäckvall and van Koten,³ a lot of reactions with other organometallic compounds have been developed rapidly. In 1999, Knochel and co-workers reported a copper-catalyzed enantioselective allylic substitution with diorganozinc compounds (Scheme 12).^{19a} Using a novel ferrocenyl amine as a chiral ligand, the copper-catalyzed coupling reaction between allyl chlorides and dialkylzinc forms the alkylation products with excellent S_N2' type regioselectivities and moderate to good enantioselectivities. In the following year, they developed the improved chiral ferrocenyl amine ligand for the reactions of sterically hindered and functionalized diorganozincs with a good level of enantioselectivity^{19b}.

Scheme 12. First example of use of organozinc reagents in copper-catalyzed asymmetric allylic alkylation



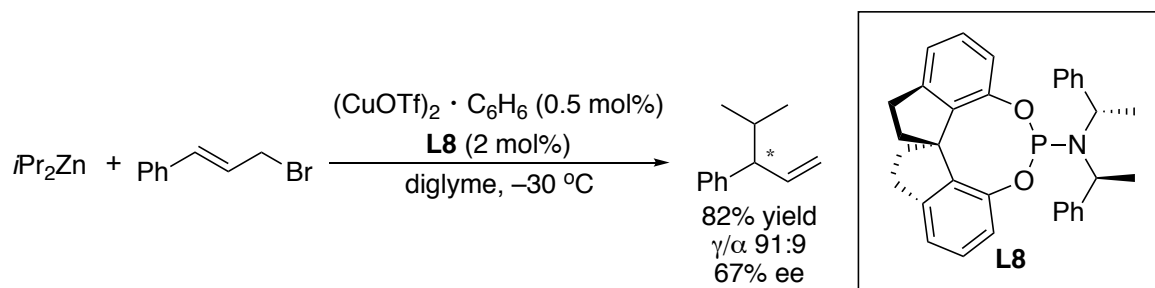
Triggered by this study, the copper-catalyzed enantioselective allylic substitution reactions with organozinc compounds have been studied actively. At that time, an implementation of highly enantioselective allylic alkylation with nonsterically demanding alkylzinc reagents remained a major challenge. Feringa's group reported the application of the phosphoramidite ligand to copper catalysis with diorganozinc reagents (Scheme 13).²⁰ Their chiral phosphoramidite ligand afforded the high regioselectivity, and good enantioselectivity in the reactions with linear dialkylzincs.

Scheme 13. Copper-catalyzed highly enantioselective allylic substitution of dialkylzinc



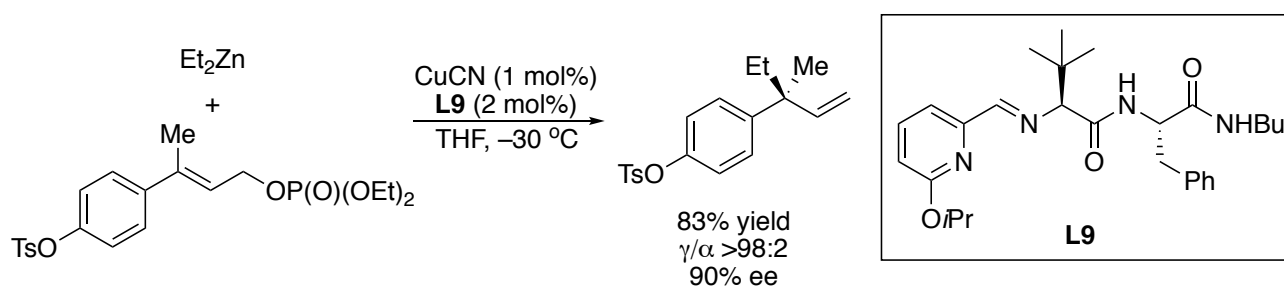
At the same time, Zhou group independently reported that the chiral spiro phosphoramidite ligand was applicable in the copper-catalyzed coupling reaction of allyl halides with dialkylzincs, and it gave good selectivities (Scheme 14).²¹

Scheme 14. Asymmetric allylic substitution with dialkylzinc in copper catalysis

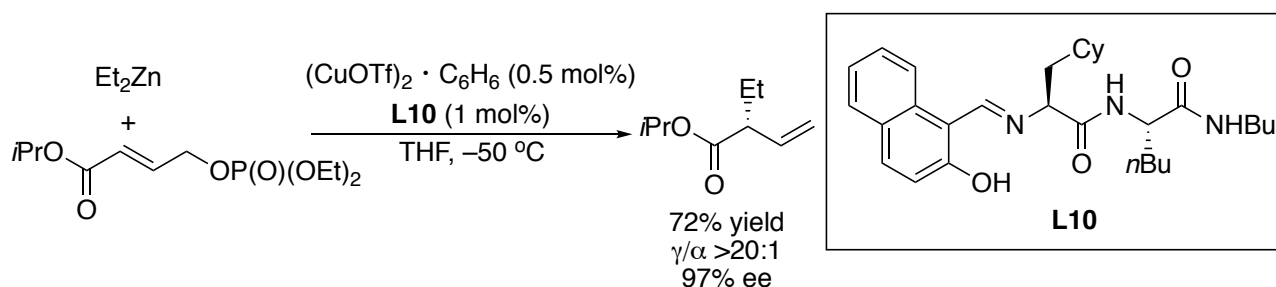


In 2001, Hoveyda and co-workers reported the application of a new class of chiral ligands for copper-catalyzed allylic substitution.²² The peptide-based ligands bearing a pyridinyl residue were suitable for enantioselective allylic coupling of dialkylzincs in copper catalysis (Scheme 15).^{22a} Not only tertiary stereogenic centers but also quaternary stereogenic centers could be constructed by this method. However, its enantioselectivity was not satisfied in this report. 2 years later, the same group disclosed that the new peptide-based ligands were efficient for the synthesis of chiral α -alkyl- β,γ -unsaturated esters (Scheme 16).^{22b} They realized lower catalyst loadings and a reusability of the chiral ligand. In addition, they also developed the copper-catalyzed highly enantioselective allylic alkylation reaction with readily available chiral amino acid-based ligand (Scheme 17).^{22c} Using the chiral amino acid-based ligands, C–C bond formations between alkylzinc reagents and allylic phosphates bearing di- and trisubstituted olefins formed the products in $\text{S}_{\text{N}}2'$ regioselectivity with high enantiocontrol.

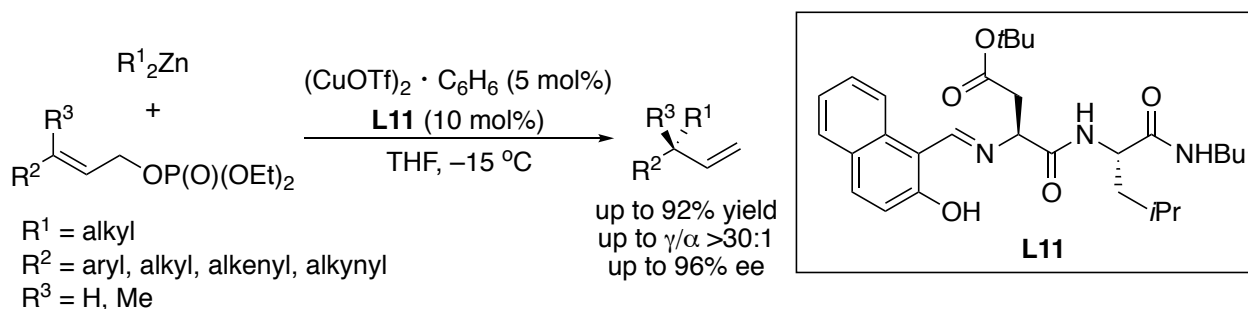
Scheme 15. Enantioselective synthesis of quaternary carbon atoms via copper-catalyzed allylic substitution



Scheme 16. Asymmetric synthesis of α -alkyl- β,γ -unsaturated esters through Cu-catalyzed allylic alkylation

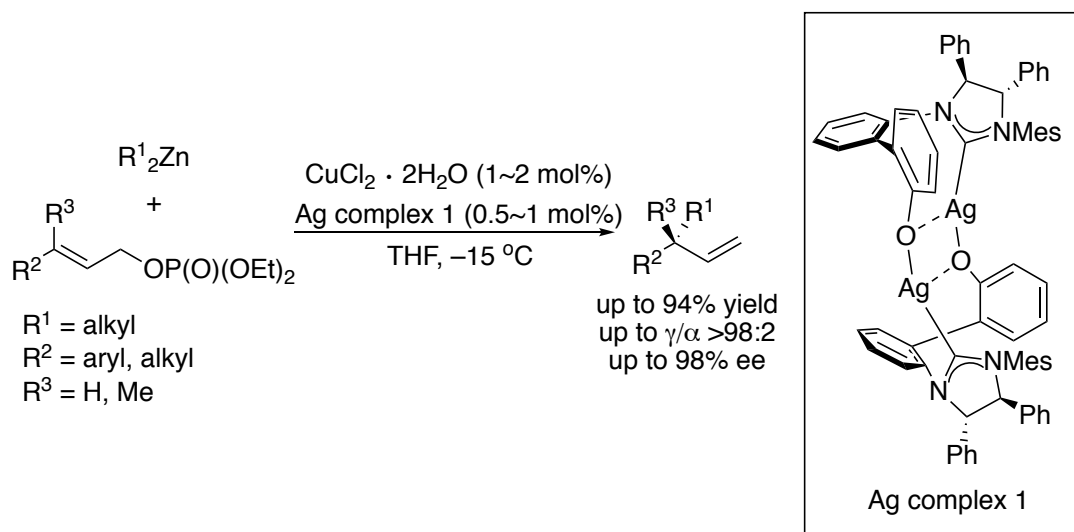


Scheme 17. Enantioselective reaction with readily available chiral amino acid-based ligand



After the development of the chiral peptide-based ligands, Hoveyda's group developed new bidentate NHC chiral ligands for efficient copper-catalyzed enantioselective allylic alkylations (Scheme 18).²³ They prepared the chiral NHC/Ag complex as a dimer, that reacted with a Cu salt and formed a chiral NHC/Cu complex in situ. Using this in situ generated chiral copper complex, the selectivities for the C–C bond formation were improved, and the amount of required copper was decreased. In contrast to peptide-ligand systems, NHC-based catalysts promote highly enantioselective reactions with the less reactive alkylzinc reagents. Furthermore, the chiral NHC ligand could be used in Ru-catalyzed asymmetric olefin metathesis reactions.^{23b}

Scheme 18. Copper-catalyzed asymmetric allylic alkylation using chiral Ag complex as catalyst precursor

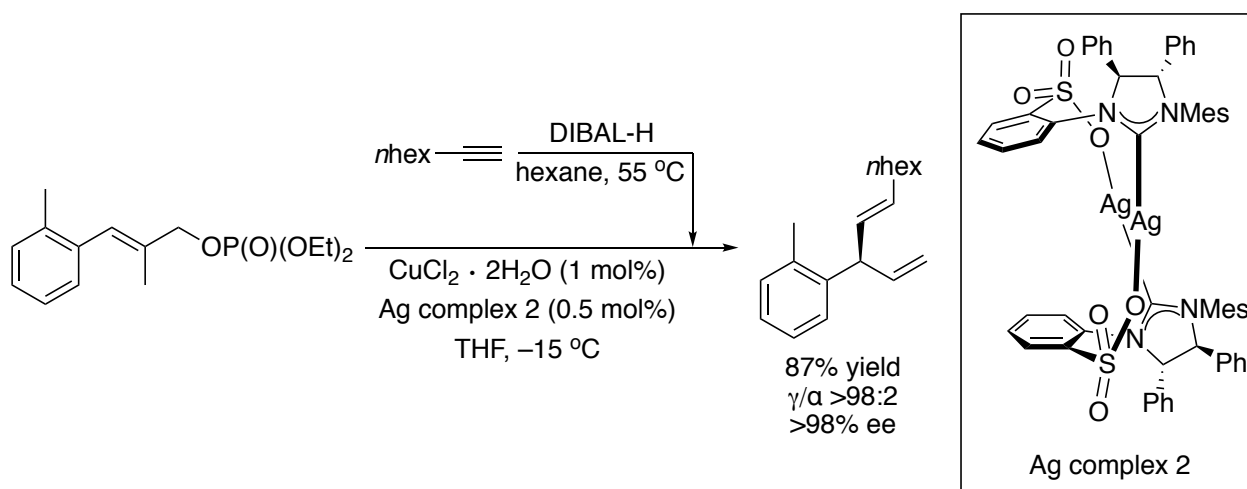


They demonstrated the useful method for a synthesis of allylsilanes bearing tertiary and quaternary Si-substituted carbons.²⁴ The copper-catalyzed enantioselective alkylations with alkylzinc and arylzinc reagents afforded various allylsilanes with high regio- and enantioselectivities using the Ag complex 1 as a source of chiral NHC ligand for copper.

2.2.3. Copper-Catalyzed Asymmetric Allylic Substitution with Organoaluminum Compounds

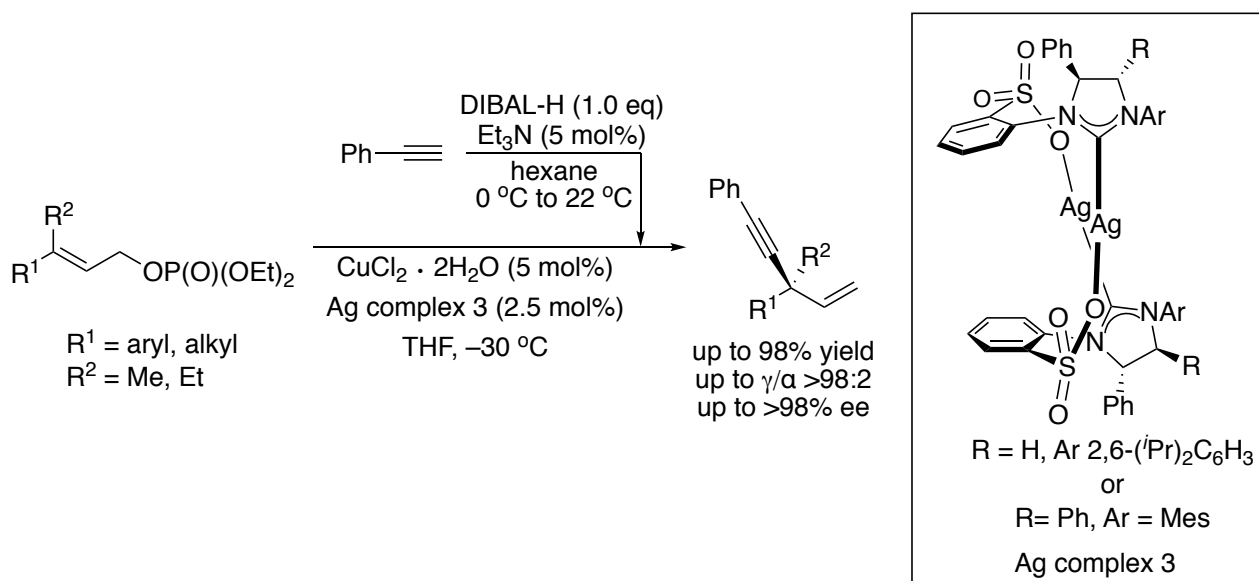
Efficient copper-catalyzed enantioselective allylic substitution reactions with Grignard reagents and organozinc compounds have been developed so far. However, in almost all cases, only alkyl units can be introduced by these methods. Considering this limitation, Hoveyda's group focused on the use of organoaluminum reagents in Cu-catalyzed enantioselective allylic substitution reactions. In 2007, as initial attempts, they investigated the Cu-catalyzed asymmetric allylic coupling of trimethylaluminum to find out if organoaluminum reagents can be used in the reaction.²⁵ As a result, the copper-catalyzed S_N2' -type reaction of allylic phosphates using a Ag complex, which act as an effective chiral NHC ligand source for copper catalyst,²⁶ proceeded effectively. Next, they proceeded to examine the use of alkenylaluminum and alkynylaluminum reagents. First, they developed the copper-catalyzed allylic coupling with alkenylaluminum reagents that are readily prepared in one-pot (Scheme 19).²⁷ Their unique chiral NHC/Cu complex derived from dimeric Ag complex afforded high regio- and enantioselectivities. This method enables the construction of tertiary and quaternary stereogenic carbon centers. In addition, the reaction was applied to the synthesis of *bakuchiol*. Not only terminal alkynes but also internal alkynes can be used as precursors of alkenylaluminum reagents.^{27c}

Scheme 19. Copper-catalyzed enantioselective allylic substitution with accessible alkenylaluminum reagents



In the similar way, they demonstrated the transformation of the terminal alkynes under the modified reaction condition and disclosed a method for enantioselective synthesis of various 1,4-dienes. The highly enantioselective transformations with alkynylaluminum reagents were catalyzed by the same chiral bidentate NHC/Cu complex as the reactions of alkenylaluminum reagents (Scheme 20).²⁸ In addition, they also showed the further transformation of the products in a stereospecific isomerization reaction with a catalytic amount of a base.^{28b}

Scheme 20. Enantioselective synthesis of alkyne-substituted quaternary carbon stereogenic centers

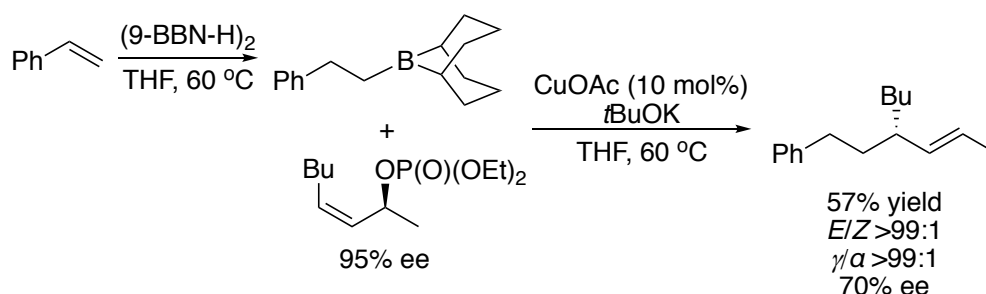


Additionally, the same group reported an addition of aryl- or heteroarylaluminum reagents to afford quaternary carbon stereogenic centers under the chiral copper catalysis.²⁹

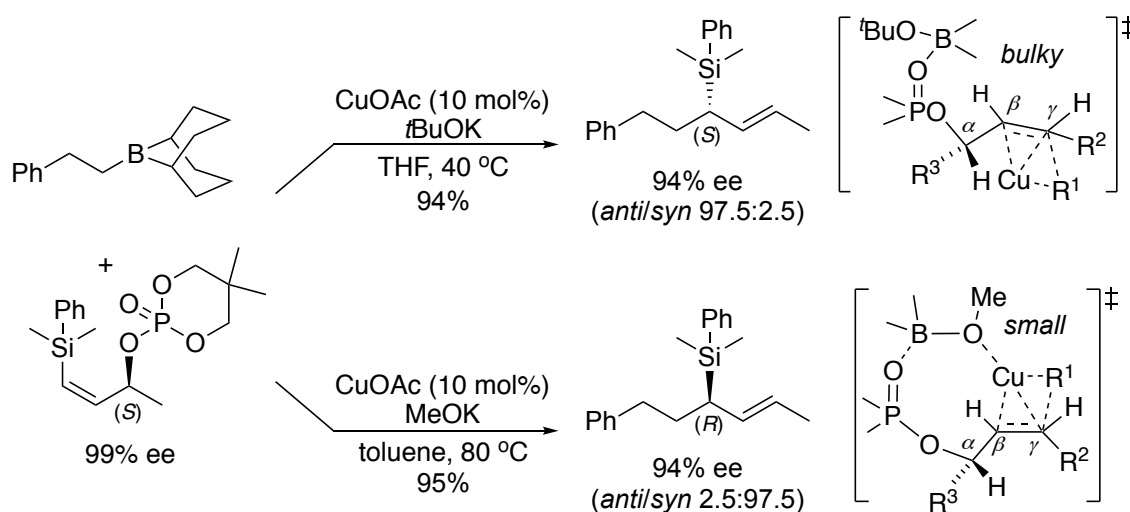
2.2.4. Copper-Catalyzed Asymmetric Allylic Substitution with Organoboron Compounds

Application of various organometallic reagents for copper-catalyzed allylic coupling have been explored for almost 15 years since the Bäckvall and van Koten's first example. However, a functional group compatibility in the reactions were not a satisfied level, because Grignard reagents, organozinc reagents and organoaluminum reagents show high reactivity to various functional groups. With this challenging point in mind, recently, the copper-catalyzed asymmetric allylic substitution using organoboron reagents as nucleophiles are actively studied.³⁰ They are attractive synthetic tools, because organoboron compounds have good chemical stabilities and functional compatibilities. In 2010, Sawamura group disclosed the first example of the copper-catalyzed asymmetric allylic alkylation with trialkylboron compounds that were prepared via hydroboration of corresponding alkenes (Scheme 21).³¹ The allylic coupling reaction between enantioenriched secondary allylic phosphates and alkylboranes proceeded with γ-regioselectivity and efficient stereospecificity. Moreover, the stereochemical courses of the copper-catalyzed allyl–alkyl coupling were switchable between 1,3-*anti* and 1,3-*syn* selectivities by the choice of solvents and alkoxide bases with different steric demand (Scheme 22).^{31b}

Scheme 21. Copper-catalyzed stereospecific allyl–alkyl coupling with alkylboranes

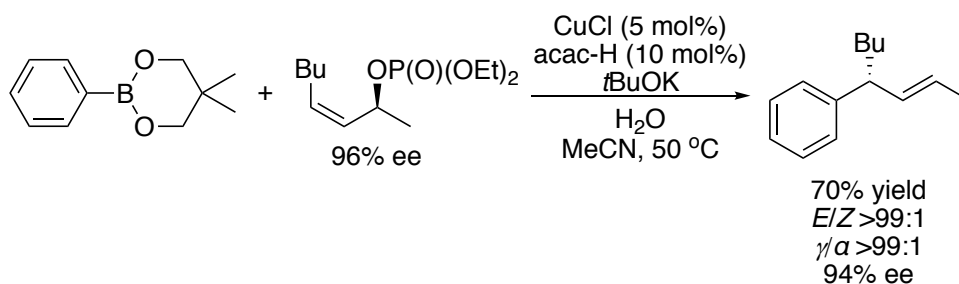


Scheme 22. Stereodivergent coupling reactions with chiral allylic phosphates



The same group developed copper-catalyzed stereospecific allylic substitution of enantioenriched allylic phosphates with arylboronates (Scheme 23).³² This reaction proceeded with excellent γ -selectivity and 1,3-*anti* stereoselectivity.

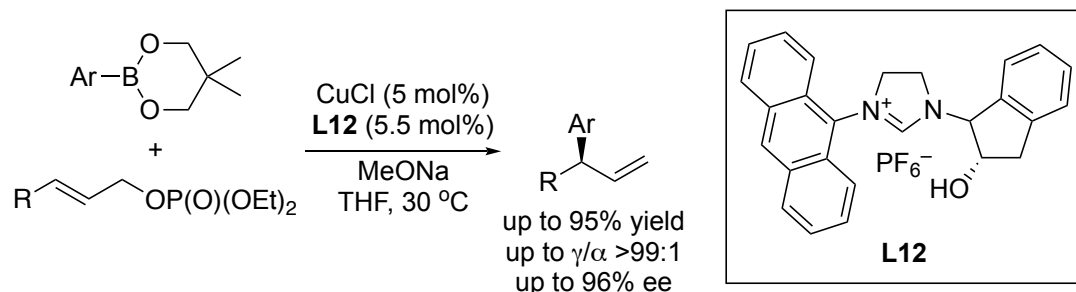
Scheme 23. Copper-catalyzed stereospecific allyl–aryl coupling with arylboronates



Not only stereospecific but also enantioselective allylic substitution using organoboron reagents as nucleophiles are actively studied. For the first example of copper-catalyzed enantioselective allylic coupling of organoboron nucleophiles, Hayashi group developed the Cu-catalyzed enantioselective allylic substitution between aryl boronic acid esters and allylic phosphates in 2011 (Scheme 24).³³ A chiral NHC/copper-catalyzed allylic coupling reaction afforded γ -substitution products with high enantioselectivities. Not only tertiary stereogenic centers but also quaternary stereogenic centers can be constructed with this method. To probe the

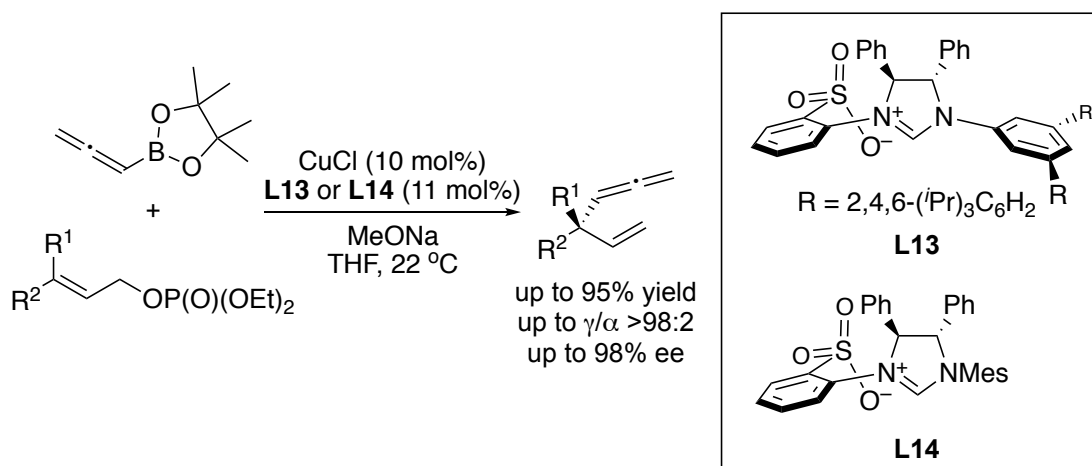
stereochemical outcome, they demonstrated the reaction of an enantioenriched monodeuterated substrate. From the result, it turned out that the allylic coupling reaction proceeded with 1,3-*anti* stereochemistry.

Scheme 24. Copper-catalyzed enantioselective allylic substitution with arylboronates



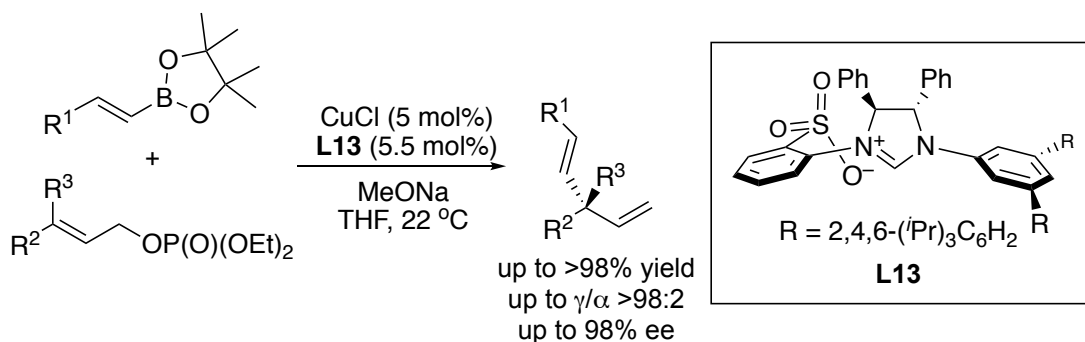
More recently, Hoveyda and co-workers reported related transformations using organoboron reagents. First, they reported the copper-catalyzed enantioselective allylic substitution reaction to introduce an allenyl unit (Scheme 25).³⁴ The transformation proceeded effectively with chiral bidentate NHC ligand bearing sulfonate group. The desired products were generated with up to 95% yield, >98% $\text{S}_{\text{N}}2'$ selectivity, and 98% ee.

Scheme 25. Enantioselective allylic substitution of allenylboronate in copper catalysis



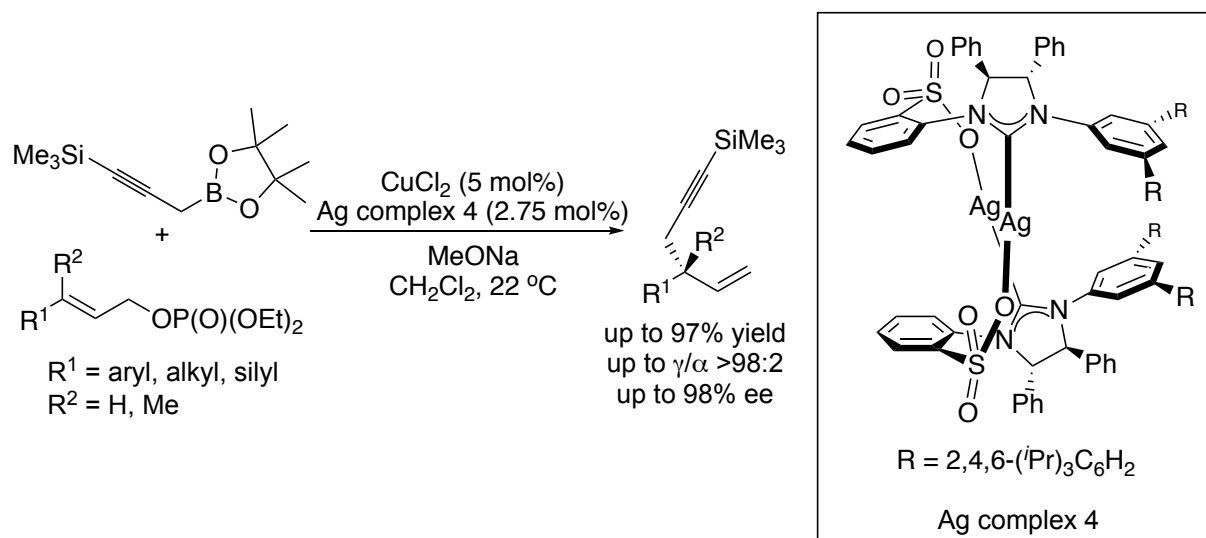
Next, they developed the copper-catalyzed enantioselective allylic cross-couplings of various alkenylboron reagents (Scheme 26).³⁵ The chiral NHC/copper-catalyzed reactions enabled to access a considerable range of chiral 1,4-dienes. Again, both tertiary and quaternary stereogenic centers were constructed with high selectivities. They applied these transformations to asymmetric synthesis of several small natural products.

Scheme 26. Chiral NHC/Cu catalyzed allylic cross-coupling with alkenylboronates



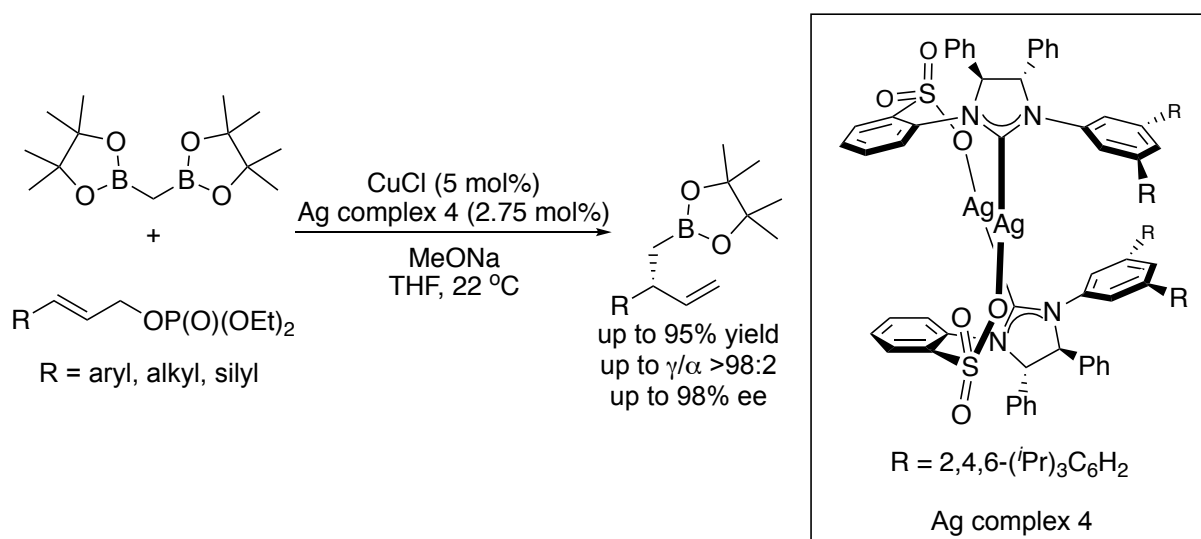
In a following year, they disclosed a novel copper-catalyzed asymmetric allylic substitution with a readily accessible silyl-containing propargylboronate (Scheme 27).³⁶ Chiral 1,5-enyne generated from this method were convertible for the alkyne unit that could be transformed without side reactions involving an alkene unit. In fact, they demonstrated the stereoselective synthesis of the diene fragment of plakinc acid A. They studied the mechanistic details of the reaction with the DFT calculation and the deuterium labeling experiments. The results revealed that chiral NHC ligand may not coordinate to a copper as a bidentate ligand, and a sodium cation bridged between a phosphate leaving group and a sulfonate tethered group. Furthermore, the phosphate leaving group was displaced with *anti* stereochemistry.

Scheme 27. Copper-catalyzed enantioselective allylic substitution with propargylboronate



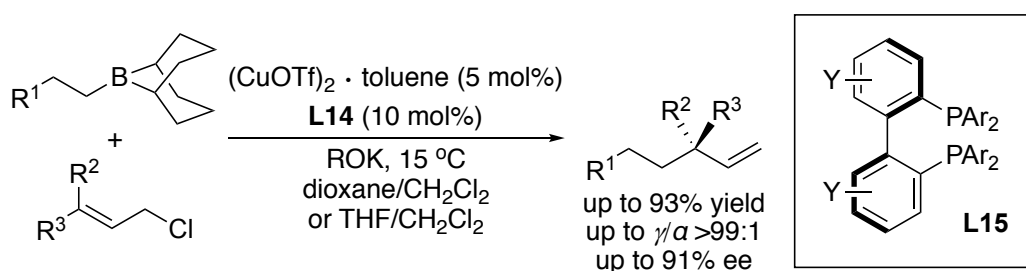
In 2016, the same group developed the copper-catalyzed site- and enantioselective allylic alkylation reactions with a commercially available diborylmethane (Scheme 28).³⁷ The reactions delivered the products containing a versatile C–B(pin) bond with exceptional $\text{S}_{\text{N}}2'$ -type regioselectivity and high enantioselectivity. By utilizing the usefulness of the products, they synthesized useful organic molecules in high enantiomeric purity.

Scheme 28. Catalytic enantioselective allylic substitution with diborylmethane reagent



Sawamura group also reported the allylic coupling reactions of organoboron reagents in copper catalysis. They developed the copper-catalyzed enantioselective allylic substitution of alkylboron compounds with primary allyl chlorides (Scheme 29).³⁸ The reaction under a chiral Cu(I)–DTBM–SEGPHOS system afforded the coupling products with excellent γ -selectivities and high enantioselectivities. By the modification of the reaction conditions, not only tertiary stereogenic centers but also quaternary ones could be constructed. The use of γ -silicon-substituted allyl chlorides in the reaction enabled the synthesis of functionalized chiral allylsilanes. In addition, more recently, they succeeded in the application of this method to enantioselective intramolecular alkylboron allylic alkylation.^{38d} Cyclization reaction with a reductive C–C bond formation produced six-membered ring compounds with a tertiary or quaternary stereogenic center in the ring with high enantioselectivity.

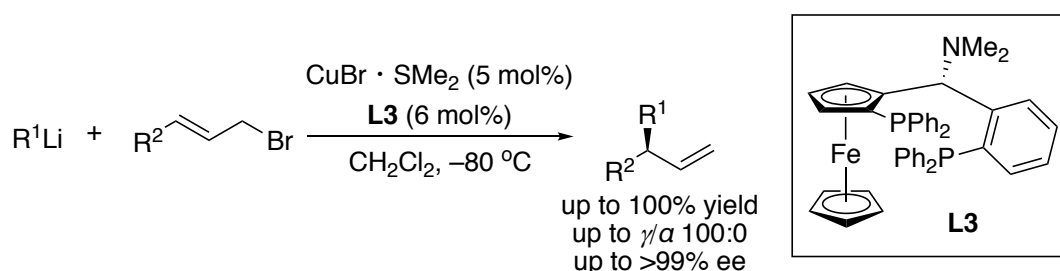
Scheme 29. Copper-catalyzed enantioselective allylic substitution with alkylboranes



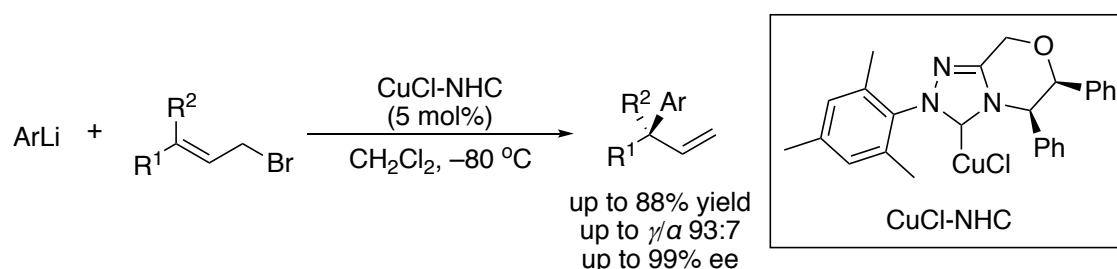
2.2.5. Copper-Catalyzed Asymmetric Allylic Substitution with Other Organometallic Compounds

Recently, the chemistry of the Cu-catalyzed enantioselective allylic coupling reaction has been actively studied for the use of organoboron reagents. This is because they have attractive features for the utilization as a nucleophile. On the other hand, the application of organolithium reagents that are extremely reactive compounds, to copper-catalyzed enantioselective C–C bond formation reactions has been advanced. Organolithium reagents have become the most versatile and widely used reagents in chemical synthesis. In 2011, Feringa group demonstrated the use of organolithium reagents for a general catalytic methodology; the copper-catalyzed asymmetric allylic substitution of alkylolithium compounds with allyl halides proceeded with a useful level of the enantioselectivity under chiral a Taniaphos or phosphoramidite/copper complex (Scheme 30).³⁹ The reactions afforded the products with good regioselectivities and high enantioselectivities. Next, they developed the copper-catalyzed enantioselective allylic arylation reaction with aryllithium compounds (Scheme 31).⁴⁰ The reaction produced chiral diarylmethanes containing tertiary or quaternary stereogenic centers. More recently, the same group reported that the desymmetrization of *meso*-dibromocycloalkenes via copper-catalyzed asymmetric allylic alkylation proceeded with high regio- and enantioselectivities.⁴¹

Scheme 30. Catalytic asymmetric allylic alkylations with organolithium compounds

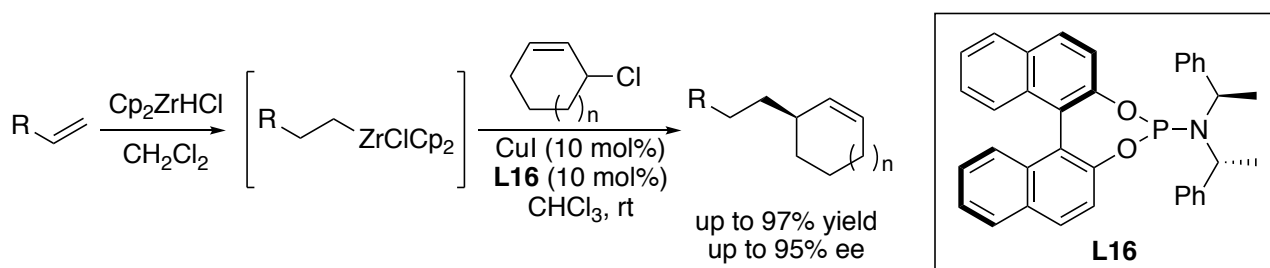


Scheme 31. Copper-catalyzed enantioselective allylic arylation with organolithium reagents



As an example using the other reagent, Fletcher and co-workers developed the Cu-catalyzed dynamic kinetic allylic alkylation of alkylzirconium reagents in 2015 (Scheme 32).⁴² The addition reactions of racemic cyclic allylic chlorides were operated under convenient reaction conditions. They applied the efficient method to the asymmetric synthesis of biologically active natural compounds. Furthermore, they studied the mechanism of the reaction in detail, taking an advantage of the mild reaction condition.

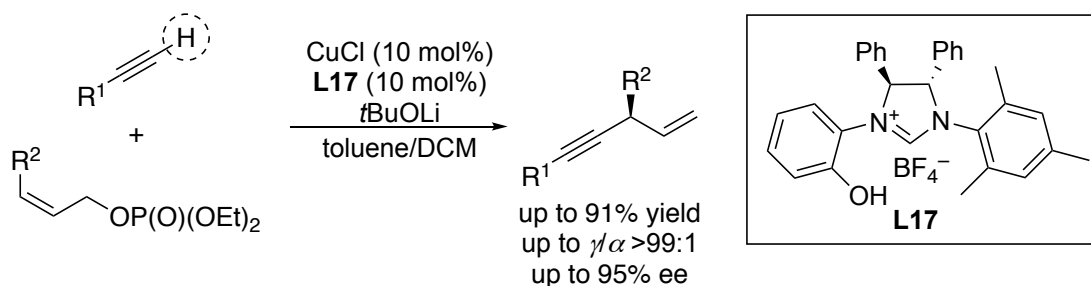
Scheme 32. Dynamic kinetic asymmetric transformation: Copper-catalyzed allylic alkylation



2.2.6. Copper-Catalyzed Asymmetric Allylic Substitution with C–H Pronucleophiles

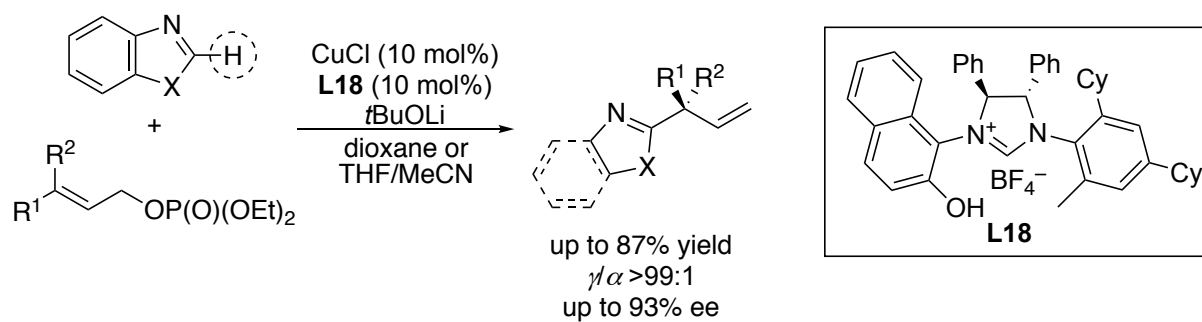
Recently, more advanced methods to afford chiral molecules via copper-catalyzed enantioselective allylic coupling reaction have been developed. Sawamura group developed the enantioselective allylic substitution with terminal alkynes as pronucleophiles (Scheme 33).⁴³ The new chiral NHC ligand bearing a phenolic hydroxyl group at the *ortho* position of one of the two *N*-aryl groups was crucial for the reaction. This reaction proceeded with excellent γ -branch regioselectivity and high enantioselectivity, delivering chiral 1,4-enyne with a tertiary stereogenic center at the allylic/propargylic position. Contrary to the allylic alkynylation reaction developed by Hoveyda group,²⁸ it is not necessary to use organometallic reagents having strongly basic and nucleophilic natures in this method. More recently, Tan group reported the chiral guanidine-copper complex catalyzed dynamic kinetic asymmetric transformation of racemic allyl bromides with terminal alkyne pronucleophiles.⁴⁴

Scheme 33. Copper-catalyzed enantioselective allylic substitution of terminal alkyne as pronucleophile



The Sawamura group disclosed the utility of a class of Phenol–NHC ligand in copper-catalyzed enantioselective allylic substitution of azoles with γ,γ -disubstituted primary allylic phosphates (Scheme 34).⁴⁵ An all-carbon quaternary stereogenic center at α position to the heteroaromatic ring was constructed in high enantiocontrol. This high enantioselectivity was controlled by a new chiral NHC ligand installed with naphtholic hydroxyl group instead of phenolic one.

Scheme 34. Copper-catalyzed enantioselective allylic substitution of azoles



The use of C–H pronucleophiles are excellent and advanced in copper-catalyzed asymmetric allylic substitutions. However, reactive agents for the copper catalysis are limited to the compounds bearing a C(sp)–H or C(sp²)–H bond with relatively high acidity.

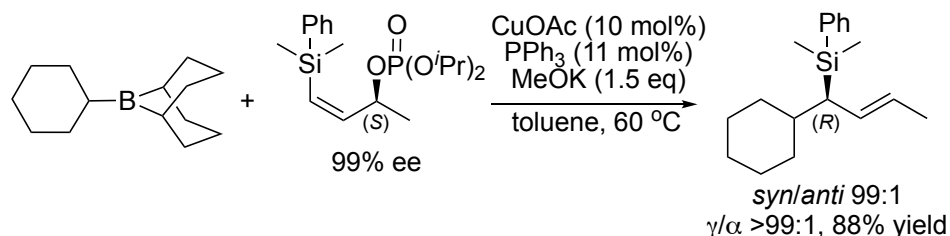
3. Overview of This Thesis

The author developed the copper-catalyzed asymmetric allylic cross-coupling with organoboron reagents. These reactions proceeded with high regioselectivities and stereoselectivities. In Chapter 1, the advancement of the organoboron chemistry under an achiral Cu(I)/PPh₃ system is described. In Chapter 2–4, the catalytic asymmetric reactions are described: the enantioselective allylic cross-couplings of organoboron reagents in copper catalysis using a chiral NHC ligand bearing a phenolic hydroxyl group, are discussed. In Chapter 2 and 3, the author describes the development of the reaction of allyl- and allenyl boronic acid esters with (*Z*)-primary allylic phosphates in the enantioselective allylation reaction. In Chapter 4, the new synthetic strategy for the construction of cyclopropanes containing a tertiary stereogenic center via copper-catalyzed asymmetric allylic substitution is described.

3.1. Copper-Catalyzed γ -Regioselective and Stereospecific Allylic Cross-Coupling with Secondary Alkylboranes

Recently, the author's laboratory reported the copper-catalyzed stereospecific allylic substitution of B-alkyl-9-borabicyclo[3.3.1]nonane (alkyl-9-BBN) with enantioenriched secondary allylic phosphates. The reaction mainly proceeded with 1,3-*anti* stereochemistry. Following this report, the same group disclosed the stereodivergency with the choice of solvents and alkoxide bases in the allyl–alkyl couplings between chiral allylic phosphates and alkylboranes. However, secondary alkylboranes were not available for these reactions. In Chapter 1, the author describes the demonstration of applicability of secondary organoboron compounds in stereospecific allylic alkylations under a Cu(I) catalyst system (Scheme 35). The copper-catalyzed allyl–alkyl coupling between secondary (*Z*)-allylic phosphates and secondary alkyl-9-BBN proceeded with complete γ -*E*-selectivity and high 1,3-*syn* stereoselectivity. The reactions with γ -silicon-substituted allylic phosphates as an allylic substrate afforded the efficient synthesis of enantioenriched α -stereogenic allylsilanes.

Scheme 35. Copper-catalyzed stereospecific allylic alkylation with secondary alkylboranes

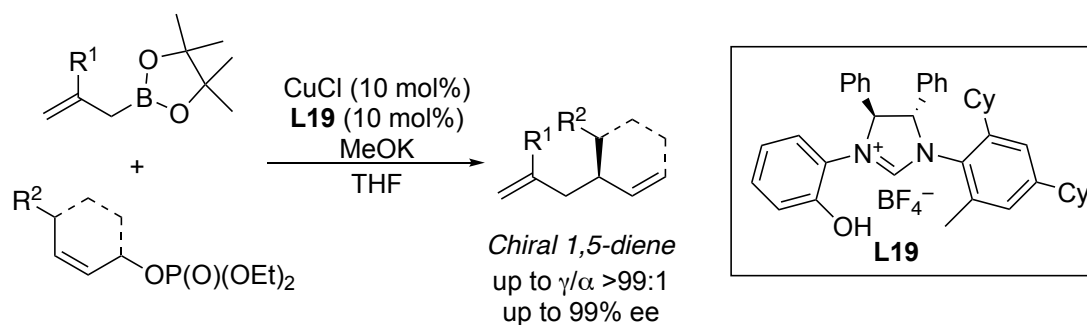


3.2. Copper-Catalyzed Enantioselective Allyl–Allyl Cross-Coupling between Allylboronates and Allylic Phosphates with a Phenol/NHC Chiral Ligand

In Chapter 2, the author describes the copper-catalyzed enantioselective allyl–allyl cross-coupling between allylboronates and primary allylic phosphates (Scheme 36). Using a chiral *N*-heterocyclic carbene ligand

bearing a phenolic hydroxy group at the ortho position of one of the two *N*-aryl groups, this reaction proceeded with exceptional S_N2'-type regioselectivity and high enantioselectivities to deliver chiral 1,5-diene derivatives with a tertiary carbon stereogenic center at the allylic/homoallylic position. Acid- or base-sensitive functional groups were compatible with this enantioselective reaction. *Z*-Aliphatic allylic substrates including acyclic and cyclic 2-alkene-1,4-diol derivatives can be used.

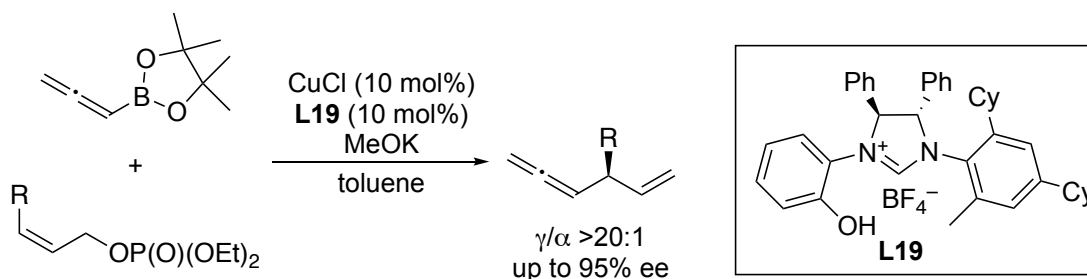
Scheme 36. Copper-catalyzed enantioselective allyl–allyl cross-coupling with allylboronates



3.3. Copper-Catalyzed Enantioselective Allylic Cross-Coupling between Allenylboronate and Primary Allylic Phosphates with a Phenol/NHC Chiral Ligand

The author developed the Cu-catalyzed enantioselective allyl–allyl coupling with allylboronates (Chapter 2). This work demonstrated the general utility of this class of chiral ligands for enantioselective copper catalysis with organoboron reagents. Based on the result, the author further applied the ligands to reactions with an allenylboronate (Scheme 37). The reactions under a Phenol/NHC chiral ligand proceeded with excellent γ-regioselectivity and high enantioselectivity.

Scheme 37. Copper-catalyzed asymmetric allylic allenylation using Phenol–NHC chiral ligand

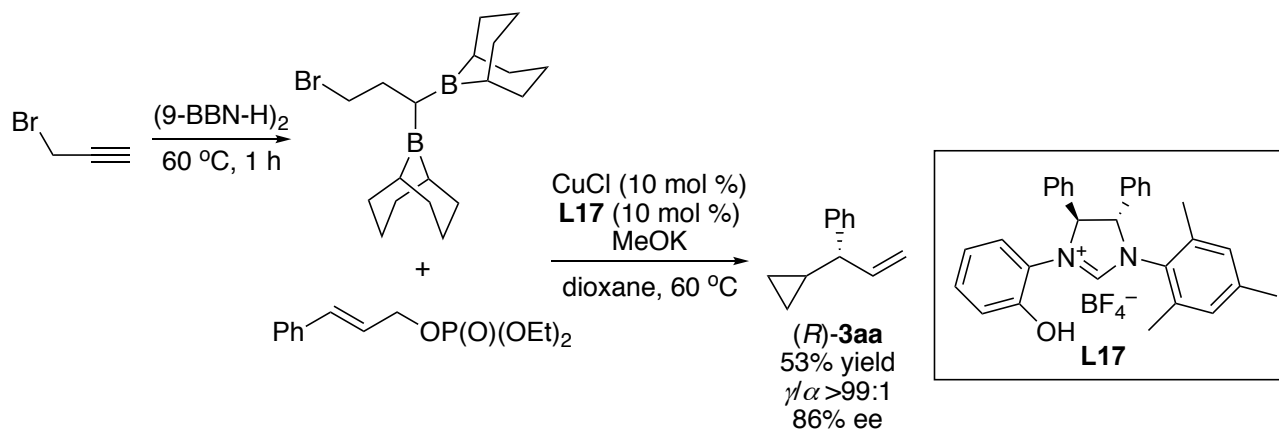


3.4. Copper-Catalyzed Enantioselective Allylic Cyclopropylation with 3-Bromo-1,1-diborylpropane using a Phenol/NHC Chiral Ligand

Cyclopropanes are beneficial and widely observed motif in natural products and pharmaceutical compounds. The representative synthetic methods are Simmons-Smith reaction and Kulinkovich reaction. However, compounds synthesized by these methods are limited, and a new synthetic strategy is demanded for an

asymmetric synthesis. In Chapter 4, the author describes the new synthetic method for various chiral compounds containing a cyclopropyl unit (Scheme 38). The copper-catalyzed enantioselective allylic alkylation reactions of 3-bromo-1,1-diborylpropane that is prepared via hydroboration of a propargyl bromide, proceeded γ -selectively with high enantioselectivity under the use of a Phenol/NHC chiral ligand.

Scheme 38. One-pot synthesis of chiral allylcyclopropane via copper-catalyzed asymmetric allylic substitution



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Chapter 1

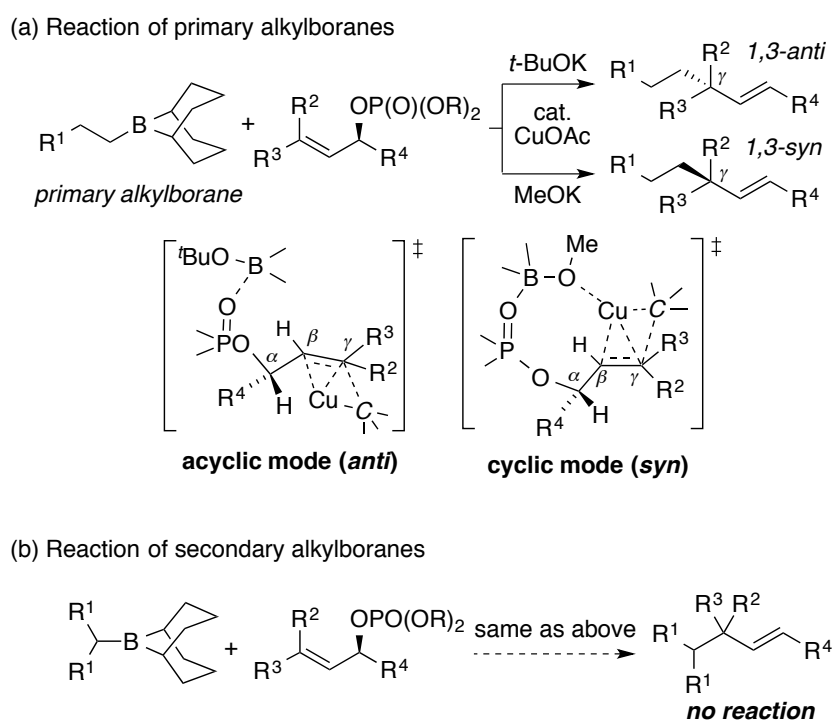
Copper-Catalyzed γ -Regioselective and Stereospecific Allylic Cross-Coupling with Secondary Alkylboranes

Introduction

Copper-catalyzed allylic substitutions with organoboron compounds are of interest due to their broad substrate scope.^{1,2} Previously the author's laboratory reported that sp^3 -alkylboron compounds, such as *B*-alkyl-9-borabicyclo[3.3.1]nonane (alkyl-9-BBN), can be coupled with internal allylic systems with complete γ -selectivity by using a catalytic amount of a copper(I) salt and a stoichiometric potassium alkoxide base.³⁻⁵ Interestingly, the stereochemistry of the cross-coupling between enantioenriched chiral allylic phosphates and alkylboranes could be switched between the 1,3-*anti* and 1,3-*syn* forms relative to the leaving group by choosing the appropriate achiral alkoxide base with a specific steric demand; *t*BuOK and MeOK led to 1,3-*anti* and 1,3-*syn* stereochemistry, respectively.^{3c} Acyclic and cyclic bimodal participation of alkoxyborane species generated in situ in an organocopper addition–elimination sequence was proposed to account for the phenomenon of the *anti/syn* stereochemical reversal (Scheme 1a). However, only primary alkylboron compounds could be used as nucleophilic coupling partners. Neither the 1,3-*anti* nor the 1,3-*syn* form was effective in the reaction of secondary alkylboranes, probably due to increased steric demands of the transferring groups (Scheme 1b).

In Chapter 1, the author describes the dramatic ligand effects of tertiary monophosphines such as PPh_3 , PCy_3 , and $PtBu_3$, which enabled copper-catalyzed allylic cross-coupling between secondary alkylboron compounds, such as alkyl-9-BBN, and (*Z*)-acyclic or cyclic allylic phosphates. These ligand effects were most pronounced when the ligands were used as additives for the 1,3-*syn*-selective protocol (CuOAc/MeOK/toluene) in a previous study.⁶ This new copper catalysis using secondary alkylboranes proceeded with complete γ -*E*-selectivity and preferential 1,3-*syn* stereoselectivity. These methods significantly broaden the scope of allylic C–C cross-coupling reactions.

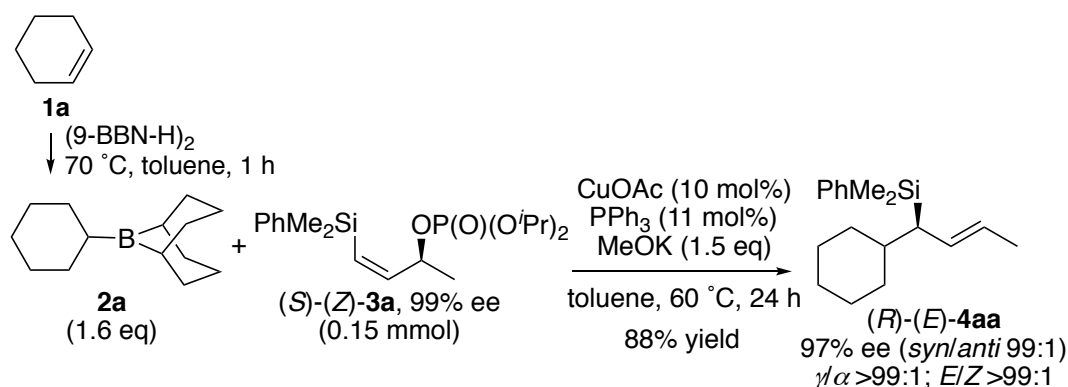
Scheme 1. Previous work^{3c}: (a) reaction of primary alkylboranes; (b) reaction of secondary alkylboranes



Results and Discussion

In numerous studies for finding reaction conditions enabling the regio- and stereoselective coupling between secondary alkylboron compounds and chiral secondary allylic electrophiles, we found critical effects of phosphine ligands for promoting this transformation. Specifically, the reaction between cyclohexylborane **2a**, which was prepared by hydroboration of cyclohexene (**1a**), and an enantioenriched chiral γ -silylated allylic phosphate, (*S*)-(*Z*)-**3a** (99% ee) containing a diisopropyl phosphate leaving group afforded allylsilane (*R*)-(*E*)-**4aa** with 97% ee and 88% yield with complete γ - and *E*-selectivities (Scheme 2 and Table 1, entry 3).⁷

Scheme 2. Hydroboration/copper-catalyzed γ -*syn*-selective allylic cross-coupling sequence



The (*R*) absolute configuration of **4aa** was determined by transforming it to chiral homoallylic alcohol by the established TiCl_4 -mediated addition of allylsilane to aldehyde (TiCl_4 , *i*PrCHO, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 2 h),⁸ followed by Mosher's NMR spectroscopic method (Figure 1).⁹

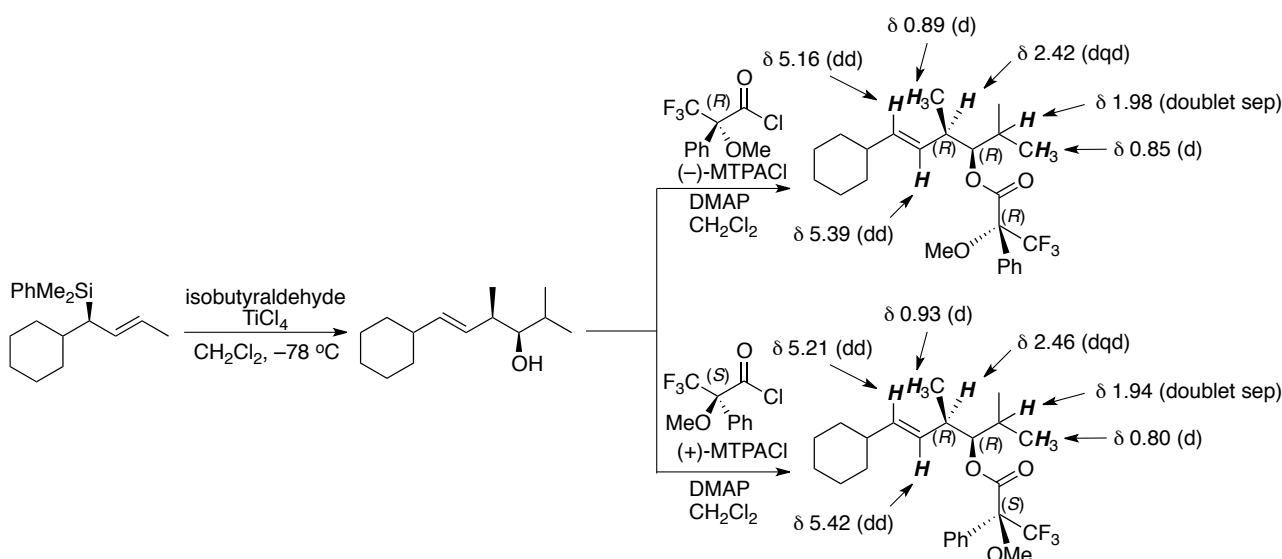


Figure 1. Mosher's NMR spectroscopic method

The absolute configuration of the coupling product indicated that the reaction occurred with 1,3-*syn* stereochemistry (*syn/anti* 99:1). The reported phosphine-free conditions, which gave 1,3-*syn* ($\text{CuOAc}/\text{MeOK}/$

toluene) or 1,3-*anti* (CuOAc/*t*BuOK/THF) stereochemical outcomes in a previous study on the reaction of primary alkylboranes (Scheme 1a), produced no coupling product, leaving the substrates almost unreacted (Table 1, entries 1 and 2).^{3c,10} The effect of ligands on the reaction between **2a** and **3a** are shown in Table 1. Use of tri(4-methoxyphenyl)phosphine resulted in a significantly lower product yield and *syn*-stereoselectivity compared to PPh₃ (Table 1, entry 4). No reaction occurred with the electron-deficient P[3,5-(CF₃)₂C₆H₃]₃ ligand (Table 1, entry 5). Use of PMe₃ produced a very low yield with moderate *syn* selectivity (*syn/anti* 88:12; Table 1, entry 6). The phosphine ligands PEt₃ and PBu₃ both promoted the coupling efficiently, but *syn* selectivity was slightly decreased compared to the excellent selectivity obtained with PPh₃ (Table 1, entries 7 and 8). Interestingly, the bulkier monodentate trialkylphosphines, such as PCy₃ and P*t*Bu₃, were as effective as PPh₃ in terms of both product yield and *syn* selectivity (Table 1, entries 9 and 10). In contrast, bisphosphines such as DPPE and Xantphos, produced no reaction (Table 1, entries 11 and 12). Monodentate *N*-heterocyclic carbene (NHC) ligands, such as IMes, SIMes, IPr, and SIPr, did not promote the reaction either (Table 1, entries 13–16). Thus, PPh₃ was selected as the most useful additive for cost-effectiveness and ease of handling (Scheme 2 and Table 1, entry 3).¹¹

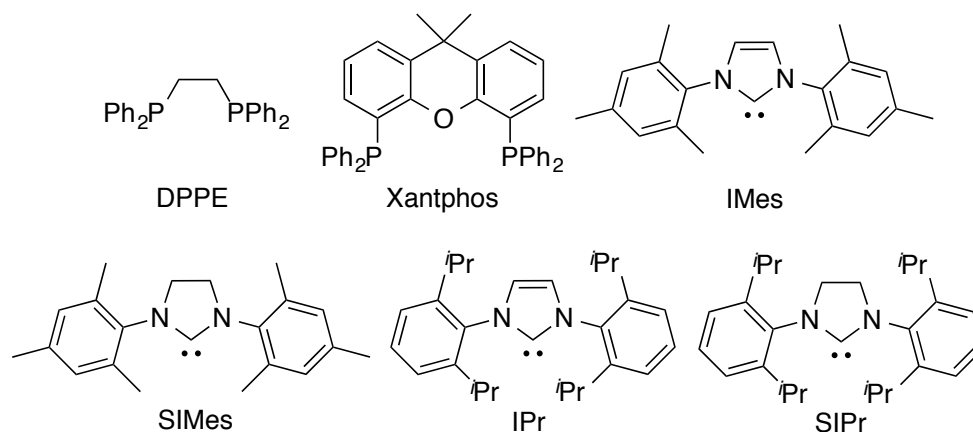
The effect of the stoichiometric base is also shown in Table 1. The use of EtOK instead of MeOK in the presence of PPh₃ resulted in a slight decrease in the *syn*-stereoselectivity (Table 1, entry 17). No reaction occurred with the sterically more demanding base *t*BuOK, which induced 1,3-*anti* stereochemistry under phosphine-free conditions in the reaction of primary alkylboranes (Table 1, entry 18).¹²

Table 1. Effects of ligands and bases^[a,b]

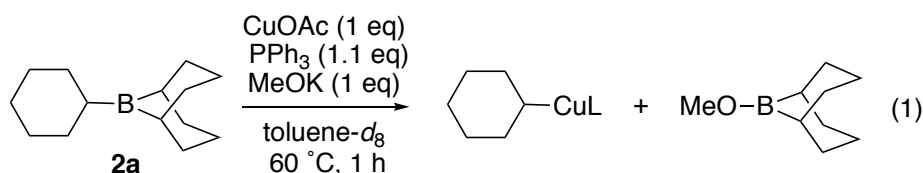
entry	ligand	base	yield ^[c,d] (%)	<i>syn:anti</i> ^[e]
1	none	MeOK	0	—
2	none	<i>t</i> BuOK	0	—
3	PPh ₃ (eq 1)	MeOK	88	99.5:0.5
4	P(4-MeOC ₆ H ₄) ₃	MeOK	55	96.5:3.5
5	P[3,5-(CF ₃) ₂ C ₆ H ₃] ₃	MeOK	0	—
6	PMe ₃	MeOK	13	88:12
7	PEt ₃	MeOK	95	98.5:1.5
8	PBu ₃	MeOK	90	92:8
9	PCy ₃	MeOK	93	99:1
10	P <i>t</i> Bu ₃	MeOK	83	99:1
11	DPPE	MeOK	0	—
12	Xantphos	MeOK	0	—
13	IMes	MeOK	0	—
14	SIMes	MeOK	0	—

15	IPr	MeOK	0	—
16	SIPr	MeOK	0	—
17	PPh ₃	EtOK	99	98:2
18	PPh ₃	^t BuOK	0	—

[a] Reaction was conducted using **3** (0.15 mmol), alkylborane **2** (0.24 mmol), CuOAc (10 mol%), ligand (11 mol%), and base (0.225 mmol) in toluene at 60 °C for 24 h. [b] Alkylborane **2** was prepared in advance by hydroboration of alkene **1** with 9-BBN dimer in toluene at 70 °C for 1 h and used without purification. [c] Isolated yield of product based on **3**. [d] Isomeric ratios ($\gamma/\alpha > 99:1$, $E/Z > 99:1$). Determined by ¹H NMR or GC of the crude product. [e] Selectivity was determined by HPLC.



To gain understanding of the mechanism of Cu-catalyzed cross-coupling with secondary alkylboranes, the effect of PPh₃ on the stoichiometric reaction of CuOAc, MeOK, and cyclohexylborane **2a** was investigated [Eq. (1)].



The stoichiometric reaction in the presence of PPh₃ is representative. The mixture of (9-BBN-H)₂ (36.7 mg, 0.15 mmol) and cyclohexene (**1a**) (31.9 μ l, 0.32 mmol) in toluene-*d*₈ (0.3 mL) was stirred at 70 °C for 1 h to prepare cyclohexylborane **2a**¹³ (δ 86.4 ppm, ¹¹B NMR) (Figure 2). Next, the alkylborane solution was added to the mixture of CuOAc (36.8 mg, 0.3 mmol), PPh₃ (86.6 mg, 0.33 mmol) and MeOK (21.0 mg, 0.3 mmol) in toluene-*d*₈ (0.3 mL) at 25 °C, and the solution was heated at 60 °C for 1 h: the peak of **2a** disappeared completely and a signal that corresponds to 9-BBN-OMe¹⁴ appeared at 55.5 ppm as a major peak in the ¹¹B NMR spectrum (Figure 3). In contrast, reaction in the absence of PPh₃ did not result in formation of 9-BBN-OMe (Figure 4), indicating that PPh₃ is essential for B/Cu transmetalation.

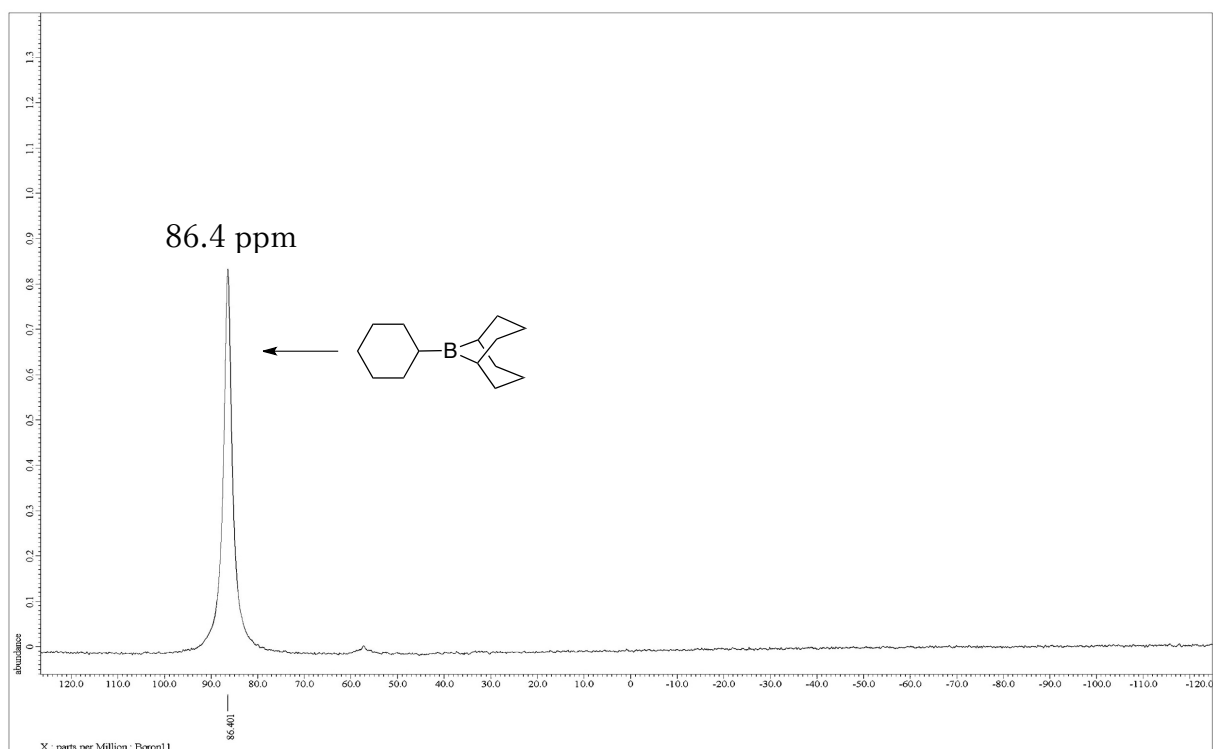


Figure 2. ^{11}B NMR spectrum for Cyclohexyl-9-BBN **2a** (128 MHz, toluene- d_8)

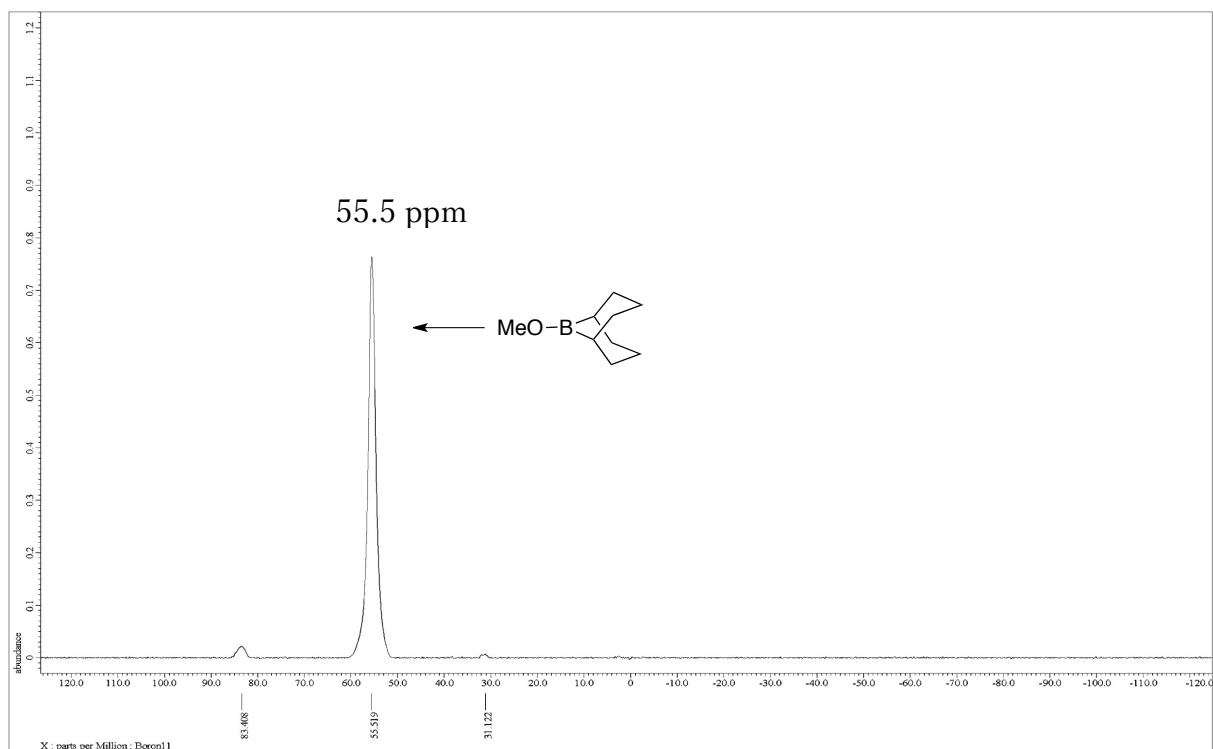


Figure 3. ^{11}B NMR spectrum for the reaction in the presence of PPh_3 (128 MHz, toluene- d_8)

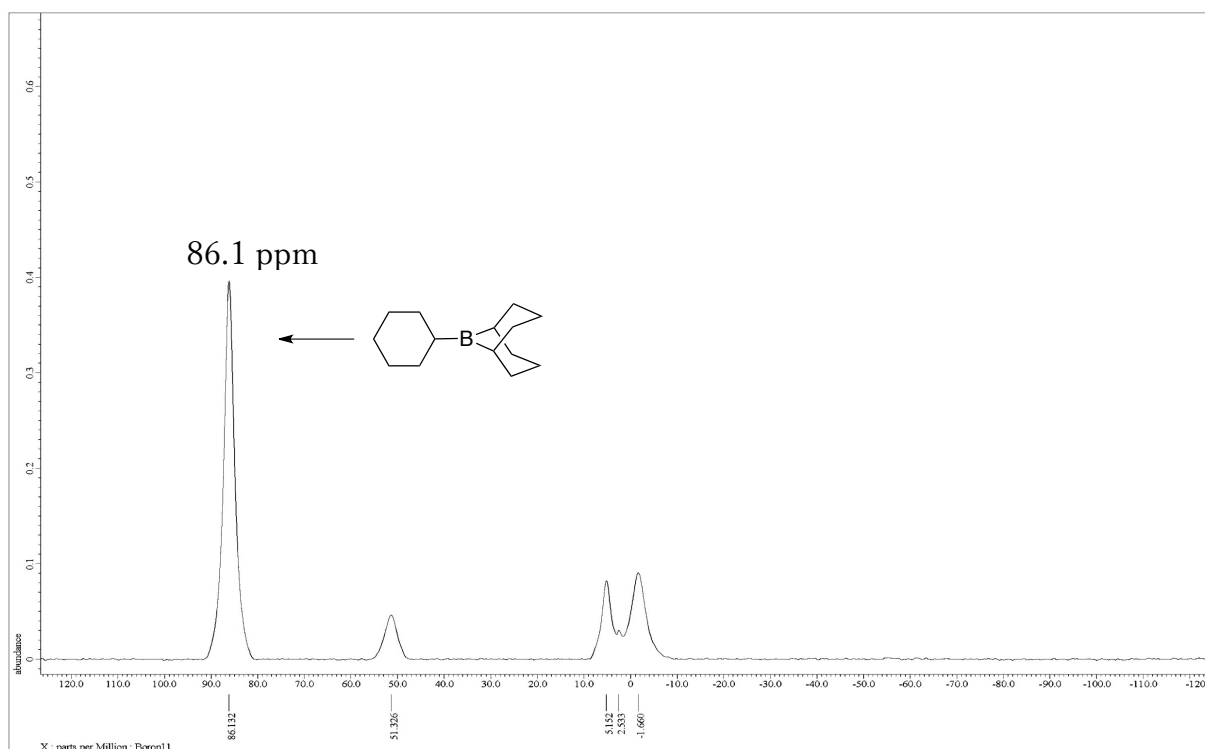
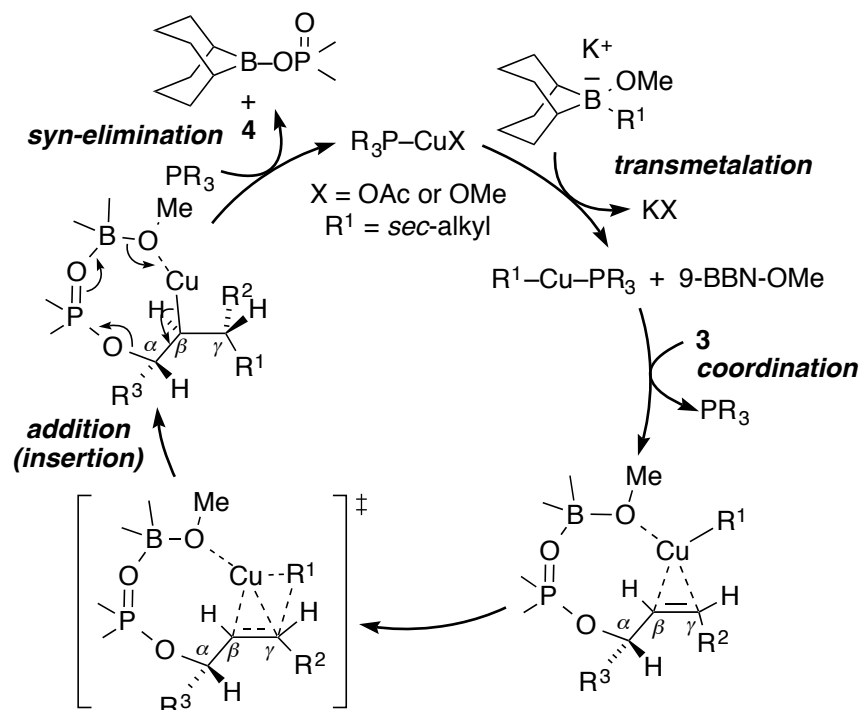


Figure 4. ^{11}B NMR spectrum for the reaction in the absence of PPh_3 (128 MHz, $\text{toluene-}d_8$)

Molecular modeling studies suggested that tertiary monophosphines would not be able to coordinate to the copper center in the cyclic organocopper addition–elimination transition state due to steric effects (Scheme 1 a).¹⁵ Therefore, a catalytic cycle for the copper-catalyzed γ -*syn*-selective allylic cross-coupling with secondary alkylboranes should involve coordination and dissociation of the phosphine ligand as shown in Scheme 3. According to these considerations, the reduction of yield and *syn* selectivity in the reaction with PMe_3 may suggest that the Cu–P interaction would be persistent in the addition–elimination step. This should be reasonable, considering the higher coordination ability of PMe_3 as a compact ligand. The marginal reduction of the *syn* selectivity in the reactions with PEt_3 and PBu_3 may be due to partial coordination of these ligands in the addition–elimination step. In this context, the common features of PPh_3 , PCy_3 , and PtBu_3 , showing the high product yields and *syn* selectivities, may be due to their moderate coordination abilities toward Cu, allowing timely coordination/dissociation equilibria; bulky phosphine ligand may have only a role to form an active specie for B/Cu transmetalation step.

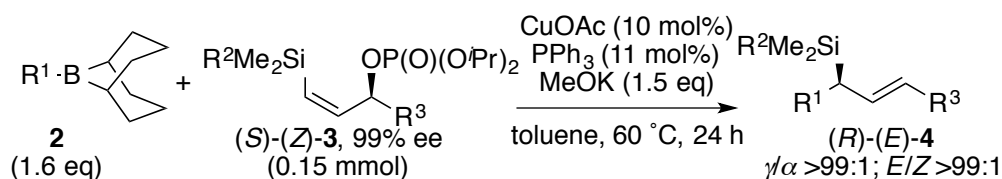
Scheme 3. Proposed catalytic cycle for the copper-catalyzed γ -*syn*-selective allylic cross-coupling between secondary alkylboranes and secondary allylic phosphates.

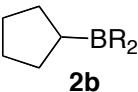
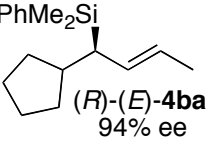
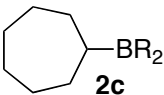
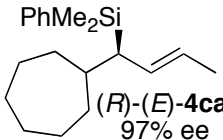
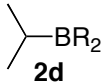
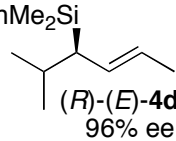
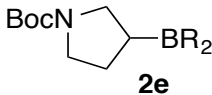
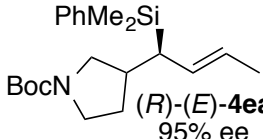
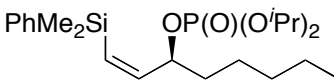
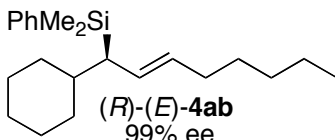
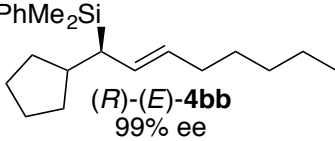
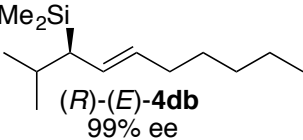
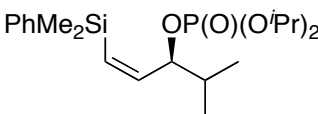
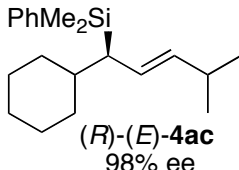
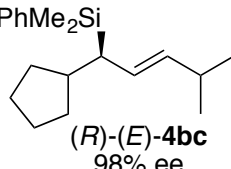


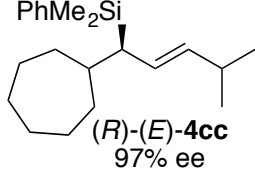
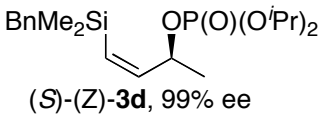
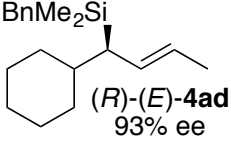
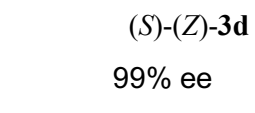
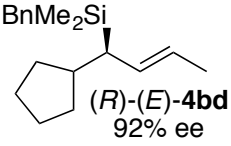
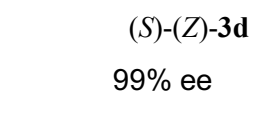
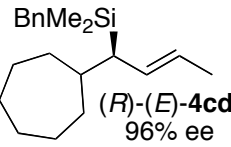
The scope of copper-catalyzed regioselective and stereospecific cross-coupling reaction between secondary alkylboranes and enantioenriched chiral γ -silylated allylic phosphates to afford enantioenriched α -stereogenic chiral allylsilanes is summarized in Table 2.^{8,16,17} Cyclic secondary alkylboranes **2b** and **2c**, with five- and seven-membered carbocycles, underwent reaction with excellent *syn*-stereoselectivities (Table 2, entries 1 and 2). Acyclic isopropylborane **2d** was also tolerated, with a high level of stereoselectivity retained (Table 2, entries 3 and 7). The heterocyclic secondary alkylborane **2e**, with a carbamate group, underwent stereospecific reaction resulting in a moderate product yield (Table 2, entry 4).

The methyl group at the α -position of **3a** could be replaced with *n*-pentyl (**3b**) or isopropyl (**3c**) groups with excellent *syn* selectivity retained (Table 2, entries 5–10). The allylic phosphate (*S*)-(*Z*)-**3d**, with a BnMe₂Si group at the γ -position, reacted with cyclic secondary alkylboranes containing five-, six-, and seven-membered carbocycles with excellent *syn* selectivities (Table 2, entries 11–13).

Table 2. Synthesis of chiral allylsilanes^[a,b]



entry	borane	phosphate	product	yield ^[c,d] (%)	syn:anti ^[e]
1	 2b	(<i>S</i>)-(Z)- 3a 99% ee	 (<i>R</i>)-(E)- 4ba 94% ee	93	97.5:2.5
2	 2c	(<i>S</i>)-(Z)- 3a 99% ee	 (<i>R</i>)-(E)- 4ca 97% ee	80	99:1
3	 2d	(<i>S</i>)-(Z)- 3a 99% ee	 (<i>R</i>)-(E)- 4da 96% ee	94	98.5:1.5
4 ^[f]	 2e	(<i>S</i>)-(Z)- 3a 99% ee	 (<i>R</i>)-(E)- 4ea 95% ee	47 ^[f]	98:2
5	2a	 (<i>S</i>)-(Z)- 3b , 99% ee	 (<i>R</i>)-(E)- 4ab 99% ee	94	>99.5:0.5
6	2b	(<i>S</i>)-(Z)- 3b 99% ee	 (<i>R</i>)-(E)- 4bb 99% ee	93	>99.5:0.5
7	2d	(<i>S</i>)-(Z)- 3b 99% ee	 (<i>R</i>)-(E)- 4db 99% ee	88	>99.5:0.5
8	2a	 (<i>S</i>)-(Z)- 3c , 99% ee	 (<i>R</i>)-(E)- 4ac 98% ee	93	99.5:0.5
9	2b	(<i>S</i>)-(Z)- 3c 99% ee	 (<i>R</i>)-(E)- 4bc 98% ee	96	99.5:0.5

10	2c	 <i>(S)-(Z)</i> - 3c 99% ee	 <i>(R)-(E)</i> - 4cc 97% ee	38	99:1
11	2a	 <i>(S)-(Z)</i> - 3d , 99% ee	 <i>(R)-(E)</i> - 4ad 93% ee	31	97:3
12	2b	 <i>(S)-(Z)</i> - 3d 99% ee	 <i>(R)-(E)</i> - 4bd 92% ee	75	96.5:3.5
13	2c	 <i>(S)-(Z)</i> - 3d 99% ee	 <i>(R)-(E)</i> - 4cd 96% ee	61	98.5:1.5

[a] Reaction was conducted with **3** (0.15 mmol), alkylborane **2** (0.24 mmol), CuOAc (10 mol%), PPh₃ (11 mol%), and MeOK (0.225 mmol) in toluene at 60 °C for 24 h. [b] Alkylborane **2** was prepared in advance by hydroboration of alkene **1** with 9-BBN dimer in toluene at 70 °C for 1 h and used without purification. [c] Isolated yield of the product based on **3**. [d] Isomeric ratios ($\gamma/\alpha > 99:1$, $E/Z > 99:1$). Determined by ¹H NMR or GC of the crude product. [e] Enantiomeric excess was determined by HPLC. [f] Diastereomeric ratio (1:1).

The usefulness of this protocol was not limited to allylsilane synthesis but could also be applied to reactions of non-silicon-substituted acyclic allylic phosphates (Table 3). For example, the reaction between allylic phosphate (*S*)-(*Z*)-**5a** (97%ee) and cyclohexylborane **2a** occurred with 96% *syn* selectivity to produce the Me-branched product (*R*)-(*E*)-**6aa** (Table 3, entry 1). The absolute configuration of **6aa** was confirmed by transforming it to the 2-cyclohexyl-1-propanol (Scheme 4). [α]_D²⁴ +1.5 (*c* 0.35, CHCl₃), [lit¹⁸, *R* isomer, 65% ee, [α]_D²⁰ +1.60 (*c* 1.3, CH₂Cl₂)]. Reaction of cyclic secondary alkylboranes with a five- or a seven-membered ring also occurred, but 1,3-*syn* stereoselectivity was only moderate (Table 3, entries 2 and 3).

Scheme 4. Derivatization of **6aa** for determining absolute configuration

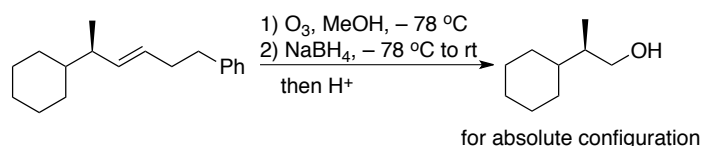
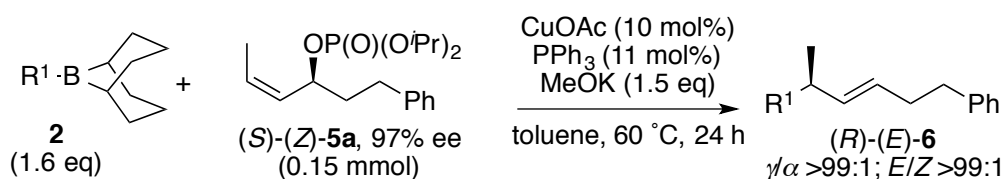
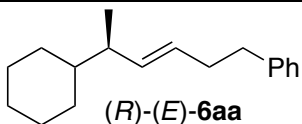
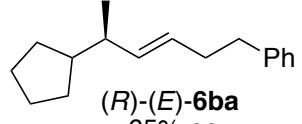
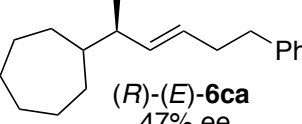


Table 3. Allyl-alkyl coupling with non-silicon-substituted allylic phosphates^[a,b]



entry	borane	product	yield ^[c,d] (%)	syn:anti ^[e]
1	2a	 <i>(R)</i> -(<i>E</i>)- 6aa 89% ee	88	96:4
2	2b	 <i>(R)</i> -(<i>E</i>)- 6ba 65% ee	98	84:16
3	2c	 <i>(R)</i> -(<i>E</i>)- 6ca 47% ee	78	74.5:25.5

[a] The reaction was carried out with **5** (0.15 mmol), alkylborane **2** (0.24 mmol), CuOAc (10 mol %), PPh₃ (11 mol %), and MeOK (0.225 mmol) in toluene at 60 °C for 24 h. [b] Alkylborane **2** was prepared in advance by hydroboration of alkene **1** with 9-BBN dimer in toluene at 70 °C for 1 h and used without purification. [c] Yield of the isolated product based on **5**. [d] Isomeric ratios ($\gamma/\alpha > 99:1$, *E/Z* > 99:1). Determined by ¹H NMR or GC of the crude product. [e] The enantiomeric excess was determined by HPLC.

Cyclic allylic phosphates also could serve as substrates (Table 4). Coupling reactions between *trans*-2-cyclohexene-1,4-diol derivative **7a** and **2a** proceeded with excellent γ -selectivity and 1,3-*syn* selectivity relative to the leaving group, giving *trans*-1,2-isomer **8aa** (Table 4, entry 1). The stereochemistry of **8aa** was assigned on the basis of ¹H NMR of the alcohol derivative¹⁹ obtained by desilylation followed by alkene reduction from **8aa** (Scheme 5). Reactions with cyclopentyl or cycloheptylboranes also occurred with excellent 1,3-*syn* selectivity (Table 4, entries 2 and 3). *Trans*-3-cyclohexene-1,2-diol derivative **7b** also underwent coupling with excellent 1,3-*syn* selectivity (Table 4, entry 4).

Scheme 5. Derivatization of **8aa**

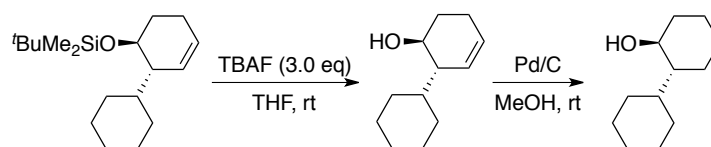
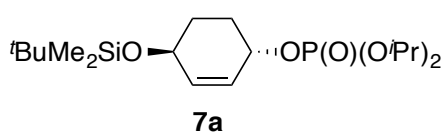
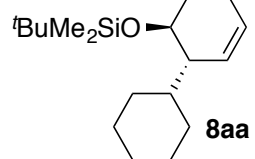
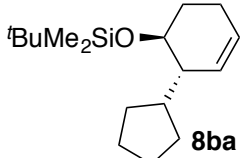
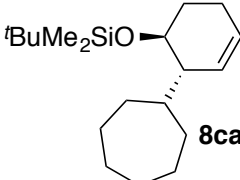
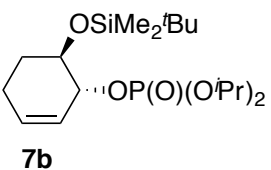
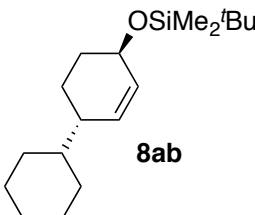


Table 4. Allyl–alkyl coupling with cyclic allylic phosphates^[a,b]

entry	borane	phosphate	product	yield ^[c,d] (%)	syn:anti ^[e]
1	2a	 7a	 8aa	85	>99:1

2	2b	7a	 8ba	90	>99:1
3	2c	7a	 8ca	73	>99:1
4	2a	 7b	 8ab	49	93:7

[a] Reaction was conducted with **7** (0.15 mmol), alkylborane **2** (0.24 mmol), CuOAc (10 mol%), PPh₃ (11 mol%), and MeOK (0.225 mmol) in toluene at 60 °C for 24 h. [b] Alkylborane **2** was prepared in advance by hydroboration of alkene **1** with 9-BBN dimer in toluene at 70 °C for 1 h and used without purification. [c] Isolated yield of the product based on **7**. [d] Isomeric ratios (γ/α >99:1, *E/Z* >99:1). Determined by ¹H NMR or GC of the crude product. [e] The syn:anti selectivity was determined by ¹H NMR.

Conclusion

In summary, the scope of copper-catalyzed coupling reactions between organoboron compounds and allylic phosphates was broadened significantly by employing triphenylphosphine as a ligand for copper, allowing the use of secondary alkylboron compounds such as alkyl-9-BBN. The reaction proceeded with complete γ -*E*-selectivity and preferential 1,3-*syn* stereoselectivity. This is the first catalytic allylic substitution reaction with secondary alkylboron derivatives.

Experimental Section

Instrumental and Chemical

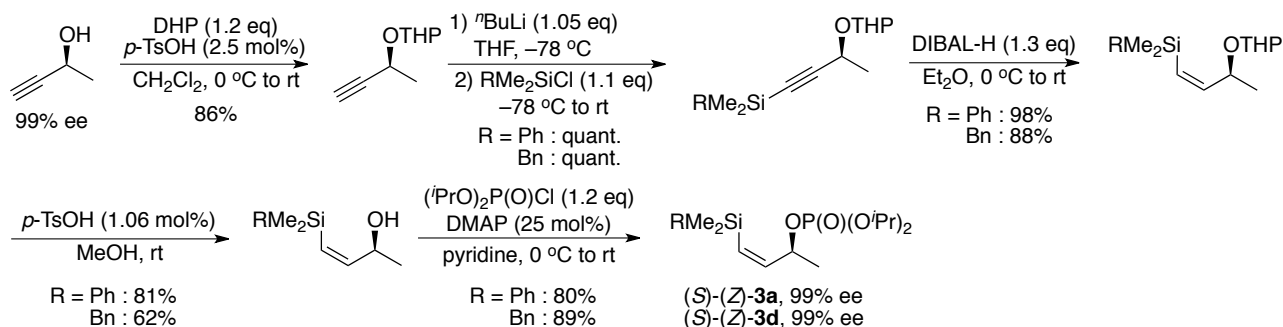
NMR spectra were recorded on a JEOL ECX-400, operating at 400 MHz for ^1H NMR, 100.5 MHz for ^{13}C NMR and 128 MHz for ^{11}B NMR. Chemical shift values for ^1H and ^{13}C are referenced to Me_4Si , the residual solvent resonances and $\text{BF}_3\cdot\text{OEt}_2$, respectively. Chemical shifts are 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, 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. 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) and aluminum oxide (Nacalai Tesuque, Alumina Activated 200) were used for column chromatography.

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. Toluene were purchased from Kanto Chemical Co., stored under argon. *t*-BuOK, MeOK and CuOAc were purchased from Aldrich Chemical Co., stored under nitrogen, and used as it is. Alkenes **1a–c** and **1e** were purchased from Tokyo Kasei Kogyo Co., Ltd., stored under nitrogen, and used as it is. **2d** was prepared by the reported procedure.²⁰

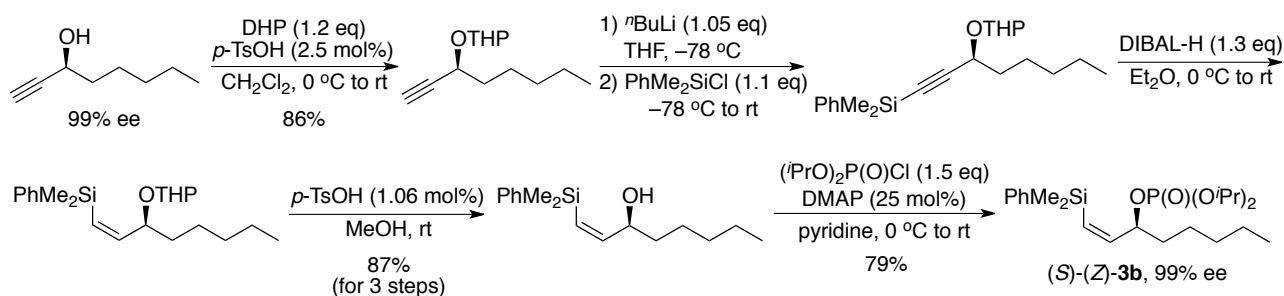
Preparation of Allylic Phosphates

Preparation of Allylic Phosphates (S)-(Z)-3a and (S)-(Z)-3d. THP-protection of commercially available (S)-3-butyne-2-ol (99% ee) followed by silylation gave γ -silylated propargylic alcohol derivatives. Next, DIBAL-H reduction followed by deprotection afforded γ -silylated allylic alcohols.²¹ Finally, (S)-(Z)-**3a** and (S)-(Z)-**3d** were prepared by the phosphorylation of the γ -silylated allylic alcohols, respectively.

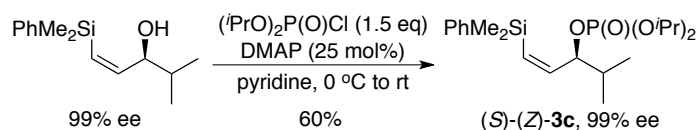
The phosphorylation of (S)-(Z)-4-dimethylphenylsilyl-3-buten-2-ol to (S)-(Z)-**3a** is representative. To a solution of (S)-(Z)-4-dimethylphenylsilyl-3-buten-2-ol (412.7 mg, 2.0 mmol) in pyridine (2.1 mL), (i PrO)₂P(O)Cl (481.4 mg, 2.4 mmol) and DMAP (61.1 mg, 0.5 mmol) were sequentially added at 0 °C. After being stirred at rt for 3 h, the reaction mixture was diluted with EtOAc (63 mL) and quenched with H₂O (5 mL). The resulting mixture was washed with sat. CuSO₄ (10 mL $\times$ 3) and brine, and was dried over anhydrous MgSO₄, filtered, and evaporated under reduced pressure. The residue was purified through a short plug of aluminum oxide (diethyl ether) to provide **3a** in 80% yield (594.0 mg, 1.6 mmol).



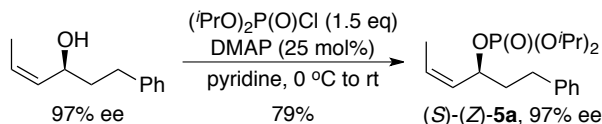
Preparation of Allylic Phosphate (S)-(Z)-3b. THP-protection of commercially available (S)-1-octyn-3-ol (99% ee) followed by silylation gave γ -silylated propargylic alcohol derivative. Next, DIBAL-H reduction followed by deprotection afforded γ -silylated allylic alcohol.^{3d} Finally, (S)-(Z)-3b was prepared by the phosphorylation of the γ -silylated allylic alcohol.



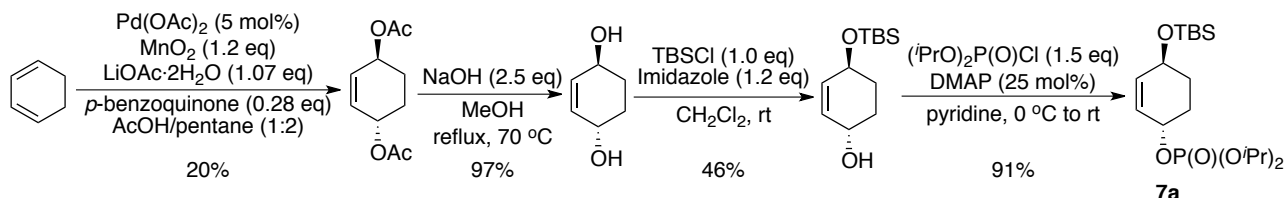
Preparation of Allylic Phosphate (S)-(Z)-3c. (S)-(Z)-3c was prepared by the phosphorylation of the corresponding γ -silylated allylic alcohol.^{3d} The ee value of (S)-(Z)-3c (99% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative of (S)-4-methyl-1-trimethylsilyl-1-pentyn-3-ol (CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, *i*PrOH/hexane 1/99, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 10.7 min for *S* isomer and 11.6 min for *R* isomer).



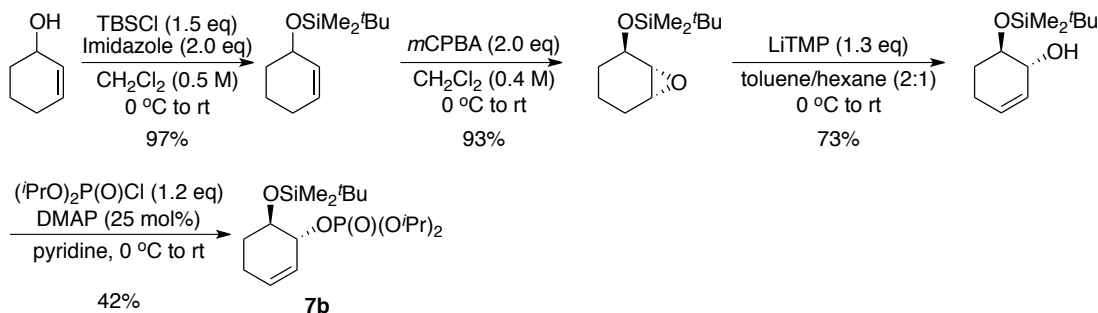
Preparation of Allylic Phosphate (S)-(Z)-5a. Allylic phosphate was prepared by the phosphorylation of the allylic alcohol. Allylic alcohol was prepared by the asymmetric reduction of the corresponding ketone according to the reported procedure.²² The ee value of (S)-(Z)-5a (97% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative of (S)-(Z)-1-phenyl-4-hexen-3-ol (CHIRALCEL[®] OJ-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, *i*PrOH/hexane 1/99, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 32.5 min for *S* isomer and 45.1 min for *R* isomer).



Preparation of Cyclic Allylic Phosphate 7a. 7a was prepared from 1,3-cyclohexadiene in 4 steps according to the reported procedure.²³

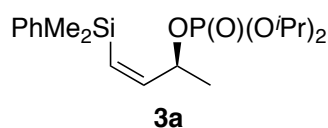


Preparation of Allylic Phosphate 7b. 7b was prepared from 2-cyclo-1-hexeneol in 4 steps according to the reported procedure.²⁴



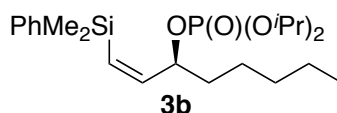
Characterization Data for Allylic Phosphates

(S)-(Z)-4-(Dimethylphenylsilyl)-3-buten-2-yl Diisopropyl Phosphate (3a)



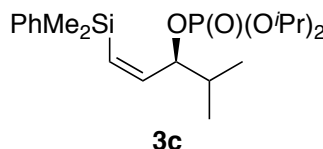
Colorless Oil. ^1H NMR (400 MHz, CDCl_3) δ 0.43 (s, 3H), 0.49 (s, 3H), 1.22 (d, J = 6.8 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H), 1.29 (d, J = 6.0 Hz, 3H), 1.29 (d, J = 6.0 Hz, 3H), 1.31 (d, J = 6.0 Hz, 3H), 4.54 (sep, J = 6.0 Hz, 1H), 4.59 (sep, J = 6.0 Hz, 1H), 4.98 (dq, J = 8.8, 6.8, 1.2 Hz, 1H), 5.77 (dd, J = 14.0, 1.2 Hz, 1H), 6.37 (dd, J = 14.0, 8.8 Hz, 1H), 7.34–7.38 (m, 3H), 7.52–7.56 (m, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ -1.28, -0.97, 22.45 (d, J = 5.0 Hz), 23.65 (d, J = 3.8 Hz, $\times$ 2C), 72.01 (d, J = 4.7 Hz), 72.06 (d, J = 4.7 Hz), 75.08 (d, J = 5.7 Hz), 127.89, 128.70, 129.11, 133.68, 138.65, 148.76 (d, J = 5.7 Hz). HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{31}\text{O}_4\text{NaPSi}$, 393.1621; found, 393.1618. $[\alpha]_D^{21} +31.4$ (c 0.52, CHCl_3).

(S)-(Z)-1-(Dimethylphenylsilyl)-1-octen-3-yl Diisopropyl Phosphate (3b)



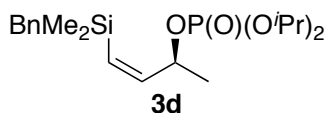
Colorless Oil. ^1H NMR (400 MHz, CDCl_3) δ 0.43 (s, 3H), 0.50 (s, 3H), 0.84 (t, $J = 7.2$ Hz, 3H), 1.11–1.35 (m, 8H), 1.27 (d, $J = 6.4$ Hz, 3H), 1.29 (d, $J = 6.4$ Hz, 3H), 1.29 (d, $J = 6.4$ Hz, 3H), 1.31 (d, $J = 6.4$ Hz, 3H), 4.55 (sep, $J = 6.4$ Hz, 1H), 4.60 (sep, $J = 6.4$ Hz, 1H), 4.82 (m, 1H), 5.80 (d, $J = 14.0$ Hz, 1H), 6.34 (dd, $J = 14.0, 9.2$ Hz, 1H), 7.34–7.37 (m, 3H), 7.53–7.57 (m, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ -1.37, -0.96, 13.96, 22.48, 23.65 (d, $J = 5.7$ Hz), 23.70 (d, $J = 5.7$ Hz), 24.46, 31.52, 36.38 (d, $J = 6.6$ Hz), 71.91 (d, $J = 5.7$ Hz), 71.95 (d, $J = 5.7$ Hz), 78.70 (d, $J = 5.7$ Hz), 127.86, 129.06, 129.60, 133.77, 138.79, 147.88 (d, $J = 3.8$ Hz). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{39}\text{O}_4\text{NaPSi}$, 449.2247; found, 449.2247. $[\alpha]_{\text{D}}^{23} +23.0$ (c 0.52, CHCl_3).

(S)-(Z)-1-(Dimethylphenylsilyl)-4-methyl-1-penten-3-yl Diisopropyl Phosphate (3c)



Colorless Oil. ^1H NMR (400 MHz, CDCl_3) δ 0.46 (s, 3H), 0.50 (s, 3H), 0.81 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 3H), 1.26 (d, $J = 6.4$ Hz, 3H), 1.29 (d, $J = 6.4$ Hz, 3H), 1.30 (d, $J = 6.4$ Hz, 3H), 1.32 (d, $J = 6.4$ Hz, 3H), 1.72 (doublet sep, $J = 6.8, 6.8$ Hz, 1H), 4.58 (sep, $J = 6.4$ Hz, 1H), 4.62 (sep, $J = 6.4$ Hz, 1H), 4.70 (m, 1H), 5.86 (d, $J = 14.8$ Hz, 1H), 6.37 (dd, $J = 14.8, 9.6$ Hz, 1H), 7.34–7.38 (m, 3H), 7.52–7.58 (m, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ -1.05, -0.90, 17.04, 18.45, 23.75 (d, $J = 4.8$ Hz), 23.83 (d, $J = 4.8$ Hz), 33.99 (d, $J = 6.7$ Hz), 71.98 (d, $J = 5.7$ Hz, $\times 2\text{C}$), 82.55 (d, $J = 6.6$ Hz), 127.93, 129.13, 131.01, 133.91, 138.92, 146.16 (d, $J = 1.9$ Hz). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{35}\text{O}_4\text{NaPSi}$, 421.1934; found, 421.1935. $[\alpha]_{\text{D}}^{24} +43.9$ (c 0.65, CHCl_3).

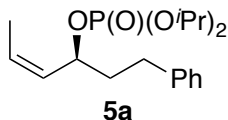
(S)-(Z)-4-(Benzyldimethylsilyl)-3-buten-2-yl Diisopropyl Phosphate (3d)



Colorless Oil. ^1H NMR (400 MHz, CDCl_3) δ 0.15 (s, 3H), 0.16 (s, 3H), 1.30 (d, $J = 6.4$ Hz, 3H), 1.30 (d, $J = 6.4$ Hz, 3H), 1.31 (d, $J = 6.4$ Hz, 3H), 1.32 (d, $J = 6.4$ Hz, 3H), 1.32 (d, $J = 6.4$ Hz, 3H), 2.19 (s, 2H), 4.58 (sep, $J = 6.4$ Hz, 1H), 4.62 (sep, $J = 6.4$ Hz, 1H), 5.02 (dq, $J = 8.8, 6.4$ Hz, 1H), 5.60 (d, $J = 14.4$ Hz, 1H), 6.32 (dd, $J = 14.4, 8.8$ Hz, 1H), 7.01 (d, $J = 7.2$ Hz, 2H), 7.07 (dd, $J = 7.6, 7.2$ Hz, 1H), 7.20 (dd, $J = 7.6, 7.2$ Hz, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ -1.77, 22.78 (d, $J = 4.7$ Hz), 23.67 (d, $J = 4.8$ Hz, $\times 2\text{C}$), 26.43, 72.06 (d, $J = 5.7$ Hz), 72.10 (d, $J = 5.7$ Hz), 75.12 (d, $J = 5.8$ Hz), 124.13, 128.16, 128.23, 128.83, 139.54, 148.29 (d,

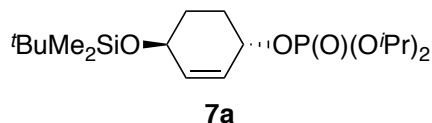
$J = 5.8$ Hz). **HRMS–ESI** (m/z): $[M+Na]^+$ calcd for $C_{19}H_{33}O_4NaPSi$, 407.1778; found, 407.1777. $[\alpha]_D^{23} +25.8$ (c 0.56, $CHCl_3$).

(S)-(Z)-Diisopropyl 1-Phenyl-4-hexen-3-yl Phosphate (5a)



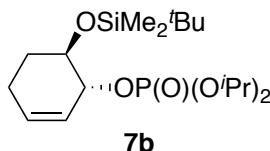
Colorless Oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.17–1.27 (m, 12H), 1.69 (dd, $J = 6.8, 1.2$ Hz, 3H), 1.87 (m, 1H), 2.11 (m, 1H), 2.68 (t, $J = 8.0$ Hz, 2H), 4.57 (sep, $J = 6.4$ Hz, 1H), 4.65 (sep, $J = 6.4$ Hz, 1H), 5.16 (dtd, $J = 9.2, 6.8, 0.8$ Hz, 1H), 5.50 (ddd, $J = 11.2, 9.2, 1.2$ Hz, 1H), 5.67 (dq, $J = 11.2, 6.8, 0.8$ Hz, 1H), 7.16–7.20 (m, 3H), 7.27–7.29 (m, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 13.49, 23.63 (d, $J = 4.7$ Hz), 23.71 (d, $J = 4.7$ Hz), 31.11, 37.99 (d, $J = 5.8$ Hz), 72.02 (d, $J = 5.8$ Hz), 72.05 (d, $J = 5.7$ Hz), 73.71 (d, $J = 5.7$ Hz), 125.90, 127.88, 128.36, 128.38, 129.65 (d, $J = 6.8$ Hz), 141.47. **HRMS–ESI** (m/z): $[M+Na]^+$ calcd for $C_{18}H_{29}O_4NaPSi$, 363.1696; found, 363.1700. $[\alpha]_D^{23} -0.5$ (c 0.56, $CHCl_3$).

trans-4-(tert-Butyldimethylsilyloxy)-2-cyclohexen-1-yl Diisopropyl Phosphate (7a)



Colorless Oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.32 (d, $J = 6.0$ Hz, 12H), 1.55 (m, 1H), 1.72 (m, 1H), 2.01 (m, 1H), 2.22 (m, 1H), 4.26 (m, 1H), 4.57–4.67 (m, 2H), 4.88 (m, 1H), 5.79 (s, 2H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ -4.69, -4.61, 18.17, 23.64 (d, $J = 4.8$ Hz), 25.83, 28.37 (d, $J = 3.8$ Hz), 30.42, 66.30, 72.35 (d, $J = 5.7$ Hz), 72.41 (d, $J = 5.7$ Hz), 128.34 (d, $J = 4.8$ Hz), 135.22. **HRMS–ESI** (m/z): $[M+H]^+$ calcd for $C_{18}H_{38}O_5PSi$, 393.2221; found, 393.2226.

trans-6-(tert-Butyldimethylsilyloxy)-2-cyclohexen-1-yl Diisopropyl Phosphate (7b)



Colorless Oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 1.33 (d, $J = 6.4$ Hz, 12H), 1.67 (m, 1H), 1.83 (m, 1H), 2.02 (m, 1H), 2.19 (m, 1H), 3.95 (m, 1H), 4.50 (m, 1H), 4.63 (sep, $J = 6.4$ Hz, 1H), 4.65 (sep, $J = 6.4$ Hz, 1H), 5.78 (d, $J = 10.0$ Hz, 1H), 5.89 (m, 1H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ -4.86, -4.72, 18.05, 22.22, 23.69 (d, $J = 4.7$ Hz), 23.77 (d, $J = 4.7$ Hz), 25.77, 27.09, 69.85 (d, $J = 6.7$ Hz), 72.11 (d, $J = 5.7$ Hz), 72.15 (d, $J = 5.7$ Hz), 75.69 (d, $J = 6.6$ Hz), 124.21 (d, $J = 2.9$ Hz), 132.02. **HRMS–ESI**

(*m/z*): [M+Na]⁺ calcd for C₁₈H₃₇O₅NaPSi, 415.2040; found, 415.2041.

Procedures for Copper-Catalyzed Allylic Cross-Coupling

Typical Procedure for Copper-Catalyzed Allylic Cross-Coupling of Silicon-Substituted Allylic Phosphates. The reaction in eq. 1 is representative. (9-BBN-H)₂ (30.2 mg, 0.12 mmol) was 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. Toluene (0.3 mL) and cyclohexene **1a** (0.027 mL, 0.27 mmol) were added to the vial, and then the mixture was stirred at 70 °C for 1 h to prepare a secondary alkylborane **2a**. Meanwhile, CuOAc (1.8 mg, 0.015 mmol), PPh₃ (4.0 mg, 0.0165 mmol) and MeOK (15.7 mg, 0.225 mmol) were placed in another vial containing a magnetic stirring bar. This vial was sealed with a Teflon[®]-coated silicon rubber septum and then evacuated and filled with argon. After toluene (0.3 mL) was added to the vial, the mixture was stirred at 25 °C for 1 h. Next, the alkylborane **2a** solution was transferred to the vial containing the Cu salt. Then, (*S*)-(*Z*)-**3a** (55.6 mg, 0.15 mmol) was added to the mixture. After 24 h stirring at 60 °C, the mixture was filtered through a short plug of aluminum oxide, which was washed with diethyl ether. After the solvent was removed under reduced pressure, flash chromatography on silica gel (hexane) gave (*R*)-(*E*)-**4aa** (35.6 mg, 0.132 mmol) in 88% yield.

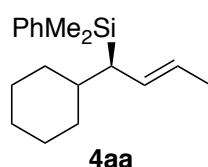
Typical Procedure for Copper-Catalyzed Allylic Cross-Coupling of Non-Silicon-Substituted Allylic Phosphates. The reaction in Table 3, entry 1 is representative. (9-BBN-H)₂ (30.2 mg, 0.12 mmol) was placed in a vial containing a magnetic stirring bar. The vial was sealed with a Teflon[®]-coated silicon rubber septum and the vial was evacuated and filled with argon. Toluene (0.3 mL) and cyclohexene **1a** (0.027 mL, 0.27 mmol) were added to the vial, and then the mixture was stirred at 70 °C for 1 h to prepare a secondary alkylborane **2a**. Meanwhile, CuOAc (1.8 mg, 0.015 mmol), PPh₃ (4.0 mg, 0.0165 mmol) and MeOK (15.7 mg, 0.225 mmol) were placed in another vial containing a magnetic stirring bar. This vial was sealed with a Teflon[®]-coated silicon rubber septum and then evacuated and filled with argon. After toluene (0.3 mL) was added to the vial, the mixture was stirred at 25 °C for 1 h. Next, the alkylborane **2a** solution was transferred to the vial containing the Cu salt. Then, (*S*)-(*Z*)-**5a** (51.0 mg, 0.15 mmol) was added to the mixture. After 24 h stirring at 60 °C, the mixture was filtered through a short plug of aluminum oxide, which was washed with diethyl ether. After the solvent was removed under reduced pressure, flash chromatography on silica gel (hexane) gave (*R*)-(*E*)-**6aa** (32.0 mg, 0.132 mmol) in 88% yield.

Typical Procedure for Copper-Catalyzed Allylic Cross-Coupling of Cyclic Allylic Phosphates. The reaction in Table 4, entry 1 is representative. (9-BBN-H)₂ (30.2 mg, 0.12 mmol) was 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. Toluene (0.3 mL) and cyclohexene (**1a**) (0.027 mL, 0.27 mmol) were added to

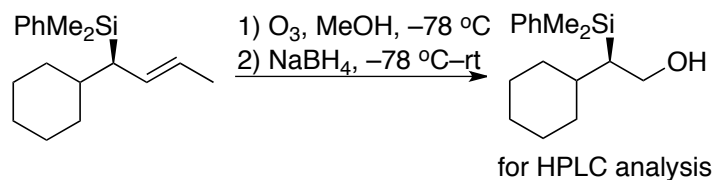
the vial, and then the mixture was stirred at 70 °C for 1 h to prepare a secondary alkylborane **2a**. Meanwhile, CuOAc (1.8 mg, 0.015 mmol), PPh₃ (4.0 mg, 0.0165 mmol) and MeOK (15.7 mg, 0.225 mmol) were placed in another vial containing a magnetic stirring bar. This vial was sealed with a Teflon[®]-coated silicon rubber septum and then evacuated and filled with argon. After toluene (0.3 mL) was added to the vial, the mixture was stirred at 25 °C for 1 h. Next, the alkylborane **2a** solution was transferred to the vial containing the Cu salt. Then, **7a** (58.9 mg, 0.15 mmol) was added to the mixture. After 24 h stirring at 60 °C, the mixture was filtered through a short plug of aluminum oxide, which was washed with diethyl ether. After the solvent was removed under reduced pressure, flash chromatography on silica gel (hexane) gave **8aa** (37.4 mg, 0.127 mmol) in 85% yield.

Characterization Data for Coupling Products

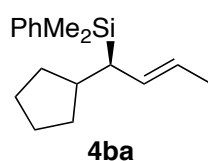
(*R*)-(*E*)-(1-Cyclohexyl-2-buten-1-yl)dimethylphenylsilane (**4aa**)



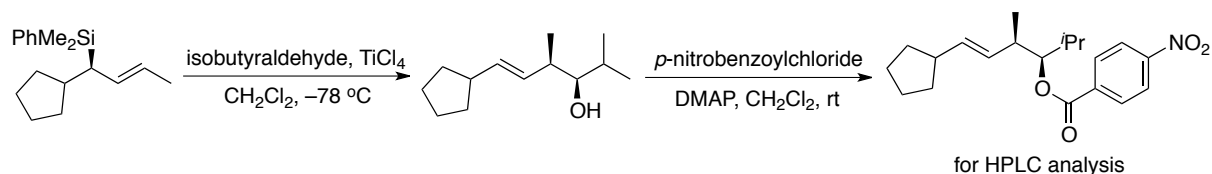
The product **4aa** was purified by flash chromatography on silica gel (hexane) [88% isolated yield from **3a**]. Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 0.25 (s, 3H), 0.28 (s, 3H), 0.87–1.19 (m, 5H), 1.36–1.45 (m, 2H), 1.57–1.62 (m, 5H), 1.65 (dd, *J* = 6.4, 1.2 Hz, 3H), 5.18 (dq, *J* = 14.8, 6.4 Hz, 1H), 5.31 (ddd, *J* = 14.8, 10.8, 1.2 Hz, 1H), 7.30–7.36 (m, 3H), 7.46–7.50 (m, 2H). ¹³C NMR (100.5 MHz, CDCl₃) δ –3.41, –2.65, 18.13, 26.27, 26.73, 26.76, 31.40, 34.12, 38.70, 40.27, 124.23, 127.46, 128.53, 129.67, 133.94, 139.43. **Anal.** Calcd for C₁₈H₂₈Si: C, 79.34; H, 10.36%. Found: C, 79.08; H, 10.26%. [α]_D²⁶ +16.5 (*c* 0.50, CHCl₃). The ee value (97% ee) was determined by chiral HPLC analysis of the alcohol obtained by the ozonolysis followed by reduction with NaBH₄ from **4aa**, [CHIRALCEL[®] OJ-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, ⁱPrOH/hexane 2/98, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 14.5 min for the *S* isomer and 15.3 min for the *R* isomer].



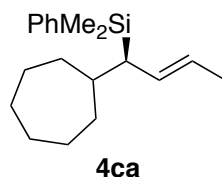
(*R*)-(*E*)-(1-Cyclopentyl-2-buten-1-yl)dimethylphenylsilane (**4ba**)



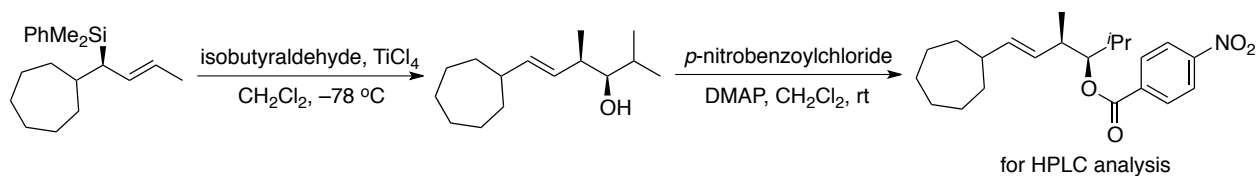
The product **4ba** was purified by flash chromatography on silica gel (hexane) [93% isolated yield from **3a**]. Colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.25 (s, 3H), 0.28 (s, 3H), 1.01–1.15 (m, 2H), 1.34–1.56 (m, 5H), 1.58–1.67 (m, 2H), 1.64 (dd, $J = 6.0, 1.2$ Hz, 3H), 1.84 (doublet quin, $J = 9.6, 7.2$ Hz, 1H), 5.17 (dq, $J = 15.2, 6.0$ Hz, 1H), 5.27 (ddd, $J = 15.2, 10.0, 1.2$ Hz, 1H), 7.30–7.36 (m, 3H), 7.45–7.52 (m, 2H). $^{13}\text{C NMR}$ (100.5 MHz, CDCl_3) δ –3.80, –2.91, 18.12, 25.05, 25.25, 31.56, 32.64, 38.18, 40.52, 123.76, 127.44, 128.59, 130.45, 134.01, 139.19. **Anal.** Calcd for $\text{C}_{17}\text{H}_{26}\text{Si}$: C, 79.00; H, 10.14%. Found: C, 78.70; H, 10.25%. $[\alpha]_{\text{D}}^{25} +11.5$ (c 0.48, CHCl_3). The ee value (94% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by the established TiCl_4 -mediated addition of allylsilane to aldehyde followed by benzylation from **4ba**, [CHIRALCEL[®] OJ-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, i PrOH/hexane 1/99, 0.5 mL/min, 40 $^\circ\text{C}$, 250 nm UV detector, retention time = 19.8 min for the *R* isomer and 28.1 min for the *S* isomer]. The absolute configuration of **4ba** was assigned by consideration of the stereochemical pathway.



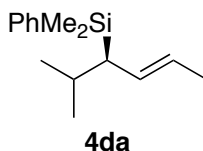
(*R*)-(*E*)-(1-Cycloheptyl-2-buten-1-yl)dimethylphenylsilane (4ca**)**



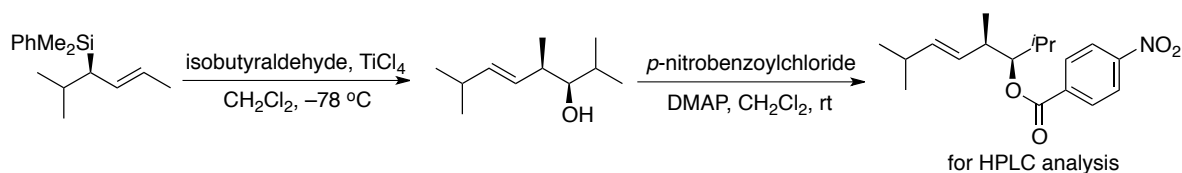
The product **4ca** was purified by flash chromatography on silica gel (hexane) [80% isolated yield from **3a**]. Colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.26 (s, 3H), 0.28 (s, 3H), 1.15–1.63 (m, 14H), 1.65 (dd, $J = 6.0, 1.2$ Hz, 3H), 5.18 (dq, $J = 14.4, 6.0$ Hz, 1H), 5.32 (ddd, $J = 14.4, 10.0, 1.2$ Hz, 1H), 7.29–7.35 (m, 3H), 7.46–7.50 (m, 2H). $^{13}\text{C NMR}$ (100.5 MHz, CDCl_3) δ –3.33, –2.88, 18.16, 27.17, 27.22, 27.78, 28.44, 32.08, 36.15, 40.05, 41.61, 124.31, 127.45, 128.55, 129.52, 134.00, 139.37. **Anal.** Calcd for $\text{C}_{19}\text{H}_{30}\text{Si}$: C, 79.64; H, 10.55%. Found: C, 79.30; H, 10.75%. $[\alpha]_{\text{D}}^{26} +12.5$ (c 0.78, CHCl_3). The ee value (97% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by the established TiCl_4 -mediated addition of allylsilane to aldehyde followed by benzylation from **4ca**, [CHIRALCEL[®] OJ-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, i PrOH/hexane 1/99, 0.5 mL/min, 40 $^\circ\text{C}$, 250 nm UV detector, retention time = 9.3 min for the *R* isomer and 10.9 min for the *S* isomer]. The absolute configuration of **4ca** was assigned by consideration of the stereochemical pathway.



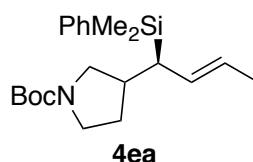
(*R*)-(*E*)-Dimethyl(2-methyl-4-hexen-3-yl)phenylsilane (4da**)**



The product **4da** was purified by flash chromatography on silica gel (hexane) [94% isolated yield from **3a**]. Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 0.25 (s, 3H), 0.29 (s, 3H), 0.81 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), 1.58 (dd, J = 10.4, 4.8 Hz, 1H), 1.67 (dd, J = 6.0, 1.2 Hz, 3H), 1.79 (doublet sep, J = 6.8, 4.8 Hz, 1H), 5.21 (dq, J = 15.2, 6.0 Hz, 1H), 5.31 (ddd, J = 15.2, 10.4, 1.2 Hz, 1H), 7.32–7.35 (m, 3H), 7.47–7.52 (m, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ -3.61, -2.83, 18.16, 20.67, 23.79, 28.36, 40.69, 124.76, 127.49, 128.59, 128.82, 133.98, 139.25. **Anal.** Calcd for $\text{C}_{15}\text{H}_{24}\text{Si}$: C, 77.51; H, 10.41%. Found: C, 77.53; H, 10.63%. $[\alpha]_{\text{D}}^{26} +13.8$ (c 0.74, CHCl_3). The ee value (96% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by the established TiCl_4 -mediated addition of allylsilane to aldehyde followed by benzylation from **4da**, [CHIRALCEL[®] OJ-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, *i*PrOH/hexane 1/99, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 8.5 min for the *R* isomer and 9.7 min for the *S* isomer]. The absolute configuration of **4da** was assigned by consideration of the stereochemical pathway.



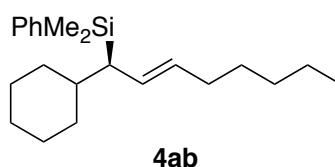
***tert*-Butyl 3-[(1*S*)-(*E*)-1-(Dimethylphenylsilyl)-2-buten-1-yl]pyrrolidine-1-carboxylate (**4ea**)**



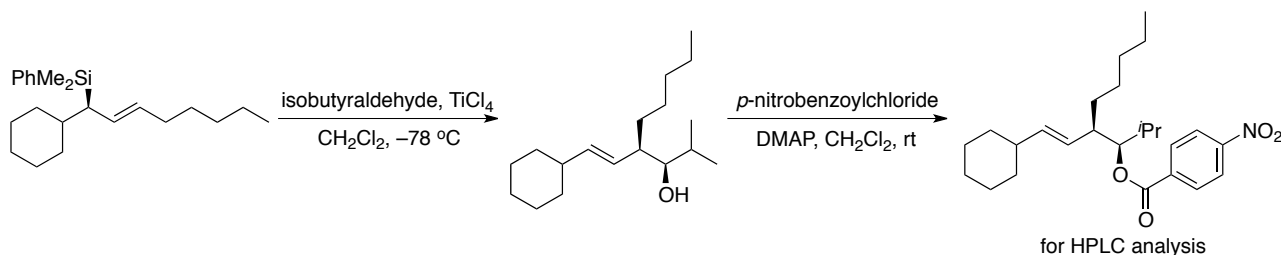
The product **4ea** (dr 1:1) was purified by flash chromatography on silica gel (0–10% EtOAc/hexane) [47% isolated yield from **3a**]. Colorless oil. Signals for the rotamers were given. ^1H NMR (400 MHz, CDCl_3) δ 0.26–0.31 (m, 6H), 1.38–1.42 (m, 9H), 1.40 (m, 1H), 1.64–1.88 (m, 5H), 2.14 (m, 1H), 2.54–2.87 (m, 1H), 3.01–3.51 (m, 3H), 5.19–5.32 (m, 2H), 7.32–7.38 (m, 3H), 7.47–7.52 (m, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ -4.86, -

4.48, -4.28, -3.71, -3.27, -3.12, -2.98 ($\times 2C$), 18.08 ($\times 4C$), 28.51 ($\times 4C$), 30.69, 31.13, 31.30, 31.87, 35.91, 36.10, 36.40, 36.47, 38.79, 38.87, 39.49, 39.61, 44.98, 45.50, 45.57, 45.95, 50.60, 50.66, 50.99, 51.12, 78.74 ($\times 2C$), 78.80 ($\times 2C$), 124.88, 125.08 ($\times 2C$), 125.13, 127.69 ($\times 4C$), 128.96 ($\times 3C$), 129.02 ($\times 3C$), 129.07 ($\times 2C$), 133.87 ($\times 3C$), 133.99, 137.72, 138.15 ($\times 2C$), 138.21, 154.48 ($\times 2C$), 154.55 ($\times 2C$). **HRMS–EI** (m/z): $[M+Na]^+$ calcd for $C_{21}H_{33}O_2NNaSi$, 382.2173; found, 328.2175. $[\alpha]_D^{26} +18.0$ (c 0.50, $CHCl_3$). The ee value (95% ee) was determined by chiral HPLC analysis of **4ea**, [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, i PrOH/hexane 1/99, 0.3 mL/min, 40 $^\circ C$, 220 nm UV detector, retention time = 18.8 min for the *R* isomer and 20.4 min for the *S* isomer]. The absolute configuration of **4ea** was assigned by consideration of the stereochemical pathway.

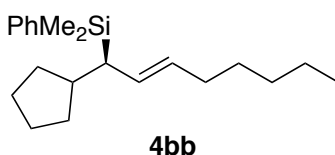
(*R*)-(E)-(1-Cyclohexyl-2-octen-1-yl)dimethylphenylsilane (4ab)



The product **4ab** was purified by flash chromatography on silica gel (hexane) [94% isolated yield from **3b**]. Colorless oil. **¹H NMR** (400 MHz, $CDCl_3$) δ 0.25 (s, 3H), 0.28 (s, 3H), 0.88 (t, J = 7.2 Hz, 3H), 0.94–1.17 (m, 5H), 1.22–1.34 (m, 6H), 1.37–1.45 (m, 2H), 1.57–1.66 (m, 5H), 1.97 (q, J = 6.8 Hz, 2H), 5.15 (dt, J = 15.2, 6.8 Hz, 1H), 5.28 (dd, J = 15.2, 10.4 Hz, 1H), 7.26–7.33 (m, 3H), 7.47–7.50 (m, 2H). **¹³C NMR** (100.5 MHz, $CDCl_3$) δ -3.35, -2.68, 14.11, 22.51, 26.30, 26.74, 26.77, 29.62, 31.37, 31.40, 32.81, 34.12, 38.70, 40.21, 127.46, 128.49, 128.53, 130.27, 133.95, 139.43. **HRMS–EI** (m/z): $[M]^+$ calcd for $C_{22}H_{36}Si$, 328.2586; found, 328.2579. $[\alpha]_D^{26} +12.2$ (c 0.66, $CHCl_3$). The ee value (99% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by the established $TiCl_4$ -mediated addition of allylsilane to aldehyde followed by benzoylation from **4ab**, [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, i PrOH/hexane 1/99, 0.5 mL/min, 40 $^\circ C$, 250 nm UV detector, retention time = 8.9 min for the *R* isomer and 9.9 min for the *S* isomer]. The absolute configuration of **4ab** was assigned by consideration of the stereochemical pathway.

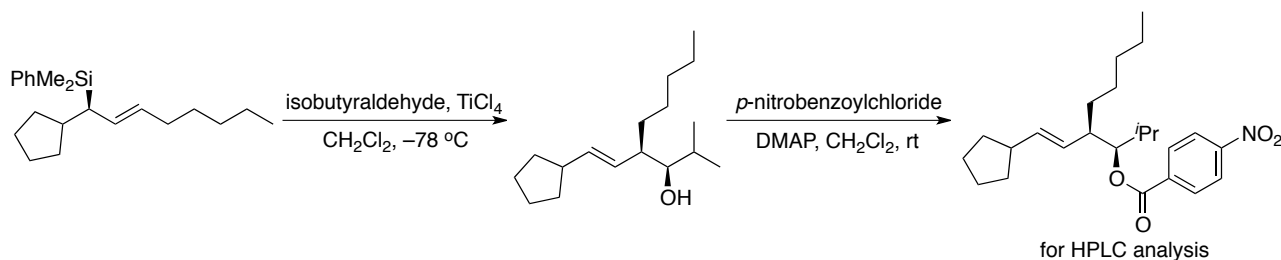


(*R*)-(*E*)-(1-Cyclopentyl-2-octen-1-yl)dimethylphenylsilane (4bb)

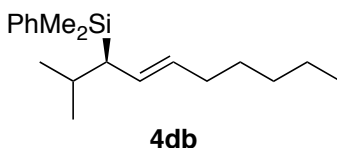


4bb

The product **4bb** was purified by flash chromatography on silica gel (hexane) [93% isolated yield from **3b**]. Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 0.26 (s, 3H), 0.28 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H), 1.02–1.16 (m, 2H), 1.19–1.57 (m, 11H), 1.59–1.67 (m, 2H), 1.87 (doublet quin, *J* = 9.6, 8.0 Hz, 1H), 1.96 (dt, *J* = 6.8, 6.4 Hz, 2H), 5.18 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.24 (dd, *J* = 15.2, 8.8 Hz, 1H), 7.29–7.35 (m, 3H), 7.48–7.50 (m, 2H). ¹³C NMR (100.5 MHz, CDCl₃) δ –3.73, –2.94, 14.10, 22.52, 25.09, 25.29, 29.63, 31.34, 31.58, 32.64, 34.81, 38.17, 40.50, 127.45, 128.59, 129.31, 129.79, 134.02, 139.19. **Anal.** Calcd for C₂₁H₃₄Si: C, 80.18; H, 10.89%. Found: C, 79.98; H, 10.91%. [α]_D²⁶ +7.4 (*c* 0.78, CHCl₃). The ee value (99% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by the established TiCl₄-mediated addition of allylsilane to aldehyde followed by benzoylation from **4bb**, [CHIRALCEL[®] OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, ⁱPrOH/hexane 1/99, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 9.1 min for the *R* isomer and 10.0 min for the *S* isomer]. The absolute configuration of **4bb** was assigned by consideration of the stereochemical pathway.



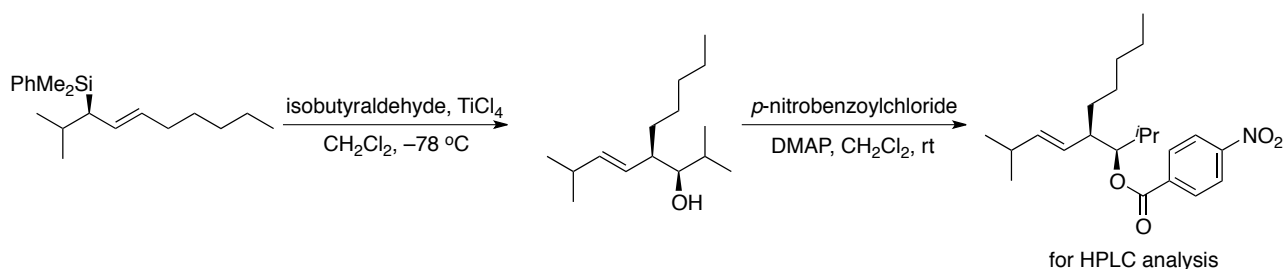
(*R*)-(*E*)-Dimethyl(2-methyl-4-decen-3-yl)phenylsilane (4db)



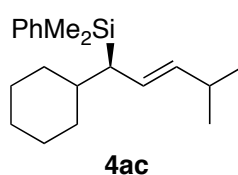
4db

The product **4db** was purified by flash chromatography on silica gel (hexane) [88% isolated yield from **3b**]. Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 0.26 (s, 3H), 0.29 (s, 3H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H), 1.21–1.36 (m, 6H), 1.58 (dd, *J* = 10.0, 5.2 Hz, 1H), 1.80 (dq, *J* = 6.8, 6.4, 5.2 Hz, 1H), 1.99 (dt, *J* = 6.8, 6.8 Hz, 2H), 5.21 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.28 (dd, *J* = 15.2, 10.0 Hz, 1H), 7.29–7.35 (m, 3H), 7.47–7.51 (m, 2H). ¹³C NMR (100.5 MHz, CDCl₃) δ –3.55, –2.85, 14.10, 20.69, 22.52, 23.79, 28.36, 29.63, 31.35, 32.86, 40.65, 127.49, 127.68, 128.59, 130.82, 133.99, 139.25. **Anal.** Calcd for C₁₉H₃₂Si: C, 79.09; H, 11.18%. Found: C, 78.84; H, 11.09%. [α]_D²⁶ +9.9 (*c* 0.66, CHCl₃). The ee value (99% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by the established TiCl₄-mediated addition of allylsilane to aldehyde followed by benzoylation from **4db**, [CHIRALCEL[®] OD-3 column,

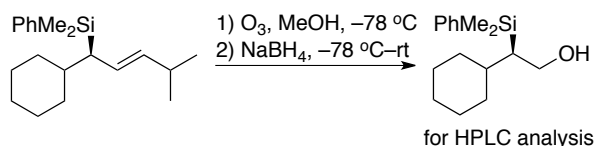
4.6 mm × 250 mm, Daicel Chemical Industries, ¹PrOH/hexane 1/99, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 8.7 min for the *R* isomer and 9.6 min for the *S* isomer]. The absolute configuration of **4db** was assigned by consideration of the stereochemical pathway.



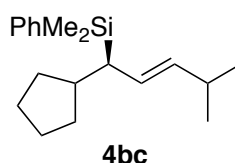
(*R*)-(*E*)-(1-Cyclohexyl-4-methyl-2-penten-1-yl)dimethylphenylsilane (4ac**)**



The product **4ac** was purified by flash chromatography on silica gel (hexane) [93% isolated yield from **3c**]. Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 0.25 (s, 3H), 0.28 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.97–1.25 (m, 5H), 1.37–1.46 (m, 2H), 1.54–1.66 (m, 5H), 2.23 (doublet sep, *J* = 6.8, 6.4 Hz, 1H), 5.11 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.22 (dd, *J* = 15.2, 10.4 Hz, 1H), 7.29–7.35 (m, 3H), 7.46–7.50 (m, 2H). ¹³C NMR (100.5 MHz, CDCl₃) δ -3.36, -2.72, 22.85, 23.11, 26.30, 26.75 (× 2C), 31.43, 31.47, 34.07, 38.68, 40.03, 125.38, 127.44, 128.52, 133.97, 137.38, 139.43. **Anal.** Calcd for C₂₀H₃₂Si: C, 79.92; H, 10.73%. Found: C, 79.58; H, 10.92%. [α]_D²⁴ +16.1 (*c* 0.51, CHCl₃). The ee value (98% ee) was determined by chiral HPLC analysis of the alcohol derivative obtained by the ozonolysis followed by reduction with NaBH₄ from **4ac**, [CHIRALCEL[®] OJ-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, ¹PrOH/hexane 2/98, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 12.8 min for the *S* isomer and 13.7 min for the *R* isomer]. The absolute configuration of **4ac** was assigned by consideration of the stereochemical pathway.

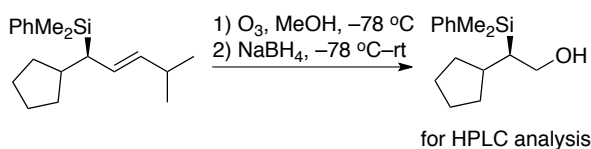


(*R*)-(*E*)-(1-Cyclopentyl-4-methyl-2-penten-1-yl)dimethylphenylsilane (4bc**)**

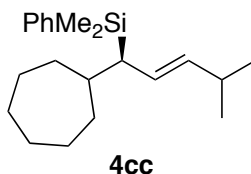


The product **4bc** was purified by flash chromatography on silica gel (hexane) [96% isolated yield from **3c**].

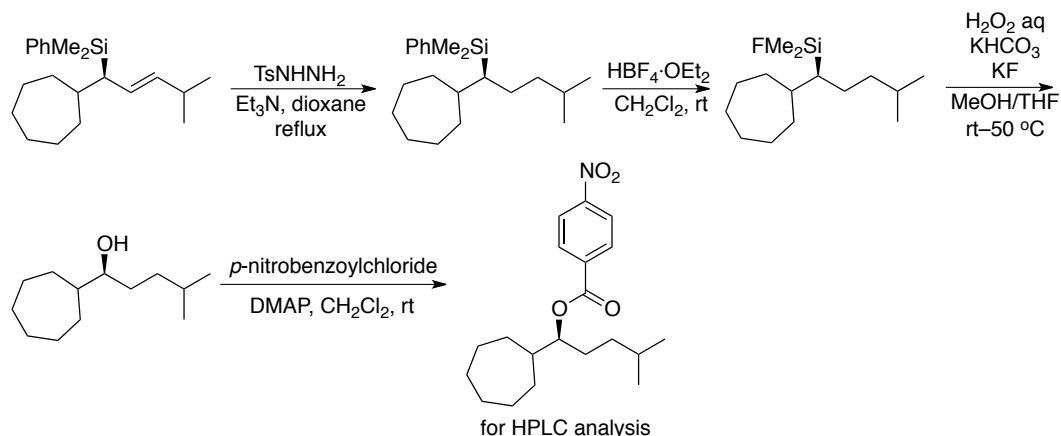
Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 0.26 (s, 3H), 0.28 (s, 3H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.93 (d, $J = 6.4$ Hz, 3H), 1.01–1.15 (m, 2H), 1.33–1.43 (m, 2H), 1.44–1.57 (m, 3H), 1.58–1.66 (m, 2H), 1.87 (doublet quin, $J = 9.6, 7.6$ Hz, 1H), 2.20 (doublet sep, $J = 6.4, 6.4$ Hz, 1H), 5.14 (dd, $J = 14.8, 6.4$ Hz, 1H), 5.19 (dd, $J = 14.8, 8.4$ Hz, 1H), 7.31–7.35 (m, 3H), 7.46–7.51 (m, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ -3.72, -3.01, 22.86, 23.08, 25.03, 25.30, 31.42, 31.64, 32.62, 38.06, 40.50, 126.25, 127.43, 128.58, 134.04, 136.89, 139.16. **Anal.** Calcd for $\text{C}_{19}\text{H}_{30}\text{Si}$: C, 79.64; H, 10.55%. Found: C, 79.35; H, 10.83%. $[\alpha]_{\text{D}}^{24} +9.6$ (c 0.57, CHCl_3). The ee value (98% ee) was determined by chiral HPLC analysis of the alcohol derivative prepared by the ozonolysis followed by reduction with NaBH_4 from **4bc**, [CHIRALCEL[®] OJ-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, i PrOH/hexane 2/98, 0.5 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 13.1 min for the *S* isomer and 14.4 min for the *R* isomer]. The absolute configuration of **4bc** was assigned by consideration of the stereochemical pathway.



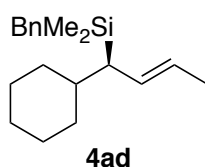
(*R*)-(*E*)-(1-Cycloheptyl-4-methyl-2-penten-1-yl)dimethylphenylsilane (4cc**)**



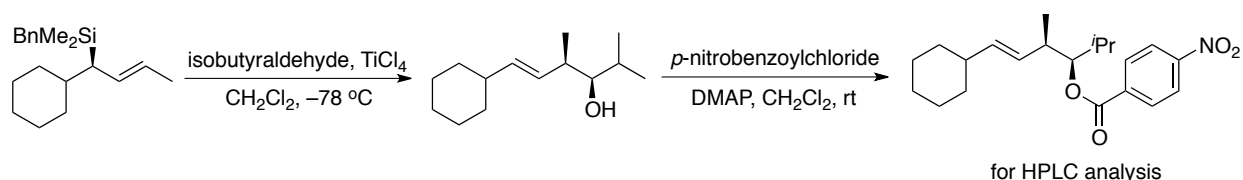
The product **4cc** was purified by flash chromatography on silica gel (hexane) [38% isolated yield from **3c**]. Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 0.26 (s, 3H), 0.28 (s, 3H), 0.94 (d, $J = 6.4$ Hz, 6H), 1.15–1.68 (m, 14H), 2.23 (doublet sep, $J = 6.8, 6.4$ Hz, 1H), 5.23 (dd, $J = 14.8, 6.8$ Hz, 1H), 5.25 (ddd, $J = 14.8, 10.4, 0.8$ Hz, 1H), 7.31–7.34 (m, 3H), 7.46–7.50 (m, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ -3.33, -2.95, 22.88, 23.11, 27.12, 27.19, 27.88, 28.52, 31.45, 32.07, 36.04, 39.95, 41.34, 125.16, 127.42, 128.54, 134.04, 137.54, 139.35. **HRMS–EI** (m/z): $[\text{M}]^+$ calcd for $\text{C}_{21}\text{H}_{34}\text{Si}$, 314.2430; found, 314.2423. $[\alpha]_{\text{D}}^{25} +10.2$ (c 0.62, CHCl_3). The ee value (97% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by alkene reduction, Fleming–Tamao Oxidation followed by benzylation from **4cc** (Scheme S17), [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane, 0.3 mL/min, 40 $^\circ\text{C}$, 250 nm UV detector, retention time = 47.5 min for the *R* isomer and 53.4 min for the *S* isomer]. The absolute configuration of **4cc** was assigned by consideration of the stereochemical pathway.



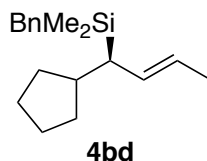
(*R*)-(E)-Benzyl(1-cyclohexyl-2-buten-1-yl)dimethylsilane (4ad)



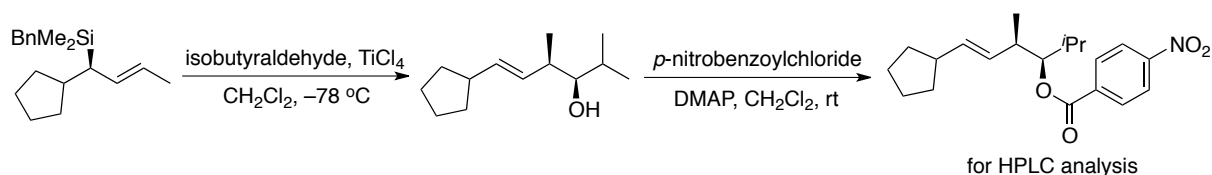
The product **4ad** was purified by flash chromatography on silica gel (hexane) [31% isolated yield from **3d**]. Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ –0.08 (s, 3H), –0.06 (s, 3H), 0.99–1.28 (m, 5H), 1.43–1.54 (m, 3H), 1.68 (d, J = 6.0 Hz, 3H), 1.60–1.71 (m, 4H), 2.08 (s, 2H), 5.23 (dq, J = 15.2, 6.0 Hz, 1H), 5.31 (dd, J = 15.2, 8.8 Hz, 1H), 6.98 (d, J = 7.2 Hz, 2H), 7.05 (t, J = 7.2 Hz, 1H), 7.20 (t, J = 7.2 Hz, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ –3.54, –3.51, 18.13, 24.97, 26.31, 26.84, 26.89, 31.43, 34.13, 38.79, 39.58, 123.77, 124.25, 128.02, 128.30, 129.76, 140.55. HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{19}\text{H}_{30}\text{Si}$, 286.2117; found, 286.2116. $[\alpha]_{\text{D}}^{26} +15.8$ (c 0.32, CHCl_3). The ee value (93% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by the established TiCl_4 -mediated addition of allylsilane to aldehyde followed by benzylation from **4ad**, [CHIRALCEL[®] OJ-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, *i*PrOH/hexane 1/99, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 11.3 min for the *R* isomer and 15.9 min for the *S* isomer]. The absolute configuration of **4ad** was assigned by consideration of the stereochemical pathway.



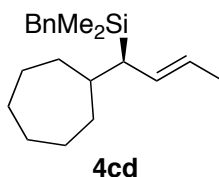
(*R*)-(E)-Benzyl(1-cyclopentyl-2-but-1-yl)dimethylsilane (4bd)



The product **4bd** was purified by flash chromatography on silica gel (hexane) [75% isolated yield from **3d**]. Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ -0.08 (s, 3H), -0.07 (s, 3H), 1.13–1.26 (m, 2H), 1.42–1.61 (m, 5H), 1.68 (d, J = 6.0 Hz, 3H), 1.62–1.73 (m, 2H), 1.95 (doublet quin, J = 9.6, 7.2 Hz, 1H), 2.09 (s, 2H), 5.26 (dq, J = 15.6, 6.0 Hz, 1H), 5.30 (dd, J = 15.6, 8.8 Hz, 1H), 6.99 (d, J = 7.6 Hz, 2H), 7.05 (t, J = 7.2 Hz, 1H), 7.20 (dd, J = 7.6, 7.2 Hz, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ -3.94, -3.66, 18.14, 24.72, 25.08, 25.24, 31.58, 32.66, 37.33, 40.68, 123.77, 123.83, 128.03, 128.29, 130.55, 140.55. **Anal.** Calcd for $\text{C}_{18}\text{H}_{28}\text{Si}$: C, 79.34; H, 10.36%. Found: C, 79.31; H, 10.00%. $[\alpha]_{\text{D}}^{26} +16.2$ (c 0.60, CHCl_3). The ee value (92% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by the established TiCl_4 -mediated addition of allylsilane to aldehyde followed by benzoylation from **4bd**, [CHIRALCEL[®] OJ-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, i PrOH/hexane 1/99, 0.5 mL/min, 40 $^\circ\text{C}$, 250 nm UV detector, retention time = 9.7 min for the *R* isomer and 11.5 min for the *S* isomer]. The absolute configuration of **4bd** was assigned by consideration of the stereochemical pathway.

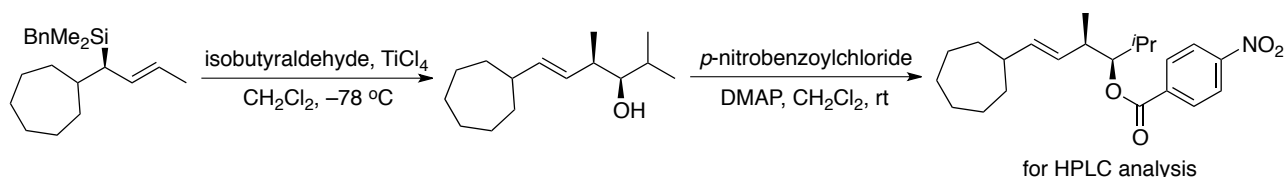


(*R*)-(E)-Benzyl(1-cycloheptyl-2-buten-1-yl)dimethylsilane (4cd)

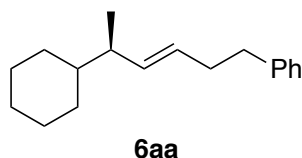


The product **4cd** was purified by flash chromatography on silica gel (hexane) [61% isolated yield from **3d**]. Colorless oil. ^1H NMR (400 MHz, CDCl_3) δ -0.07 (s, 3H), -0.06 (s, 3H), 1.26–1.71 (m, 14H), 1.68 (dd, J = 6.0, 1.2 Hz, 3H), 2.08 (s, 2H), 5.26 (dq, J = 15.2, 6.0 Hz, 1H), 5.34 (ddd, J = 15.2, 10.8, 1.2 Hz, 1H), 6.99 (d, J = 7.6 Hz, 2H), 7.05 (t, J = 7.2 Hz, 1H), 7.20 (dd, J = 7.6, 7.2 Hz, 2H). ^{13}C NMR (100.5 MHz, CDCl_3) δ -3.60, -3.53, 18.20, 24.98, 27.26, 27.33, 27.85, 28.40, 32.25, 36.15, 40.21, 40.85, 123.77, 124.38, 128.03, 128.30, 129.57, 140.55. **Anal.** Calcd for $\text{C}_{20}\text{H}_{32}\text{Si}$: C, 79.92; H, 10.73%. Found: C, 79.53; H, 10.64%. $[\alpha]_{\text{D}}^{26} +19.5$ (c 0.56, CHCl_3). The ee value (96% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by the established TiCl_4 -mediated addition of allylsilane to aldehyde followed by benzoylation from

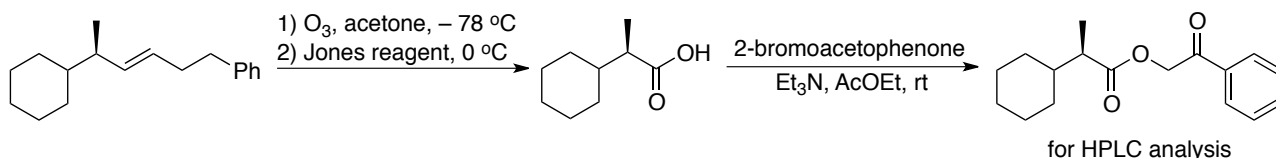
4cd, [CHIRALCEL[®] OJ-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, ⁱPrOH/hexane 1/99, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 9.3 min for the *R* isomer and 10.6 min for the *S* isomer]. The absolute configuration of **4cd** was assigned by consideration of the stereochemical pathway.



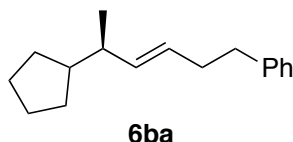
(*R*)-(E)-5-Cyclohexyl-1-phenyl-3-hexene (6aa)



The product **6aa** was purified by flash chromatography on silica gel (hexane) [88% isolated yield from **5a**]. Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 0.76–0.88 (m, 2H), 0.91 (d, *J* = 6.8 Hz, 3H), 1.01–1.32 (m, 5H), 1.60–1.71 (m, 4H), 1.86 (dq, *J* = 7.2, 6.8 Hz, 1H), 2.30 (dt, *J* = 8.0, 6.4 Hz, 2H), 2.67 (t, *J* = 8.0 Hz, 2H), 5.28 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.35 (dd, *J* = 15.2, 6.8 Hz, 1H), 7.15–7.19 (m, 3H), 7.25–7.30 (m, 2H). ¹³C NMR (100.5 MHz, CDCl₃) δ 17.77, 26.65, 26.68 (× 2C), 30.24, 30.34, 34.48, 36.19, 42.36, 43.12, 125.61, 128.02, 128.16, 128.52, 135.81, 142.17. HRMS–EI (*m/z*): [*M*]⁺ calcd for C₁₈H₂₆, 242.2035; found, 242.2032. [*α*]_D²⁶ – 18.4 (*c* 0.94, CHCl₃). The ee value (89% ee) was determined by chiral HPLC analysis of the ester derivative obtained by the ozonolysis, Jones oxidation, followed by esterification from **6aa**, [CHIRALCEL[®] OD-3 column, 4.6 mm × 250 mm, Daicel Chemical Industries, ⁱPrOH/hexane 1/99, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 40.3 min for the *R* isomer and 53.2 min for the *S* isomer].

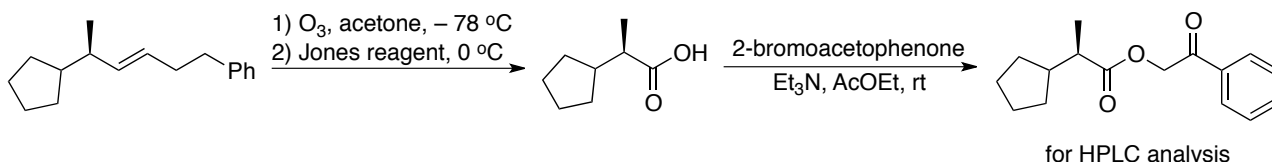


(*R*)-(E)-5-Cyclopentyl-1-phenyl-3-hexene (6ba)

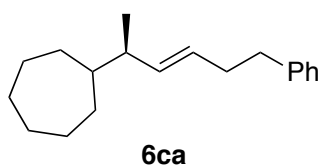


The product **6ba** was purified by flash chromatography on silica gel (hexane) [98% isolated yield from **5a**]. Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 0.94 (d, *J* = 6.8 Hz, 3H), 1.06–1.14 (m, 2H), 1.41–1.61 (m, 6H), 1.70 (m, 1H), 1.86 (dq, *J* = 7.2, 6.8 Hz, 1H), 2.29 (dt, *J* = 8.0, 6.4 Hz, 2H), 2.66 (t, *J* = 8.0 Hz, 2H), 5.31 (dt, *J* = 15.2, 6.4 Hz, 1H), 5.38 (dd, *J* = 15.2, 6.8 Hz, 1H), 7.14–7.18 (m, 3H), 7.24–7.29 (m, 2H). ¹³C NMR (100.5

MHz, CDCl₃) δ 19.70, 25.33, 25.40, 30.57, 30.62, 34.48, 36.24, 42.25, 46.13, 125.62, 127.53, 128.17, 128.50, 136.42, 142.19. **Anal.** Calcd for C₁₇H₂₄: C, 89.41; H, 10.59%. Found: C, 89.05; H, 10.86%. [α]_D²⁶ –14.5 (*c* 0.67, CHCl₃). The ee value (65% ee) was determined by chiral HPLC analysis of the ester derivative obtained by the ozonolysis, Jones oxidation, followed by esterification from **6ba**, [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, ⁱPrOH/hexane 1/99, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 43.8 min for the *R* isomer and 54.4 min for the *S* isomer]. The absolute configuration of **6ba** was assigned by consideration of the stereochemical pathway.

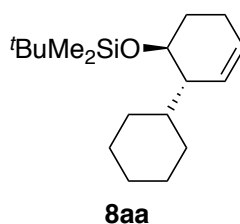


(*R*)-(E)-(6-Phenyl-3-hexen-2-yl)cycloheptane (6ca)



The product **6ca** was purified by flash chromatography on silica gel (hexane) [78% isolated yield from **5a**]. Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 0.90 (d, *J* = 6.8 Hz, 3H), 1.09–1.20 (m, 2H), 1.30–1.48 (m, 4H), 1.51–1.71 (m, 7H), 2.00 (dq, *J* = 6.4, 6.0 Hz, 1H), 2.31 (dt, *J* = 7.2, 6.0 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 5.31 (dt, *J* = 15.6, 6.0 Hz, 1H), 5.37 (dd, *J* = 15.6, 6.0 Hz, 1H), 7.15–7.19 (m, 3H), 7.25–7.29 (m, 2H). ¹³C NMR (100.5 MHz, CDCl₃) δ 17.33, 27.20, 27.27, 28.21, 28.36, 31.14, 31.56, 34.51, 36.20, 42.79, 44.46, 125.62, 128.04, 128.16, 128.51, 135.60, 142.17. **HRMS–EI** (*m/z*): [*M*]⁺ calcd for C₁₉H₂₈, 256.2191; found, 256.2189. [α]_D²⁶ –10.0 (*c* 0.67, CHCl₃). The ee value (47% ee) was determined by chiral HPLC analysis of **6ca**, [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane, 0.25 mL/min, 40 °C, 220 nm UV detector, retention time = 15.6 min for the *R* isomer and 16.4 min for the *S* isomer]. The absolute configuration of **6ca** was assigned by consideration of the stereochemical pathway.

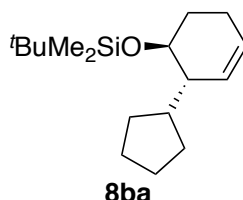
***trans*-*tert*-Butyl[(2-cyclohexyl-3-cyclohexen-1-yl)oxy]dimethylsilane (8aa)**



The product **8aa** was purified by flash chromatography on silica gel (hexane) [85% isolated yield from **7a**].

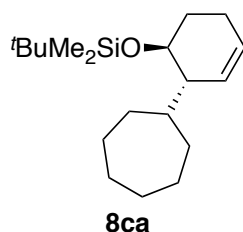
Colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.07 (s, 6H), 0.89 (s, 9H), 0.90 (m, 1H), 1.05–1.29 (m, 4H), 1.54–1.83 (m, 8H), 1.91–2.14 (m, 3H), 3.70 (m, 1H), 5.50 (ddd, $J = 10.0, 4.0, 2.4$ Hz, 1H), 5.62 (m, 1H). $^{13}\text{C NMR}$ (100.5 MHz, CDCl_3) δ –4.74, –4.09, 18.10, 24.30, 25.90, 26.58, 26.76, 27.12, 27.83, 31.53, 31.66, 37.46, 49.91, 69.11, 126.56, 127.14. **Anal.** Calcd for $\text{C}_{18}\text{H}_{34}\text{OSi}$: C, 73.40; H, 11.63%. Found: C, 73.03; H, 11.64%.

***trans-tert*-Butyl[(2-cyclopentyl-3-cyclohexen-1-yl)oxy]dimethylsilane (**8ba**)**



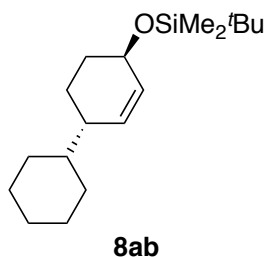
The product **8ba** was purified by flash chromatography on silica gel (hexane) [90% isolated yield from **7a**]. Colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.14 (m, 1H), 1.28 (m, 1H), 1.43–1.66 (m, 6H), 1.71–1.79 (m, 2H), 1.92–2.07 (m, 3H), 2.14 (m, 1H), 3.68 (m, 1H), 5.52 (ddd, $J = 10.4, 4.4, 2.4$ Hz, 1H), 5.68 (m, 1H). $^{13}\text{C NMR}$ (100.5 MHz, CDCl_3) δ –4.68, –4.24, 18.11, 23.24, 25.50, 25.71, 25.90, 28.30, 29.77, 30.58, 41.09, 48.03, 70.84, 126.99, 127.23. **Anal.** Calcd for $\text{C}_{17}\text{H}_{32}\text{OSi}$: C, 72.79; H, 11.50%. Found: C, 72.78; H, 11.54%. The stereochemistry of **8ba** was assigned by consideration of the stereochemical pathway.

***trans-tert*-Butyl[(2-cycloheptyl-3-cyclohexen-1-yl)oxy]dimethylsilane (**8ca**)**



The product **8ca** was purified by flash chromatography on silica gel (hexane) [73% isolated yield from **7a**]. Colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.09 (m, 1H), 1.35–1.75 (m, 12H), 1.79–1.91 (m, 2H), 2.01–2.10 (m, 3H), 3.61 (m, 1H), 5.46 (dd, $J = 10.0, 2.0$ Hz, 1H), 5.63 (dd, $J = 10.0, 3.2$ Hz, 1H). $^{13}\text{C NMR}$ (100.5 MHz, CDCl_3) δ –4.66, –3.87, 18.08, 24.79, 25.91, 27.51, 28.05 ($\times 2$ C), 28.15, 28.74, 31.98, 34.16, 37.95, 51.90, 70.04, 126.90, 127.24. **Anal.** Calcd for $\text{C}_{19}\text{H}_{36}\text{OSi}$: C, 73.95; H, 11.76%. Found: C, 74.13; H, 11.86%. The stereochemistry of **8ca** was assigned by consideration of the stereochemical pathway.

***trans-tert*-Butyl[(4-cyclohexyl-2-cyclohexen-1-yl)oxy]dimethylsilane (**8ab**)**



The product **8ab** (*trans/cis* 93:7) was purified by flash chromatography on silica gel (hexane) [49% isolated yield from **7b**]. Colorless oil. **¹H NMR** (400 MHz, CDCl₃) δ 0.05–0.09 (m, 0.93 $\times$ 6H, 0.07 $\times$ 6H), 0.90 (s, 0.93 $\times$ 9H, 0.07 $\times$ 9H), 0.93–1.35 (m, 0.93 $\times$ 8H, 0.07 $\times$ 8H), 1.47 (m, 0.93 $\times$ 1H, 0.07 $\times$ 1H), 1.57–1.74 (m, 0.93 $\times$ 7H, 0.07 $\times$ 7H), 1.94–2.00 (m, 0.93 $\times$ 2H, 0.07 $\times$ 2H), 4.12 (m, 0.07 $\times$ 1H), 4.23 (m, 0.93 $\times$ 1H), 5.58 (ddd, J = 10.0, 3.6, 1.2 Hz, 0.93 $\times$ 1H), 5.64 (dd, J = 10.0, 3.2 Hz, 0.93 $\times$ 1H), 5.70 (m, 0.07 $\times$ 2H). **¹³C NMR** (100.5 MHz, CDCl₃) δ –4.66, –4.50, 18.29, 20.98, 24.16, 25.94, 26.68, 29.57, 29.70, 30.09, 30.24, 30.50, 31.23, 32.99, 40.87, 41.04, 42.14, 42.47, 65.42, 68.34, 130.09, 132.02, 132.17, 133.12. **HRMS–EI** (m/z): [M]⁺ calcd for C₁₈H₃₄OSi, 294.2379; found, 294.2370. The stereochemistry of **8ab** was assigned by consideration of the stereochemical pathway.

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- (8) The use of Cu(acac)₂ or copper(I) thiophene-2-carboxylate instead of CuOAc under phosphine-free conditions (Table 1, entry 1) resulted in no reaction.
- (9) The effect of ligands on the reaction of primary alkylborane also was examined (CuOAc/MeOK/toluene/60 °C). Reaction between 2-phenyl-ethyl-9-BBN and (*S*)-(*Z*)-**3a** with PPh₃ or PCy₃ gave moderate 1,3-*syn* selectivity (*syn/anti* 79:21, 81% yield and *syn/anti* 89:11, 84% yield, respectively). In contrast, phosphine-free conditions resulted in greater 1,3-*syn* selectivity (*syn/anti* 97.5:2.5, 95% yield).
- (10) Several observations concerning the optimum reaction conditions should be noted. Reaction with cyclohexylboronic acid and its pinacolate ester instead of secondary alkyl-9-BBN reagents did not produce

any coupling product, leaving unreacted substrates. Using diethyl phosphate instead of diisopropyl phosphate as a leaving group was useful, although it produced a slightly decreased stereoselectivity (*syn/anti* 98:2, 87%).

- (11) Details of the DFT calculations will be reported elsewhere.
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Chapter 2

Copper-Catalyzed Enantioselective Allyl–Allyl Cross-Coupling between Allylboronates and Allylic Phosphates with a Phenol/NHC Chiral Ligand

Introduction

Chiral 1,5-dienes with a stereogenic center at the allylic/homoallylic position are found in many important biologically active molecules such as FK-506, Plakortide E, and Chaetoglobosin A (Figure 1),¹ and also serve as useful building blocks in organic synthesis due to the versatility of the two alkene functionalities for further transformations. While several methods have been developed to produce chiral 1,5-dienes,² enantioselective γ -substitution of allyl alcohol derivatives with organometal reagents (allyl–allyl coupling) using the chiral transition metal complexes as catalysts is the most straightforward because it uses readily available substrates.³

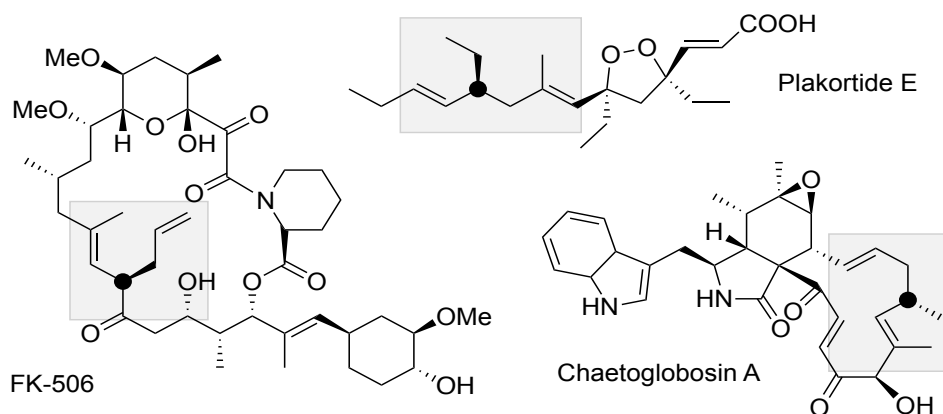


Figure 1. Biologically active compounds

In 2010, Morken and co-workers reported the pioneering example of catalytic asymmetric allyl–allyl coupling; Pd-catalyzed allyl–allyl coupling between substituted allylboronates⁴ and (*E*)-allylic carbonates occurred with high regio- and enantioselectivity.⁵ This protocol enabled access to chiral 1,5-dienes containing contiguous stereogenic centers with high diastereo- and enantioselectivity. More recently, Feringa's group reported asymmetric cross-coupling between allyl Grignard reagents and (*E*)-allyl bromides using the copper-chiral monodentate phosphoramidite catalyst, but only moderate S_N2' regioselectivity was obtained.⁶ In 2014, Carreira *et al.* developed Ir-catalyzed regio- and enantioselective allylic cross-coupling between allylsilanes and secondary aromatic allylic alcohols.⁷ Despite these efforts, the allyl–allyl coupling was limited to use of acyclic (*E*)-allylic electrophiles.

In Chapter 2, the author describes the Cu-catalyzed enantioselective allyl–allyl coupling between allylboronates and allylic phosphates^{8–10} using a new chiral *N*-heterocyclic carbene (NHC) ligand bearing a phenolic hydroxyl group.^{11,12} This reaction occurs with exceptional γ -regioselectivity and high enantioselectivity. Various functional groups were tolerated. The ability to use (*Z*)-aliphatic allylic substrates in the copper catalysis was complementary to Morken's Pd system (in their reports, only primary (*E*)-allylic electrophiles were used).⁵

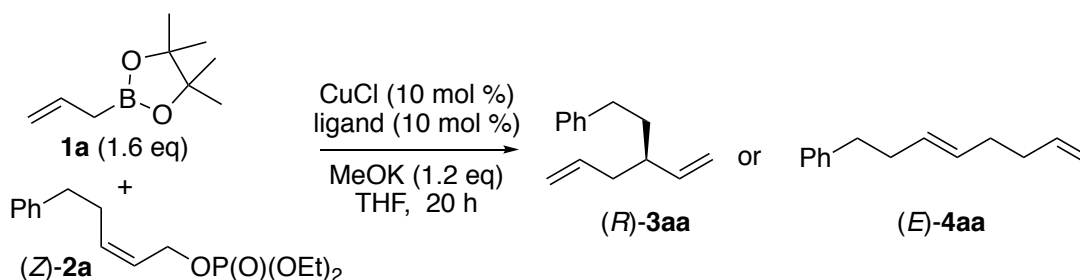
Results and Discussion

Enantioselective S_N2' allylic alkylation between non-allylic alkylboranes (alkyl-9-BBN) and primary allylic substrates using a catalytic amount of a chiral bisphosphine/Cu(I) complex and a stoichiometric amount of potassium alkoxide base has been reported.¹³ The results prompted the initiation of a program to develop a Cu-catalyzed enantioselective allylic substitution with allylboron reagents. For screening of the reaction conditions, commercially available allylboronic acid pinacolate esters were used instead of the allyl-9-BBN reagents (Table 1).¹⁴ While investigating an effective achiral ligand that could selectively produce the racemic, branched γ -substitution product (**3aa**), a ring-saturated NHC/Cu complex prepared *in situ* from 1,3-bis(2,4,6-trimethylphenyl)imidazolinium chloride (SIMes·HCl), CuCl, and MeOK was produced in high yield (93%) with exclusive γ -regioselectivity ($\gamma/\alpha > 99:1$) to form the branched coupling product **3aa** from reaction between 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1a**) and γ -monosubstituted primary (*Z*)-allylic phosphate **2a** in THF at -20°C (entry 1). In contrast to the excellent performance of the ring-saturated NHC ligand SIMes, the corresponding unsaturated NHC ligand IMes, derived from 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl), gave a mixture of branched and linear products with a low γ/α regioselectivity (62:38) and moderate total product yield (entry 2). Without a ligand, or with 1,10-phenanthroline (Phen) or 1,2-bis(diphenylphosphino)ethane (DPPE) ligands, no reaction occurred (entries 3–5). The use of triphenylphosphine (Ph_3P) as a monodentate phosphine ligand gave only the linear α -substitution product (*E*)-**4aa** (entry 6).

Based on these results, focus was placed on ring-saturated chiral NHC ligands (Table 1, entries 7–14). The C_2 -symmetric imidazolinium chloride [(*S,S*)-**L1**·HCl],¹⁵ which has two stereogenic carbon centers in the imidazolidine ring with two *N*-mesityl groups, did not result in enantioselectivity; the branched, nearly racemic coupling product **3aa** was obtained with exclusive regioselectivity and moderate yield (entry 7). When similar chiral NHC ligands (**L2**, **L3**) bearing 2-methylphenyl (**L2**) or 2-methoxyphenyl (**L3**) groups were used instead of one of the mesityl groups in **L1**, enantioselectivity was moderate (50% and 54% ee), but yields were low (entries 8 and 9). Next, the imidazolinium salt **L4**·HBF₄ bearing a 2-hydroxyphenyl group was used (entry 10). A previous report indicated that **L4** exhibited high ligand performance in enantioselective Cu-catalyzed allylic substitution with terminal alkyne as pronucleophiles.^{11a} Fortunately, the Cu-**L4** catalyst system produced better results; the coupling product was formed in greater yield (77%) and with greater enantioselectivity (85% ee) compared to the system using (*S,S*)-**L2** or **L3**, without decreasing regioselectivity. These results indicated that the phenolic hydroxy group in **L4** has a functional role. Changing the *N*-mesityl group of **L4**·HBF₄ to a *N*-2,4-dicyclohexyl-6-methylphenyl group to afford the new phenol-NHC chiral ligand precursor **L5**·HBF₄, resulted in greater enantioselectivity (92% ee), a high yield (83%), and exceptional regioselectivity ($\gamma/\alpha > 99:1$) (entry 11). Furthermore, the enantioselectivity was achieved (99% ee) by decreasing the reaction temperature to -40°C (entry 12). In contrast, the naphthol-NHC chiral ligands **L6** and **L7**^{11b} were not effective (entries 13 and

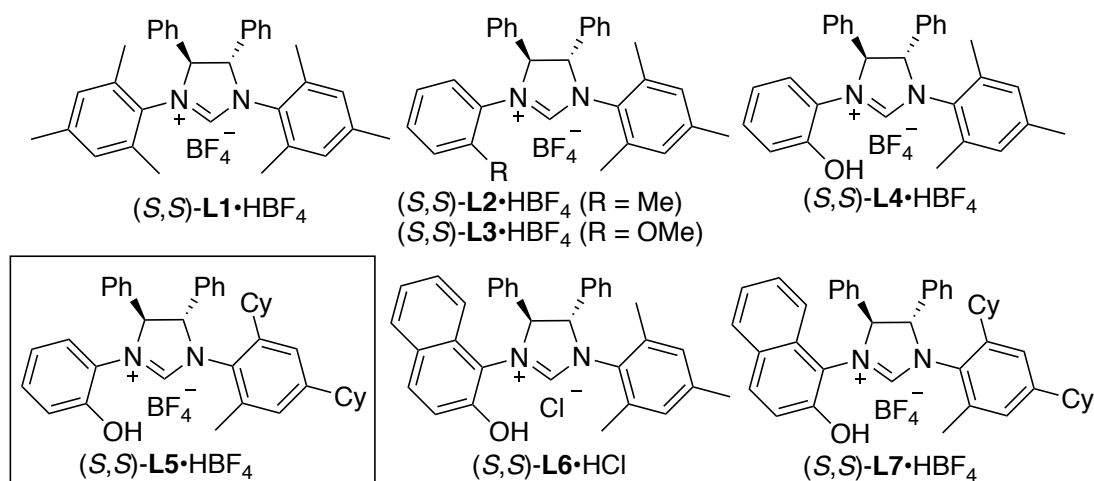
14).

Table 1. Ligand effects for reaction between **1a** and (Z)-**2a**^a



Entry	Ligand	Temp (°C)	Yield (%) ^b	γ/α (3aa : 4aa) ^c	Ee (%) ^d
1	SIMes·HCl	−20	93	>99:1	—
2	IMes·HCl	−20	65	62:38	—
3	none	−20	0	—	—
4	Phen	−20	0	—	—
5	DPPE	−20	0	—	—
6	PPh ₃	−20	57	1:>99	—
7	(<i>S,S</i>)- L1 ·HBF ₄	−20	49	>99:1	2
8	(<i>S,S</i>)- L2 ·HBF ₄	−20	13	>99:1	50
9	(<i>S,S</i>)- L3 ·HBF ₄	−20	10	>99:1	54
10	(<i>S,S</i>)- L4 ·HBF ₄	−20	77	>99:1	85
11	(<i>S,S</i>)- L5 ·HBF ₄	−20	83	>99:1	92
12 ^[e]	(<i>S,S</i>)- L5 ·HBF ₄	−40	80	>99:1	99
13	(<i>S,S</i>)- L6 ·HCl	−20	34	92:8	67
14	(<i>S,S</i>)- L7 ·HBF ₄	−20	56	>99:1	82

[a] Conditions: **1a** (0.24 mmol), (Z)-**2a** (0.15 mmol), CuCl/ligand (10 mol %), MeOK (0.18 mmol), THF (0.6 mL) for 20 h. [b] Yield of isolated product. [c] Determined by ¹H NMR analysis of the crude product. [d] The ee was determined by HPLC. [e] **1a** (1.9 mmol) and (Z)-**2a** (1.2 mmol) were used. Reaction was conducted for 48 h.



Next, the effect of copper salts (Table 2) was investigated. When CuOAc was used as the catalyst, regioselectivity (γ/α 91:9) and enantioselectivity (76% ee) decreased. The use of Cu(OAc)₂ instead of Cu(I) salt, resulted in a modest yield and low selectivities. Changing CuCl to CuOTf•toluene_{1/2} afforded similar selectivity but a lower product yield. Use of MesCu and cationic Cu(MeCN)₄PF₆ was as effective as CuCl, and gave comparable results.

The effect of solvent is also shown in Table 2. Reaction in toluene gave only the racemic product in moderate yield (43%) and low regioselectivity (γ/α 64:36). Dichloromethane was ineffective in the reaction (26% yield, γ/α 71:29, 51% ee). No reaction occurred in MeCN or hexane.

Table 2. Effects of copper salts and solvents^a

Entry	Copper Salt	Solvent	Yield (%) ^b	γ/α [(<i>R</i>)- 3aa :(<i>E</i>)- 4aa] ^c	Ee (%) ^d
1 ^e	CuCl	THF	83	>99:1	92
2	CuOAc	THF	85	91:9	76
3	Cu(OAc) ₂	THF	68	73:27	52
4	CuOTf• toluene _{1/2}	THF	48	>99:1	90
5	MesCu	THF	85	>99:1	89
6	Cu(MeCN) ₄ PF ₆	THF	73	>99:1	88
7	CuCl	toluene	43	64:36	0
8	CuCl	DCM	26	71:29	51
9	CuCl	MeCN	0	—	—
10	CuCl	hexane	0	—	—

[a] Conditions: **1a** (0.24 mmol), (*Z*)-**2** (0.15 mmol), Cu salt/(*S,S*)-**L5**•HBF₄ (10 mol%), MeOK (0.18 mmol), solvent (0.6 mL), −20 °C for 20 h. [b] Yield of isolated product. [c] Determined by ¹H NMR of crude product. [d] The ee was determined by HPLC. [e] Table 1, entry 11.

The effects of leaving groups and bases are summarized in Table 3. The use of allyl bromide or chloride as an allylic electrophile under the conditions described for Table 1, entry 11, decreased both regio- and enantioselectivity (entries 2 and 3).

The nature of the base had a significant impact on yield and selectivities (Table 3). Use of MeONa instead of MeOK decreased regioselectivity (γ/α 89:11) and enantioselectivity (74% ee) (entry 4). No reaction occurred with MeOLi, due to the greater solubility of LiCl or LiOP(O)(OEt)₂, which may form inactive Cu species through ionic interactions (entry 5). The structure of the alkoxide moiety of the base also had a strong impact on yield, regioselectivity, and enantioselectivity. Thus, when MeOK was changed to a sterically more demanding base, *t*BuOK, product yield was moderate and both regioselectivity and enantioselectivity decreased

significantly (entry 6). This result suggests that the trialkoxyboron ROBpin may participate in the reaction because Lewis acids activate the phosphate leaving group (see Figure 3). Coupling reaction with K₂CO₃ did not occur (entry 7).

Table 3. Effect of leaving group and bases^a

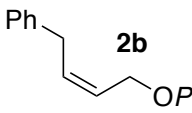
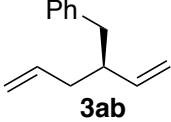
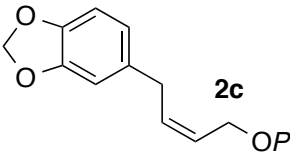
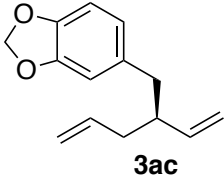
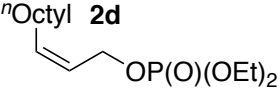
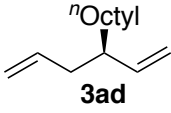
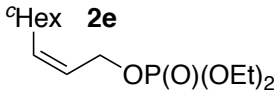
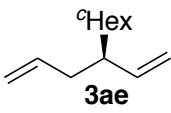
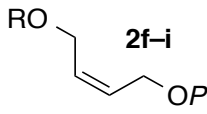
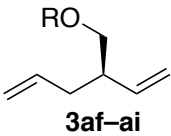
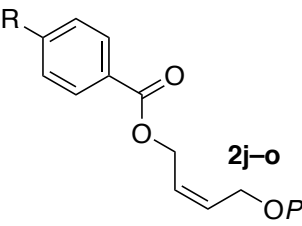
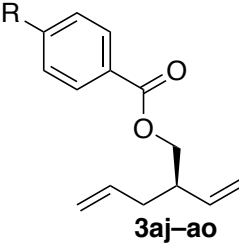
Entry	Leaving group	Base	Yield (%) ^b	γ/α [(<i>R</i>)- 3aa :(<i>E</i>)- 4aa] ^c	Ee (%) ^d
1 ^e	OP(O)(OEt) ₂ (2a)	MeOK	83	>99:1	92
2	Cl ^f	MeOK	89	94:6	64
3	Br ^g	MeOK	85	82:18	20
4	OP(O)(OEt) ₂ (2a)	MeONa	91	89:11	74
5	OP(O)(OEt) ₂ (2a)	MeOLi	0	—	—
6	OP(O)(OEt) ₂ (2a)	<i>t</i> BuOK	67	63:37	50
7	OP(O)(OEt) ₂ (2a)	K ₂ CO ₃	0	—	—

[a] Conditions: **1a** (0.24 mmol), (*Z*)-**2** (0.15 mmol), CuCl/(*S,S*)-**L5**·HBF₄ (10 mol%), base (0.18 mmol), THF (0.6 mL), −20 °C for 20 h. [b] Yield of isolated product. [c] Determined by ¹H NMR of crude product. [d] The ee was determined by HPLC. [e] Table 1, entry 11. [f] (*Z*)-(5-Chloro-3-penten-1-yl)benzene. [g] (*Z*)-(5-Bromo-3-penten-1-yl)benzene.

(*Z*)-Allylic phosphates with various aliphatic substituents were reacted with **1a** in the Cu-**L5** catalyst system (Table 4). When the 2-phenylethyl group of **2a** was replaced with a benzyl or octyl group, coupling proceeded with excellent γ -selectivity and preservation of enantioselectivity (entries 1 and 3). A sterically more demanding γ -substituent, such as a cyclohexyl group, was also tolerated and produced a high level of enantioselectivity (80% ee) (entry 4). Notably, the enantioselective reaction with 2-butene-1,4-diol derivatives, which have two potential leaving groups at different allylic positions, occurred with the allylic C–O bonds in the ether or carboxylic ester leaving groups untouched (entries 5–12 and 15).

The reaction has a great functional group compatibility (entries 2 and 5–12, 15–17). For example, an allylic phosphate (**2**) bearing a 1,3-benzodioxole (**2c**), THP ether (**2f**), benzyl ether (**2g**), silyl ether (**2h**, **q**), pivalate (**2i**), carbamate (**2p**) or *p*-toluenesulfonate (**2r**) group as the aliphatic γ -substituent, reacted with **1a** to produce the corresponding 1,5-diene derivatives in good yields with high enantioselectivities (85–97% ee) (entries 2, 5–8, 15–17). The absolute configuration of **3ae** {[α]_D²⁴ +3.7 (*c* 0.58, CHCl₃)} {lit^{5a}, (*S*) isomer, 91% ee, [α]_D²⁰ − 4.322 (*c* 0.62, CHCl₃)} and **3ah** {[α]_D²⁶ −3.6 (*c* 0.61, CHCl₃)} {lit^{5a}, (*S*) isomer, 90% ee, [α]_D²⁰ +6.3 (*c* 1.2, CHCl₃)} were determined by comparison of the specific rotations with the values reported previously. Methoxy, trifluoromethyl, bromo, or dimethylamino substituents were tolerated in the aromatic ring of the benzoate groups (entries 9–12). However, no reaction occurred with the allylic phosphate bearing a nitro (**2n**) or cyano (**2o**) group (entries 13 and 14).

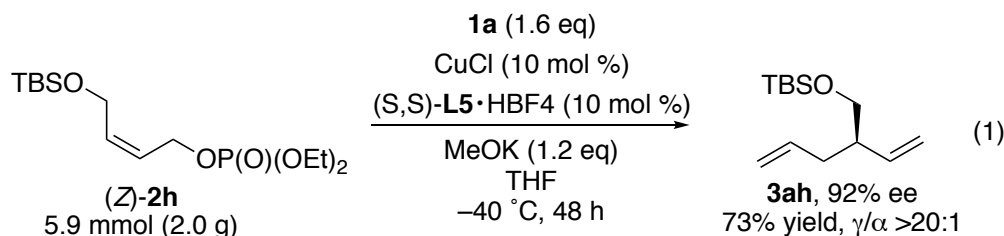
Table 4. Scope of allylic phosphates^a

Entry	Phosphate $OP = OP(O)(OEt)_2$	Product	Temp (°C)	Yield (%) ^{b,c}	Ee (%) ^d
1			-50	62	86
2			-30	97	86
3			-40	85	84
4			-50	59	80
					
5	R = THP (2f)	3af	-30	83	90
6	R = Bn (2g)	3ag	-50	75	85
7	R = TBS (2h)	3ah	-50	78	97
8	R = Piv (2i)	3ai	-30	70	91
					
9	R = MeO (2j)	3aj	-30	85	92
10	R = F ₃ C (2k)	3ak	-30	61	90
11	R = Br (2l)	3al	-30	65	90
12	R = Me ₂ N (2m)	3am	-30	87	91
13	R = NO ₂ (2n)	3an	-10	0	—
14	R = CN (2o)	3ao	-10	0	—

15			-30	80	90
16			-40	78	96
17			-30	88	92

[a] Conditions: **1a** (0.24 mmol), (*Z*)-**2** (0.15 mmol), CuCl/(*S,S*)-**L5**·HBF₄ (10 mol%), MeOK (0.18 mmol), THF (0.6 mL) for 48 h. [b] Yield of isolated product. [c] Constitutional isomer ratio $\gamma/\alpha > 20:1$ (determined by ¹H NMR of crude product). [d] The ee was determined by HPLC.

The potential for scaling up the enantioselective allyl–allyl coupling was examined on a preparative scale (Eq. 1). Reaction between allylboronate **1a** (9.4 mmol, 1.5 g) and allylic phosphate **2h** (5.9 mmol, 2.0 g) afforded only the branched coupling product in 73% yield (0.98 g, 4.3 mmol) with 92% ee.



The copper-catalyzed allyl–allyl coupling reaction between **1a** and enantioenriched 2-butene-1,4-diol derivative (*S*)-**2s** (99% ee) with (*R,R*)-**L5**·HBF₄ (*i.e.*, an enantiomeric isomer of (*S,S*)-**L5**·HBF₄) gave the corresponding 1,5-diene **3as** with two adjacent stereogenic centers with a 2*S*,3*S*-configuration in modest yield (51%) and high diastereoselectivity (d.r. 90:10) (Eq. 2). Without a ligand, or with (*S,S*)-**L5**·HBF₄, the reaction gave no or only a trace of the coupling product. Thus, the use of **L5** is mandatory, and (*R,R*)-**L5**-Cu system and the (*S*)-**2s** substrate is a matched pair, while (*S,S*)-**L5**/Cu complex and (*S*)-**2s** is mismatched. This result is in accord with a consideration of the Felkin-Anh model as depicted in Figure 2, which predicts preferred approach of organocopper nucleophile to *Si*-face of the allylic plain with a minimum *A*^{1,3}-strain.

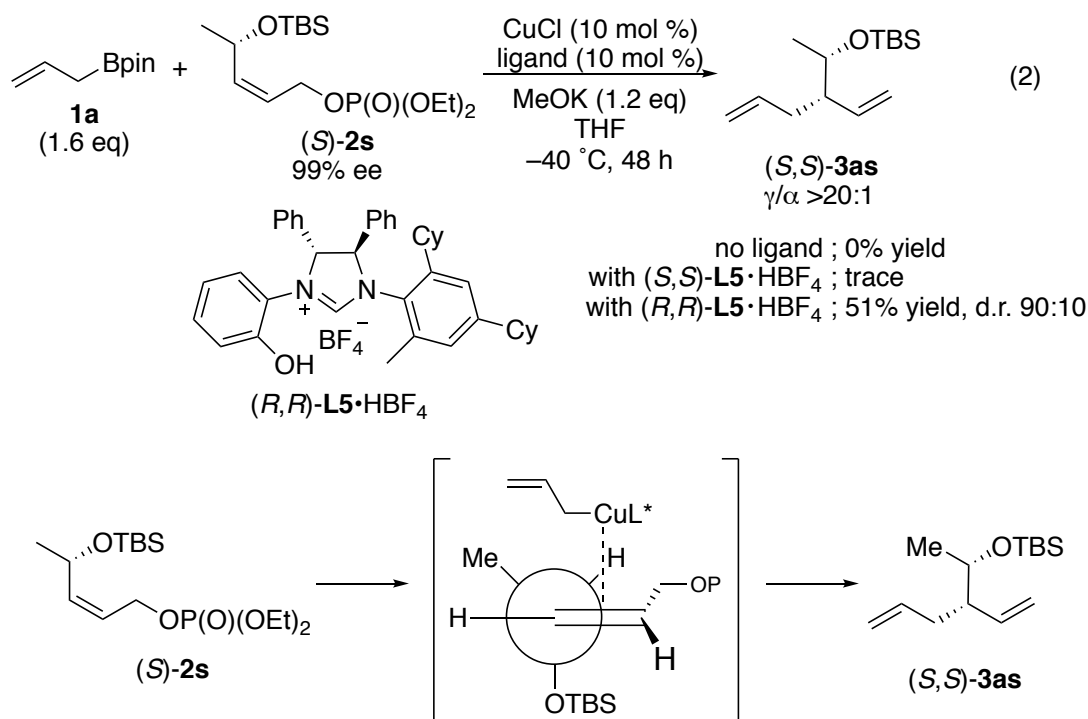
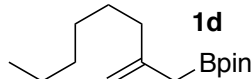
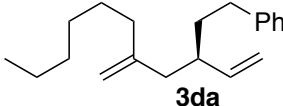
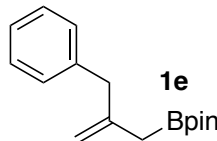
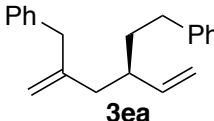
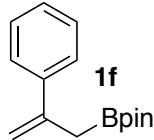
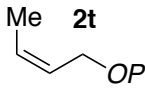
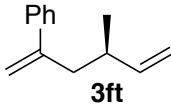
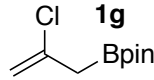
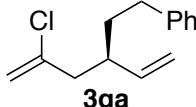


Figure 2. A Felkin-Anh-type stereoselection model

Reactions of β -substituted allylboronate derivatives using the Cu-**L5** catalyst system were investigated (Table 5). Methallylboronate **1b** and 2-ethyl-2-propen-1-ylboronate **1c** reacted with (Z)-**2a** with excellent γ -selectivity ($\gamma/\alpha > 20:1$) and high enantioselectivity (95% and 80% ee, respectively) (entries 1 and 2). An allylboronate with a hexyl, benzyl, or phenyl group at the β -position (**1d–f**) underwent reaction to afford the coupling products with enantiomeric excesses greater than 80%, while the regioselectivities were moderate (entries 3–5).¹⁶ The allylboronate with a chloro group at the β -position did not react (entry 6). In addition, no reaction occurred with γ -substituted allylboronates such as *trans*- or *cis*-crotylboronates.

Table 5. Scope of allylboronates^a

Entry	Allylboronate	Phosphate OP = OP(O)(OEt) ₂	Product	Yield (%) ^b	γ/α^c	Ee (%) ^d
1	1b 	2a 	3ba 	77	>20:1	95
2	1c 	2a 	3ca 	50	>20:1	80

3		1d Bpin	2a		3da	87	84:16	80	
4		1e Bpin	2a		3ea	59	87:13	82	
5		1f Bpin		2t		3ft	89	78:22	83
6		1g Bpin	2a		3ga	0	—	—	

[a] Data are taken from ref 8 for entries 1–5. Conditions: **1** (0.24 mmol), (*Z*)-**2** (0.15 mmol), CuCl/(*S,S*)-**L5**·HBF₄ (10 mol%), MeOK (0.18 mmol), THF (0.6 mL), –50 °C (entry 1) or –30 °C (entries 2–6) for 48 h. [b] Yield of isolated product. [c] Determined by ¹H NMR of crude product. [d] The ee was determined by HPLC.

The coupling reaction between **1a** and *cis*-4-cyclopentene-1,3-diol diphosphate **2u** catalyzed by the Cu-**L5** system occurred with adequate enantioselectivity, giving the *trans*-1,2-isomer **3au** (Eq. 3). The absolute configuration of **3au** was determined by the Mosher's NMR spectroscopic method (Figure 3).¹⁷ The *anti* stereochemistry of **3au** was assigned on the basis of ¹H NMR of *trans*-2-allyl-3-cyclopenten-1-ol¹⁸ obtained by dephosphorylation. The *cis* isomer was not detected by ¹H NMR. Reaction with *cis*-4-cyclohexene-1,3-diol derivative **2v** gave the *trans*-1,2-isomer **3av** with moderate enantiocontrol (66% ee) (Eq. 4). The *anti* stereochemistry of **3av** was also assigned on the basis of ¹H NMR of *trans*-2-allyl-3-cyclohexen-1-ol¹⁸ obtained by dephosphorylation. The *cis* isomer was not detected by ¹H NMR. These stereochemical results indicate that the present Cu-catalyzed reaction proceeded through an *anti*-S_N2' type reaction pathway. Morken's Pd-catalyzed protocol has not been applied to this type of cyclic allylic electrophile involving a *Z* alkene moiety.⁵

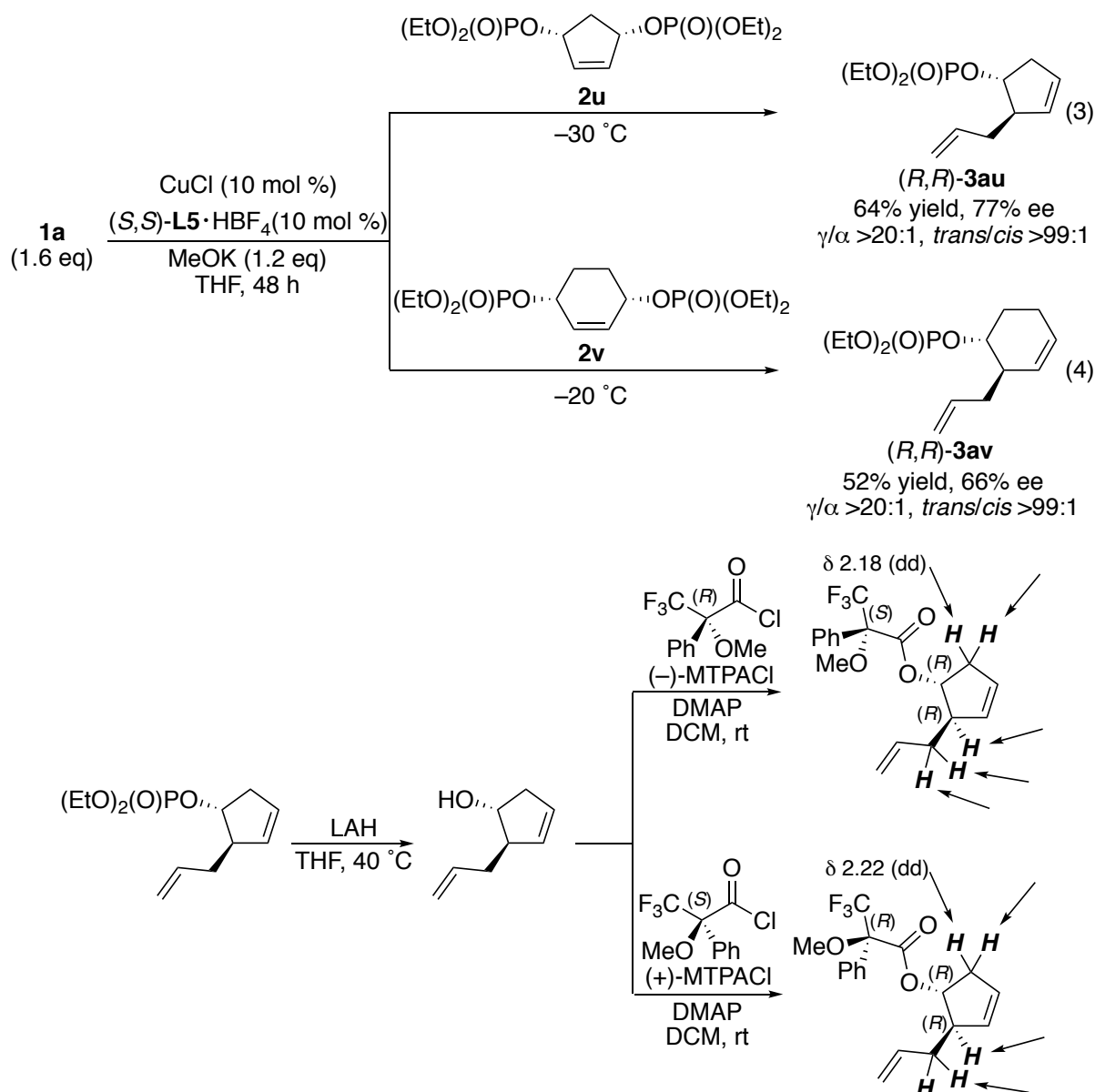


Figure 3. Determination for absolute configuration of **3au**

The alkene geometry of the allylic phosphates influenced both regio- and enantioselectivity. Thus, reaction between **1a** and (*E*)-**2a** under the conditions described in Table 1, entry 11 gave the linear α -substitution product (*E*)-**4aa** preferentially with minor formation of (*S*)-**3aa** (71% ee), the antipode of the product derived from (*Z*)-**2a** (Eq. 5). This α -selectivity appeared to occur *via* allylic 1,3-migration of Cu in the allylcopper(III) species. To gain insight into the nature of the postulated allylcopper(III) species, secondary allylic phosphate **2a'**, a constitutional isomer of (*Z*)-**2a**, was reacted under the same conditions (Eq. 6). Interestingly, this reaction gave results similar to reaction with (*E*)-**2a**. The convergence observed in the regioselectivity and stereochemistry suggests that (*E*)-**2a** and **2a'** led to a common equilibrium mixture of the allylcopper(III) species prior to reductive elimination to form the product mixture (Figure 4).¹⁹

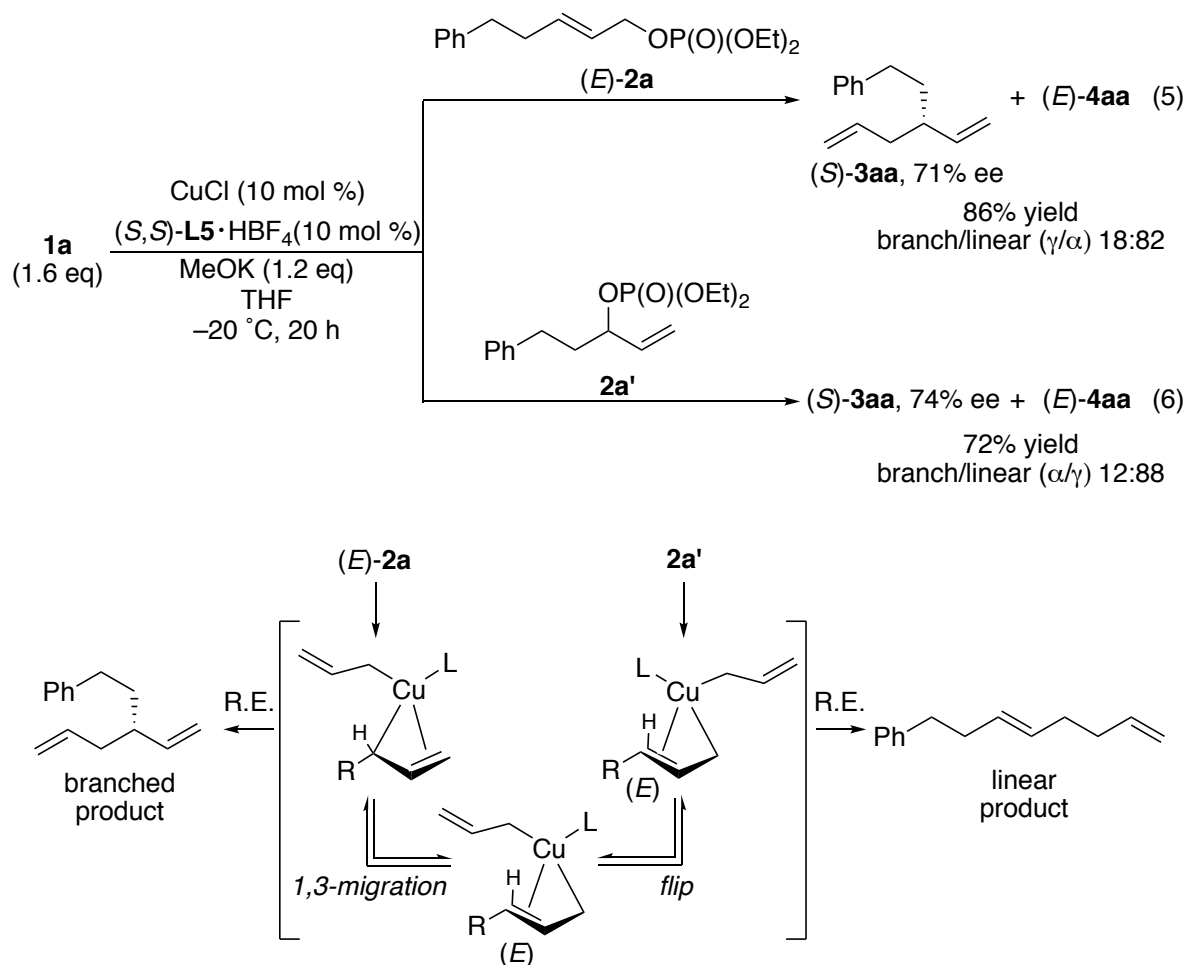


Figure 4. Allylcopper(III) species

Based on the assumption that γ -selective reaction of (Z)-**2** also occurs *via* allylcopper(III) intermediates, a catalytic cycle was proposed for the enantioselective allyl-allyl coupling catalyzed by the Cu-**L5** system, as shown in Figure 5.¹⁹ An alkoxycopper(I) complex (**A**) was formed from reaction between CuCl, **L5**·HBF₄, and MeOK. For this complex, the chiral NHC ligand coordinated to Cu as an anionic C,O-bidentate ligand. Then, transmetalation between **A** and an allylborate (**B**) afforded the potassium phenoxo(allyl)cuprate (**C**). Compound **C** formed a π -complex (**D**) with the allylic phosphate **2**, in which the Cu was *anti* to the phosphate leaving group. The MeOBpin may activate the phosphate group as a Lewis acid.^{13d} Subsequently, oxidative addition produced (π -en- σ -yl)copper(III) complex **E1** with a secondary sp³-carbon atom bound to Cu. Facile reductive elimination of **E1**, which was faster than allylic 1,3-Cu-migration to form **E2**, produced the branched γ -substitution product **3** and regenerated alkoxycopper(I) complex **A** (Figures 7 and 8 for enantio-discrimination models).

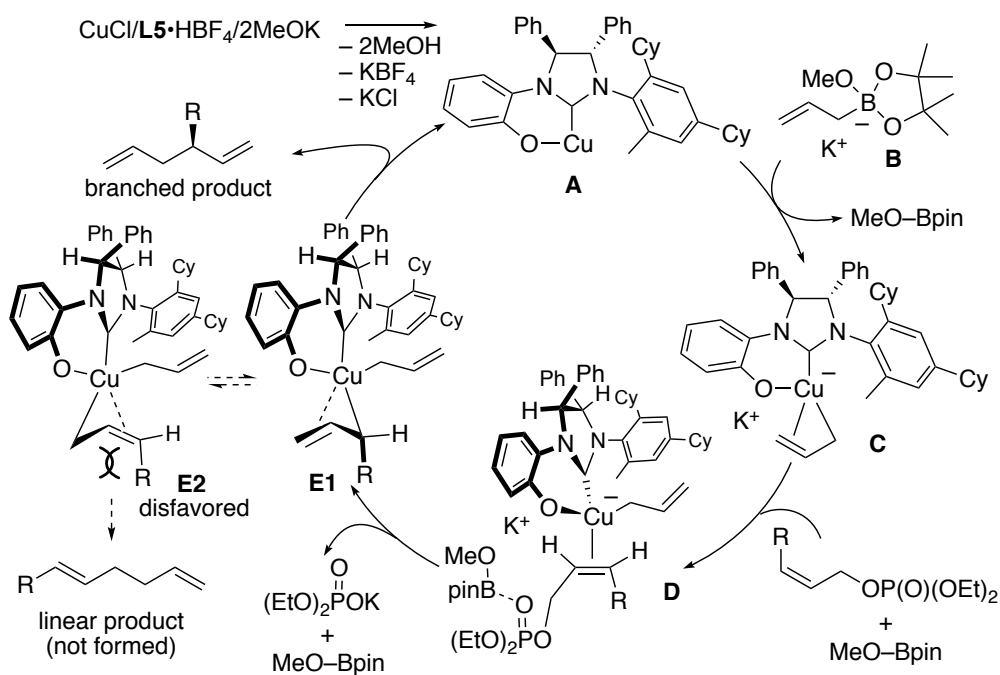


Figure 5. Postulated catalytic reaction pathway.

The formation of allylborate (**B**) was confirmed by the following method (Figure 6). The mixture of 2-allyl-5,5-dimethyl-1,3,2-dioxaborinane (**1a**) (37.8 μ L, 0.20 mmol) (Figure 6a) and MeOK (14.0 mg, 0.20 mmol) in THF-*d*₈ (0.6 mL) was stirred at 25 °C for 5 min. The mixture was then transferred to NMR tube. The ¹¹B NMR signal for **1a** (δ 32.6 ppm) disappeared and a new signal appeared upfield (δ 6.9 ppm) in the ¹¹B-NMR spectrum (Figure 6b), which was assigned to an allylborate (**B**) based on the comparison of the ¹¹B-NMR spectrum with that of the reported allylborate.²⁰

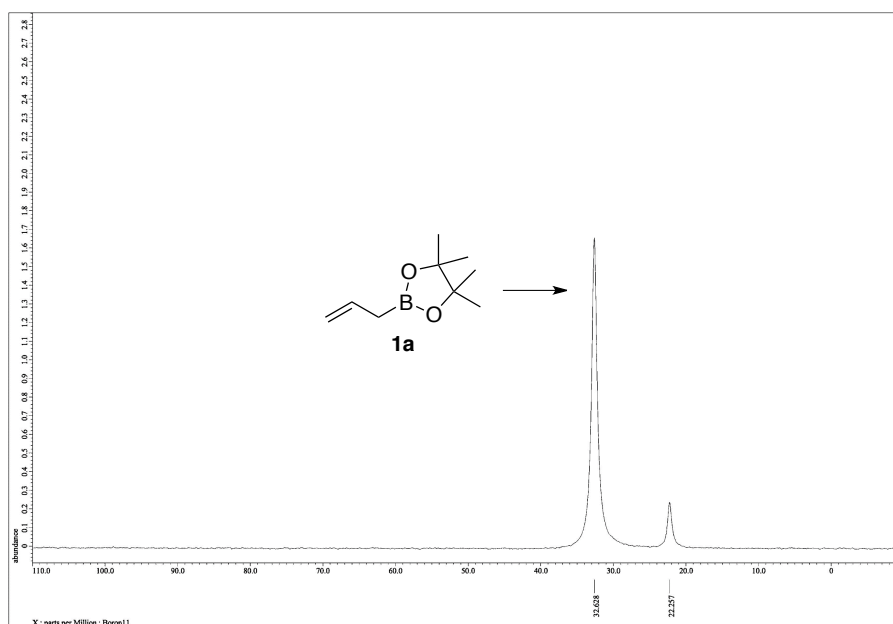


Figure 6a. [¹¹B NMR spectrum (128 MHz, rt, THF-*d*₈)]

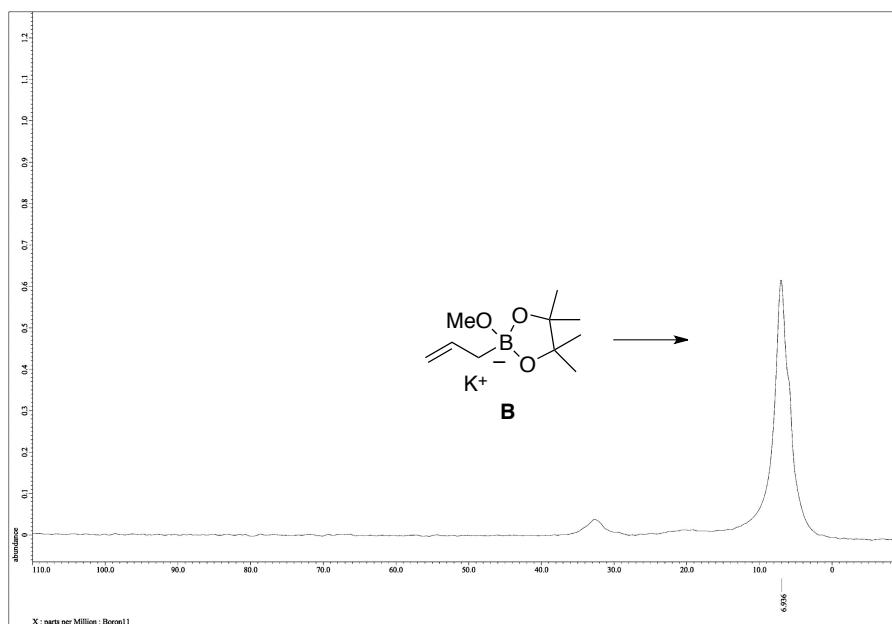


Figure 6b. [^{11}B NMR spectrum (128 MHz, rt, $\text{THF-}d_8$)]

Thus, the crucial dependence of regioselectivity on the *E/Z* geometry of the allylic substrate (**2**) can be explained by the greater instability of the allylcopper(III) intermediate **E2** compared to the corresponding Cu(III) species produced from the *E* substrate, due to larger steric repulsion in the allyl moiety derived from the *Z* substrate (Figure 4). Similar consideration may be applicable to the corresponding transition states that determine the *E/Z*-isomeric product distribution.

Reactions of *E*- and *Z*-isomers of **2a** gave the antipodes of **3aa**, (Table 1, entry 11 vs. Eq. 5), and the products from (*Z*)-**2a** were produced with greater enantioselectivity. This led to the proposal of the enantioselection models shown in Figs. 7 and 8. In the π -complex **D** (Figure 5), the chiral copper center adopted a tetrahedral coordination geometry including the C,O-bidentate chelation. The K^+ ion bridged the phenoxide oxygen and MeO-Bpin, which interacted with the phosphate leaving group as a Lewis acid. These assumptions suggest four possible π -complexes (**D1** and **D2** for the major enantiomer; **D3** and **D4** for the minor enantiomer) (Figure 7). Complex **D1** is the most favorable, because it results in the fewest steric repulsions between catalyst and allylic phosphate. Complexes **D2**, **D3**, and **D4** appear to be destabilized by the steric repulsions between the γ -substituent (R) and nonhydroxylated *N*-aryl group or one of the phenyl groups on the imidazolidine ring. These conclusions are consistent with the experimental observations that the enantioselectivity is influenced by the steric nature of the γ -substituent (R) (Table 4, entries 3 and 4) or the non-hydroxylated *N*-aryl group in the phenolic NHC ligands (Table 1, entries 10 and 11).

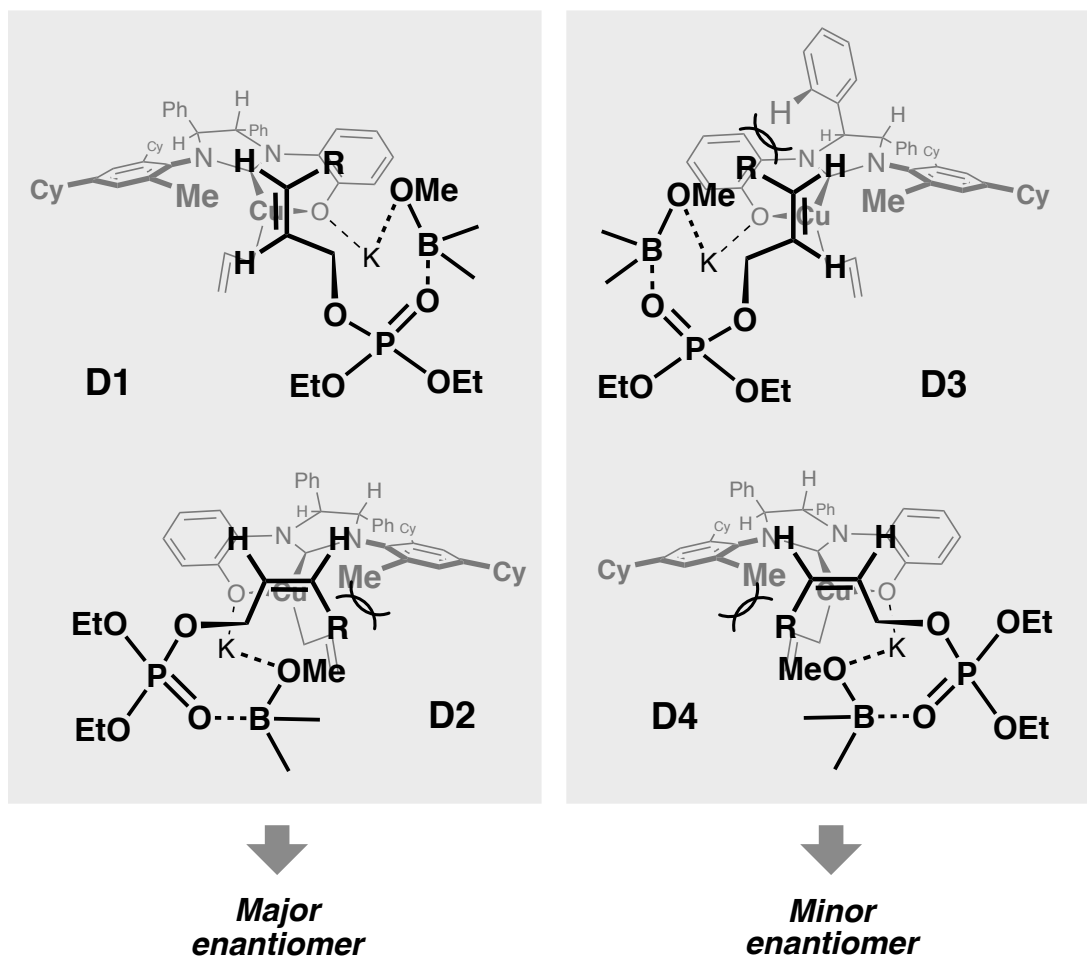


Figure 7. Models for enantioselection with (Z)-2

For reaction of (*E*)-2 (Fig. 8), the nonhydroxylated *N*-aryl group and/or the phenyl group in the imidazolidine ring caused steric repulsion toward the γ -substituent (R) for all postulated complexes **D1'**–**D4'**. These considerations explain the more efficient enantioselection in the reaction with allylic substrates having the *Z*-configuration.

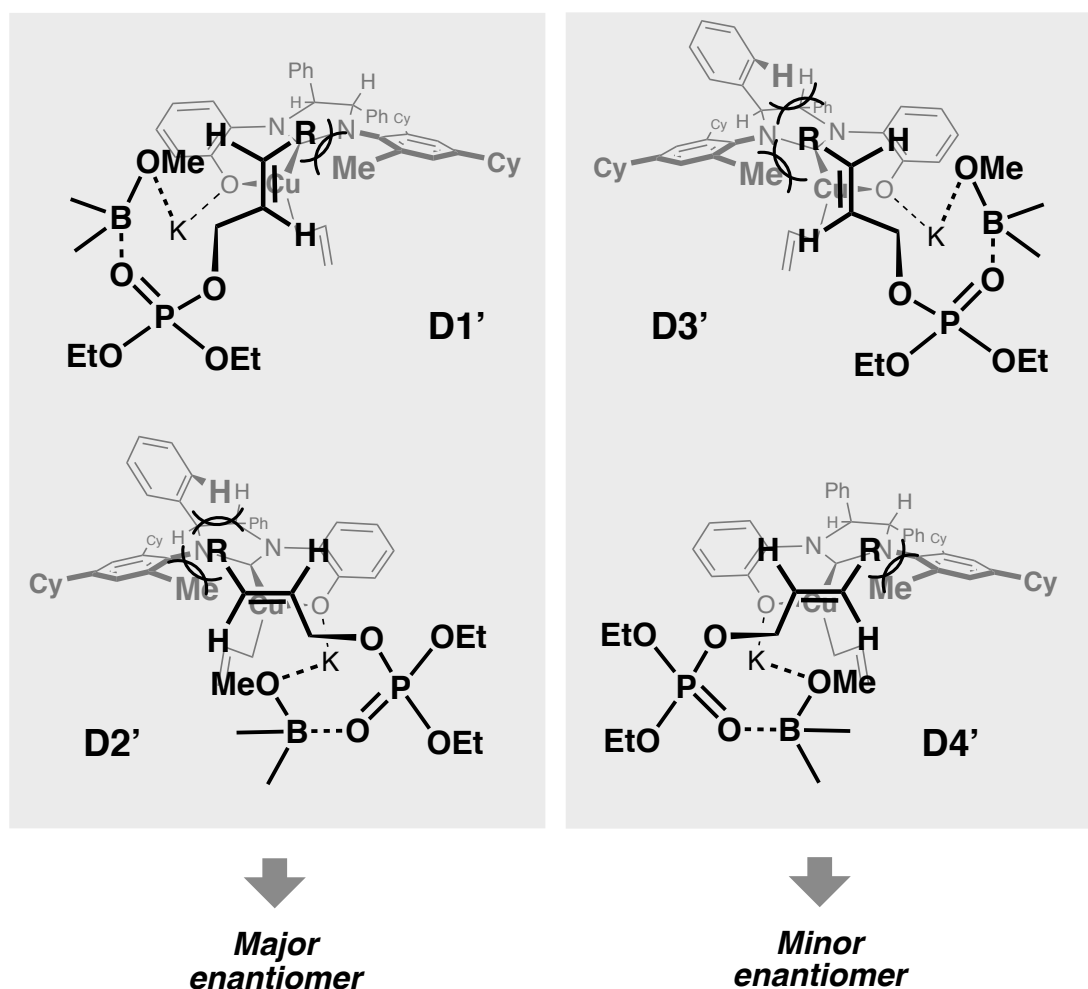


Figure 8. Models for enantioselection with (*E*)-2

Conclusion

In conclusion, a versatile method was developed for Cu-catalyzed enantioselective allyl–allyl coupling between allylboronates and (*Z*)-acyclic and cyclic allylic phosphates to form various chiral 1,5-diene derivatives. Catalysis of a Cu(I) complex with a new phenol-NHC chiral ligand enabled the reaction, demonstrating the utility of this class of chiral ligands for enantioselective copper catalysis with organoboron compounds.¹¹ This Cu-catalyzed protocol provides efficient access to functionalized, enantio-enriched chiral 1,5-dienes with a stereogenic carbon center at the allylic/homoallylic position. The broad functional group compatibility and the use of earth-abundant and relatively low-toxic Cu as a metal are attractive features of this protocol. A functional role for the phenolic hydroxy group in the chiral NHC ligand was suggested by the results.

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 128 MHz for ^{11}B 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. Silica gel (Kanto Chemical Co., Silica gel 60 N, spherical, neutral) was used for column chromatography. IR spectra were measured with a Perkin-Elmer Spectrum One. 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, CHCl_3 , 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. CuCl , and MeOK were purchased from Aldrich Chemical Co., stored under nitrogen, and used as received. THF was purchased from Kanto Chemical Co., and stored under argon. 2-Allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1a**) was obtained from commercial suppliers. Allylboronates **1b**,^{21a} **1c–e**,^{21b} **1f**,^{21c} and **1g**,²² were prepared according to the reported procedures. Allylic phosphates **2a**, **2d**, **2e**, **2q**, **2r**, **2t–v** and **2a'** are found in the literature.^{11a, 23, 24} NHC ligands **L3**, **L4**, **L6**, and **L7** are found in the literature.^{11a, b} (*E*)-**4aa** are found in the literature.^{3e}

Preparation of Allylic Phosphates

Preparation of 2a–r, 2t, (E)-2a and 2a'.^{11a} **2a–e**, **2q**, **2r** and **2t** were prepared through the phosphorylation of the corresponding allylic alcohols obtained by Lindlar reduction of the known propargylic alcohols. **2f–p** were prepared through the monoprotection of commercial available (*Z*)-2-butene-1,4-diol followed by phosphorylation. (*E*)-**2a** and **2a'** were prepared through the phosphorylation of the corresponding allylic alcohols.

The phosphorylation of (*Z*)-5-phenyl-2-penten-1-ol to **2a** is representative. To a solution of (*Z*)-5-phenyl-2-penten-1-ol (811 mg, 5 mmol) in pyridine (6 mL), $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$ (0.86 mL, 6.0 mmol) and DMAP (24.4 mg, 0.2 mmol) were sequentially added at 0 °C. After being stirred at rt for 1 h, the reaction mixture was diluted with EtOAc (20 mL) and was treated with H_2O (5 mL). The resulting mixture was washed with saturated CuSO_4 aq. (10 mL $\times$ 3) and brine, and was dried over anhydrous MgSO_4 , filtered, and evaporated under reduced pressure. The residue was purified through flash column chromatography on silica gel (10–45% EtOAc /hexane)

to provide (*Z*)-diethyl 5-phenyl-2-penten-1-yl phosphate (**2a**) in 85% yield (1.26 g, 4.24 mmol).

Preparation of Allylic Phosphate (*S*)-2s. (*S*)-3-Butyn-2-ol (99% ee) (1.2 mL, 15 mmol) and imidazole (2.0 g, 30 mmol) were dissolved in DCM (30 mL) at 0 °C. Then, TBDMSCl (3.4 g, 22 mol) was added to the mixture, and the solution was stirred at rt for 8 h. The reaction was quenched with H₂O and extracted with DCM (15 mL × 3). The combined organic layer was dried over MgSO₄. Then, the drying agent was removed by filtration, and a filtrate was evaporated under reduced pressure. A residue was purified by flash chromatography on silica gel (0–5% EtOAc/hexane) to give TBDMS-protected alcohol derivative (2.6 g, 14 mmol) in 96% yield.

"BuLi (9.6 mL, 15.8 mmol) was dropped to a solution of TBDMS-protected alcohol (2.6 g, 14 mmol) in Et₂O (29 mL) at –78 °C. The reaction mixture was stirred for 30 min before formaldehyde (877 mg, 29.2 mmol) was added to the mixture. The reaction vessel was removed from a cooling bath. After stirring at rt for 12 hours, the reaction was quenched with H₂O. The mixture was diluted with Et₂O and the organic layer was separated. The aqueous phase was extracted with Et₂O (15 mL × 2) and the combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash chromatography on silica gel (0–10% EtOAc/hexane) afforded the corresponding propargyl alcohol (2.3 g, 10 mmol) in 73% yield.

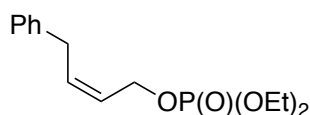
A solution of propargylic alcohol (1.1 g, 5 mmol) in hexane (4.3 mL)/acetone (790 µL) was added to the mixture of Pd/CaCO₃ (40.0 mg) and quinoline (397 µL, 3.6 mmol), and then the reaction mixture was filled with hydrogen gas. After confirming the completion of the reaction by ¹H NMR, Pd/CaCO₃ was removed 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) to give (*S,Z*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-penten-1-ol in 80% yield (874 mg, 4.0 mmol).

To a solution of (*S,Z*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-penten-1-ol (874 mg, 4.0 mmol) in pyridine (6.1 mL), (EtO)₂P(O)Cl (697 µL, 4.8 mmol) and DMAP (24 mg, 0.2 mmol) were sequentially added at 0 °C. After being stirred at rt for 3 h, the reaction mixture was diluted with EtOAc (20 mL) and was treated with H₂O (2 mL). The resulting mixture was washed with saturated CuSO₄ aq. (10 mL × 3) and brine, dried over anhydrous MgSO₄, filtered, and evaporated under reduced pressure. The residue was purified through flash column chromatography on silica gel (10–45% EtOAc/hexane) to provide (*S,Z*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-penten-1-yl diethyl phosphate (**2s**) in 94% yield (1.3 g, 3.8 mmol). The ee value of (*S*)-**2s** (99% ee) was determined by chiral HPLC analysis of the *p*-OMe-benzoate derivative of (*S,Z*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-penten-1-ol (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 = 13.7 min, for *R* isomer and 17.7 min for *S* isomer).

Preparation of 2u and 2v. **2u**²³ and **2v**²⁴ were prepared through the diphosphorylation of the corresponding 1,3-diols. The diphosphorylation of *cis*-4-cyclopentenene-1,3-diol to **2u** is representative. To a solution of *cis*-4-cyclopentenene-1,3-diol (200 mg, 2 mmol) in pyridine (8 mL), (EtO)₂P(O)Cl (0.63 mL, 4.4 mmol) and DMAP (48 mg, 0.4 mmol) were sequentially added at 0 °C. After being stirred at rt for 10 h, the reaction mixture was diluted with EtOAc (10 mL) and was treated with H₂O (1 mL). The resulting mixture was washed with saturated CuSO₄ aq. (5 mL × 3) and brine, and was dried over anhydrous MgSO₄, filtered, and evaporated under reduced pressure. The residue was purified by a short plug of aluminum oxide (Et₂O) followed by GPC (CHCl₃) to provide **2u** in 60% yield (446 mg, 1.2 mmol).

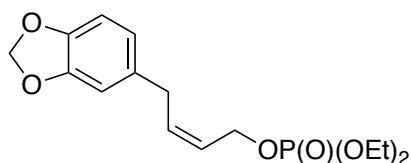
Characterization Data for Allylic Phosphates

(*Z*)-Diethyl(4-phenyl-2-buten-1-yl)phosphate (2b)



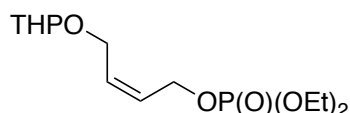
Colorless Oil. IR (neat) 698, 742, 957, 1010, 1261, 1454, 1495, 2908, 2983, 3027 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 1.33 (dt, *J* = 6.8, 0.8 Hz, 6H), 3.46 (d, *J* = 7.6 Hz, 2H), 4.12 (quintet, *J* = 6.8 Hz, 4H), 4.71 (dd, *J* = 7.6, 7.6 Hz, 2H), 5.73 (dtd, *J* = 11.2, 7.6, 1.2 Hz, 1H), 5.84 (dt, *J* = 11.2, 7.6 Hz, 1H), 7.19 (m, 3H), 7.28 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 16.0 (d, *J* = 6.7 Hz), 33.6, 62.8 (d, *J* = 5.7 Hz), 63.7 (d, *J* = 5.7 Hz), 124.8 (d, *J* = 6.7 Hz), 126.1, 128.3, 128.5, 133.3, 139.5. HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₁₄H₂₁O₄NaP, 307.10697; found, 307.10672.

(*Z*)-4-(Benzo[d][1,3]dioxol-5-yl)-2-buten-1-yl Diethyl Phosphate (2c)



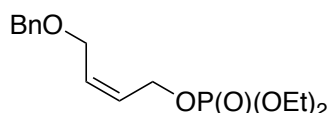
Colorless Oil. IR (neat) 782, 805, 959, 1010, 1243, 1442, 1488, 1503, 2907, 2983 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 1.34 (t, *J* = 7.2 Hz, 6H), 3.37 (d, *J* = 7.6 Hz, 2H), 4.12 (quintet, *J* = 7.6 Hz, 4H), 4.69 (dd, *J* = 7.2, 7.2 Hz, 2H), 5.71 (dt, *J* = 11.2, 7.6 Hz, 1H), 5.78 (dt, *J* = 11.2, 7.2 Hz, 1H), 5.92 (s, 2H), 6.62 (d, *J* = 7.6 Hz, 1H), 6.66 (s, 1H), 6.73 (d, *J* = 7.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 16.0 (d, *J* = 6.7 Hz), 33.2, 62.7 (d, *J* = 5.7 Hz), 63.7 (d, *J* = 5.7 Hz), 100.8, 108.1, 108.7, 121.0, 124.6 (d, *J* = 6.6 Hz), 133.2, 133.5, 145.8, 147.6. HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₁₅H₂₁O₆NaP, 351.09680; found, 351.09668.

(Z)-Diethyl{4-[(tetrahydro-2H-pyran-2-yl)oxy]-2-buten-1-yl}phosphate (2f)



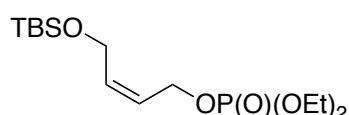
Colorless Oil. IR (neat) 752, 814, 869, 904, 970, 1016, 1119, 1262, 1392, 1442, 2941 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.34 (dt, $J = 6.8, 1.2$ Hz, 6H), 1.48–1.64 (m, 4H), 1.67–1.88 (m, 2H), 3.51 (m, 1H), 3.85 (m, 1H), 4.11 (quintet, $J = 6.8$ Hz, 4H), 4.13 (m, 1H), 4.29 (m, 1H), 4.61–4.67 (m, 3H), 5.71–5.82 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 16.0 (d, $J = 6.7$ Hz), 19.3, 25.3, 30.5, 62.1, 62.6, 63.0 (d, $J = 5.7$ Hz), 63.7 (d, $J = 5.7$ Hz), 98.0, 127.1 (d, $J = 6.6$ Hz), 130.3. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{25}\text{O}_6\text{NaP}$, 331.12810; found, 331.12813.

(Z)-4-(Benzyloxy)-2-buten-1-yl Diethyl Phosphate (2g)



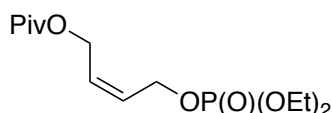
Colorless Oil. IR (neat) 698, 738, 801, 847, 974, 1017, 1071, 1262, 1368, 1454, 2908, 2983 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.32 (dt, $J = 7.6, 1.2$ Hz, 6H), 4.11 (qd, $J = 7.6, 7.2$ Hz, 6H), 4.51 (s, 2H), 4.61 (dt, $J = 6.4, 1.6$ Hz, 2H), 5.73–5.85 (m, 2H), 7.26–7.37 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3) δ 16.0 (d, $J = 6.7$ Hz), 62.9 (d, $J = 5.7$ Hz), 63.7 (d, $J = 5.7$ Hz), 65.6, 72.4, 127.2 (d, $J = 6.6$ Hz), 127.2, 127.7 (d, $J = 3.8$ Hz), 128.3, 130.6, 137.8. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{23}\text{O}_3\text{NaP}$, 337.11753; found, 337.11750.

(Z)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-buten-1-yl Diethyl Phosphate (2h)



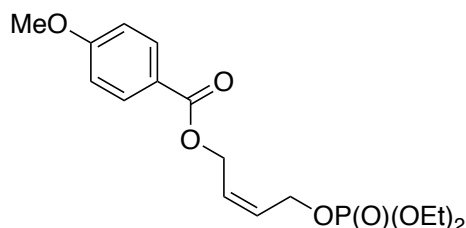
Colorless Oil. IR (neat) 666, 775, 834, 976, 1019, 1257, 1392, 1472, 2857, 2930, 2955 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.34 (t, $J = 7.2$ Hz, 6H), 4.11 (quintet, $J = 7.2$ Hz, 4H), 4.26 (d, $J = 6.0$ Hz, 2H), 4.63 (dd, $J = 8.0, 6.8$ Hz, 2H), 5.62 (dt, $J = 11.2, 7.2$ Hz, 1H), 5.73 (dt, $J = 11.2, 6.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ -5.3, 16.0 (d, $J = 6.7$ Hz), 18.2, 25.8, 59.4, 63.1 (d, $J = 4.8$ Hz), 63.7 (d, $J = 5.7$ Hz), 124.7 (d, $J = 7.6$ Hz), 133.6. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{32}\text{O}_5\text{PSi}$, 339.17511; found, 339.17452.

(Z)-4-[(Diethoxyphosphoryl)oxy]-2-buten-1-yl Pivalate (2i)



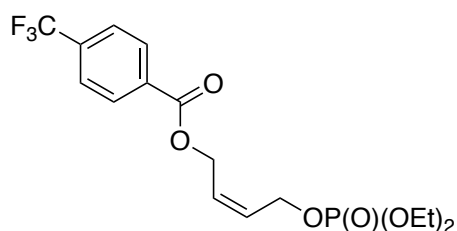
Colorless Oil. IR (neat) 746, 801, 859, 978, 1022, 1148, 1278, 1368, 1396, 1481, 1728, 2978 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.19 (s, 9H), 1.34 (t, $J = 7.6$ Hz, 6H), 4.11 (q, $J = 7.6$ Hz, 2H), 4.13 (q, $J = 7.6$ Hz, 2H), 4.64 (d, $J = 6.0$ Hz, 2H), 4.67 (d, $J = 6.0$ Hz, 2H), 5.71–5.83 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 16.0 (d, $J = 6.7$ Hz), 27.1, 38.6, 59.8, 62.7 (d, $J = 5.8$ Hz), 63.8 (d, $J = 5.7$ Hz), 128.1, 128.4 (d, $J = 6.7$ Hz), 178.1. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{25}\text{O}_6\text{NaP}$, 331.12810; found, 335.12816.

(Z)-4-[(Diethoxyphosphoryl)oxy]-2-buten-1-yl 4-Methoxybenzoate (2j)



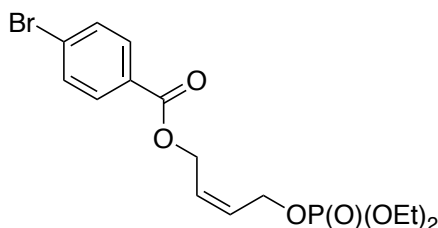
Colorless Oil. IR (neat) 696, 769, 847, 976, 1018, 1098, 1166, 1251, 1511, 1605, 1710, 2983 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.33 (t, $J = 6.8$ Hz, 6H), 3.85 (s, 3H), 4.12 (quintet, $J = 6.8$, 4H), 4.71 (dd, $J = 8.8$, 6.0 Hz, 2H), 4.87 (d, $J = 4.8$ Hz, 2H), 5.81–5.91 (m, 2H), 6.91 (d, $J = 12.0$ Hz, 2H), 7.98 (d, $J = 12.0$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 16.0 (d, $J = 6.7$ Hz), 55.3, 59.9, 62.7 (d, $J = 4.7$ Hz), 63.8 (d, $J = 5.7$ Hz), 113.6, 122.2, 128.1, 128.6 (d, $J = 6.7$ Hz), 131.6, 163.4, 165.9. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{23}\text{O}_7\text{NaP}$, 381.10736; found, 381.10742.

(Z)-4-[(Diethoxyphosphoryl)oxy]-2-buten-1-yl 4-(Trifluoromethyl)benzoate (2k)



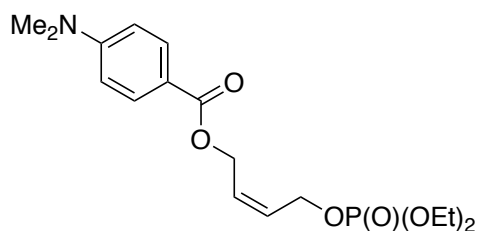
Colorless Oil. IR (neat) 703, 775, 863, 977, 1015, 1065, 1099, 1126, 1166, 1267, 1324, 1412, 1724, 2986 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.34 (t, $J = 6.8$ Hz, 6H), 4.13 (quintet, $J = 6.8$ Hz, 4H), 4.73 (dd, $J = 8.8$, 4.4 Hz, 2H), 4.94 (d, $J = 4.8$ Hz, 2H), 5.85–5.93 (m, 2H), 7.70 (d, $J = 8.4$ Hz, 2H), 8.15 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 16.0 (d, $J = 6.7$ Hz), 60.7, 62.6 (d, $J = 4.8$ Hz), 63.8 (d, $J = 5.7$ Hz), 123.5 (q, $J = 270.7$ Hz), 125.4 (q, $J = 3.8$ Hz), 127.4, 129.2 (d, $J = 6.7$ Hz), 130.0, 133.0, 134.5 (q, $J = 32.4$ Hz), 164.9. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{20}\text{O}_6\text{F}_3\text{NaP}$, 419.08418; found, 419.08422.

(Z)-4-[(Diethoxyphosphoryl)oxy]-2-buten-1-yl 4-Bromobenzoate (2l)



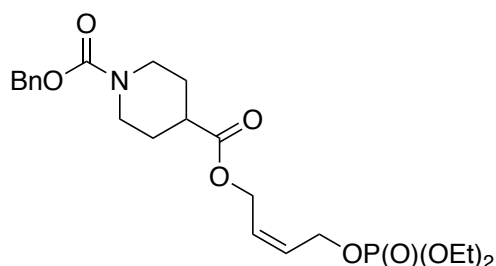
Colorless Oil. IR (neat) 682, 755, 817, 846, 976, 1010, 1021, 1100, 1172, 1263, 1397, 1590, 1719, 2983 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.34 (t, $J = 7.2$, Hz, 6H), 4.12 (quintet, $J = 7.2$ Hz, 4H), 4.72 (dd, $J = 8.4$, 5.2 Hz, 2H), 4.90 (d, $J = 5.2$ Hz, 2H), 5.83–5.91 (m, 2H), 7.58 (d, $J = 8.8$ Hz, 2H), 7.89 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 16.1 (d, $J = 5.7$ Hz), 60.5, 62.6 (d, $J = 4.8$ Hz), 63.8 (d, $J = 5.7$ Hz), 127.6, 128.2, 128.8, 129.1 (d, $J = 6.7$ Hz), 131.1, 131.7, 165.5. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{20}\text{O}_6\text{BrNaP}$, 429.00731; found, 429.00749.

(Z)-4-[(Diethoxyphosphoryl)oxy]-2-buten-1-yl 4-(Dimethylamino)benzoate (2m)



Colorless Oil. IR (neat) 698, 769, 829, 945, 975, 1019, 1098, 1181, 1269, 1367, 1445, 1527, 1604, 1699, 2909, 2983 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.34 (dt, $J = 7.2$, 0.8 Hz, 6H), 3.04 (s, 6H), 4.12 (quintet, $J = 7.2$ Hz, 4H), 4.72 (dd, $J = 7.6$, 6.0 Hz, 2H), 4.85 (dt, $J = 6$ Hz, 2H), 5.80–5.92 (m, 2H), 6.64 (dm, $J = 9.2$ Hz, 2H), 7.89 (dm, $J = 9.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 16.0 (d, $J = 6.7$ Hz), 39.9, 59.5, 62.8 (d, $J = 4.8$ Hz), 63.8 (d, $J = 5.7$ Hz), 110.6, 116.4, 128.1 (d, $J = 6.7$ Hz), 128.6, 131.2, 153.3, 166.5. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{26}\text{O}_6\text{NNaP}$, 394.13900; found, 394.13899.

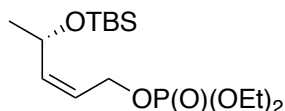
(Z)-1-Benzyl 4-{4-[(Diethoxyphosphoryl)oxy]-2-buten-1-yl} Piperidine-1,4-dicarboxylate (2p)



Colorless Oil. IR (neat) 697, 751, 978, 1020, 1166, 1224, 1269, 1429, 1695, 1731, 2983 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.34 (dt, $J = 7.2$, 0.8 Hz, 6H), 1.60–1.69 (m, 2H), 1.88–1.91 (m, 2H), 2.48 (m, 1H), 2.93 (t, $J =$

11.6 Hz, 2H), 4.08–4.15 (m, 2H), 4.12 (quintet, $J = 7.2$ Hz, 4H), 4.65 (dd, $J = 10.8, 5.6$ Hz, 4H), 5.12 (s, 2H), 5.73 (dtd, $J = 11.2, 6.8, 1.6$ Hz, 1H), 5.83 (dtd, $J = 11.2, 7.2, 1.6$ Hz, 1H), 7.29–7.38 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3) δ 16.0 (d, $J = 6.7$ Hz), 27.7, 40.8, 43.1, 59.9, 62.6 (d, $J = 4.8$ Hz), 63.8 (d, $J = 5.7$ Hz), 67.0, 127.6, 127.8, 127.9, 128.4, 128.8 (d, $J = 6.7$ Hz), 136.6, 155.1, 173.9. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{32}\text{O}_8\text{NNaP}$, 492.17577; found, 492.17570.

(*S,Z*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-penten-1-yl diethyl phosphate (2s) (99% ee)



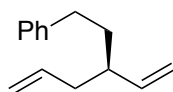
Colorless Oil. IR (neat) 667, 775, 830, 975, 1026, 1254, 1369, 1393, 1473, 2858, 2930, 2957 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.20 (d, $J = 6.4$ Hz, 3H), 1.34 (t, $J = 7.2$ Hz, 6H), 4.11 (quintet, $J = 7.2$ Hz, 4H), 4.55–4.69 (m, 3H), 5.48 (dt, $J = 11.2, 6.0$ Hz, 1H), 5.64 (dd, $J = 11.2, 8.0$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ -4.8, -4.6, 16.1 (d, $J = 6.7$ Hz), 18.1, 24.6, 25.7, 63.0 (d, $J = 4.8$ Hz), 63.7 (d, $J = 5.7$ Hz), 65.1, 122.3 (d, $J = 6.6$ Hz), 139.2. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{33}\text{O}_5\text{NaPSi}$, 375.17271; found, 375.17227. $[\alpha]_{\text{D}}^{25} +150$ (c 1.17, CHCl_3).

Procedure for the Copper-Catalyzed Enantioselective Allyl–Allyl Coupling

The reaction in Table 4, entry 1 is representative. CuCl (1.5 mg, 0.015 mmol), **L5**• HBF_4 (9.8 mg, 0.015 mmol) and MeOK (12.6 mg, 0.18 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 30 min. Next, 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1a**) (45.3 μL , 0.24 mmol) was added. Finally, allylic phosphate **2b** (42.6 mg, 0.15 mmol) was added at -50°C . After 48 h stirring at -50°C , the reaction was quenched with saturated NH_4Cl aq. and extracted with diethyl ether (1 mL $\times$ 3). The combined organic layer was 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 (hexane) to give **3ab** (15.9 mg, 0.09 mmol) in 62% yield.

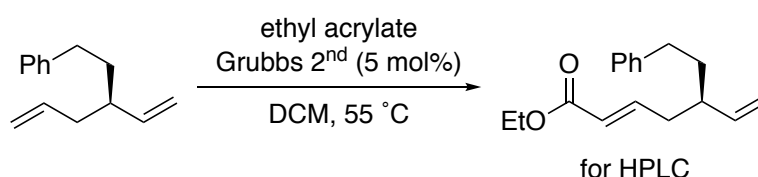
Characterization Data for Allyl–Allyl Coupling Products

(*R*)-(3-Vinyl-5-hexen-1-yl)benzene (3aa)

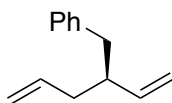


The product **3aa** was purified by flash chromatography on silica gel (hexane) (178.9 mg, 0.96 mmol, 80% isolated yield from (*Z*)-**2a**). Colorless Oil. IR (neat) 697, 745, 909, 993, 1454, 1496, 1640, 2857, 2919, 2978,

3027, 3076 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.56 (m, 1H), 1.74 (m, 1H), 2.06–2.20 (m, 3H), 2.52 (m, 1H), 2.65 (m, 1H), 4.97–5.07 (m, 4H), 5.64 (ddd, $J = 17.2, 10.8, 8.0$ Hz, 1H), 5.75 (ddt, $J = 17.2, 10.8, 6.4$ Hz, 1H), 7.16 (m, 3H), 7.26 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 33.3, 35.9, 39.4, 43.2, 114.8, 115.8, 125.6, 128.2, 128.4, 136.7, 142.2, 142.6. HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{18}$, 186.14085; found, 186.14099. $[\alpha]_{\text{D}}^{27} +4.9$ (c 0.30, CHCl_3). The ee value (99% ee) was determined by chiral HPLC analysis of (*E*)-ethyl 5-phenethyl-2,6-heptadienoate obtained by the metathesis between **3aa** and ethyl acrylate in the presence of Grubbs 2nd catalyst [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, 0.5 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 27.7 min for *S* isomer and 32.5 min for *R* isomer]. The absolute configuration of **3aa** was assigned by consideration of the stereochemical pathway.

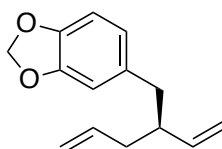


(*S*)-(2-Vinyl-4-penten-1-yl)benzene (3ab)

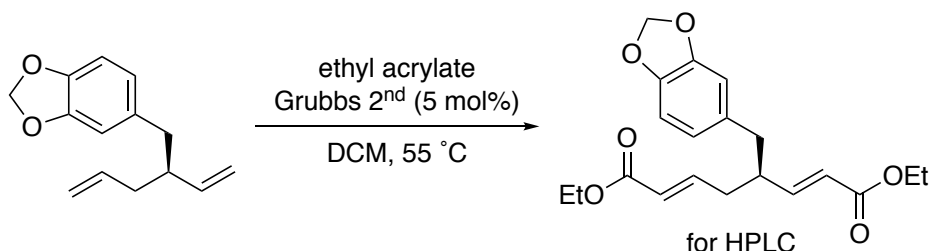


The product **3ab** was purified by flash chromatography on silica gel (hexane) (15.9 mg, 0.09 mmol, 62% isolated yield from **2b**). Colorless Oil. IR (neat) 697, 742, 910, 991, 1419, 1454, 1495, 1640, 2919, 2978, 3028, 3077 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 2.08 (m, 1H), 2.17 (m, 1H), 2.40 (dt, $J = 8.0, 7.2, 6.8$ Hz, 1H), 2.60 (dd, $J = 14.0, 7.2$ Hz, 1H), 2.70 (dd, $J = 14.0, 7.2$ Hz, 1H), 4.86–5.02 (m, 4H), 5.66 (ddd, $J = 17.2, 10.4, 8.0$ Hz, 1H), 5.78 (ddt, $J = 17.2, 14.0, 9.2$ Hz, 1H), 7.13–7.19 (m, 3H), 7.24–7.30 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 38.4, 40.8, 45.0, 114.6, 116.0, 125.8, 128.0, 129.2, 136.7, 140.3, 141.6. HRMS–APCI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{17}$, 173.13248; found, 173.13268. $[\alpha]_{\text{D}}^{27} +0.27$ (c 0.86, CHCl_3). The ee value (86% ee) was determined by chiral HPLC analysis of **3ab** [CHIRALCEL[®] OJ-3 column, 4.6 mm $\times$ 250 mm/OJ-H column, 4.6 mm $\times$ 220 mm, Daicel Chemical Industries, hexane, 0.3 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 33.2 min for *S* isomer and 34.4 min for *R* isomer]. The absolute configuration of **3ab** was assigned by consideration of the stereochemical pathway.

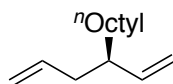
(*S*)-5-(2-Vinyl-4-penten-1-yl)benzo[*d*][1,3]dioxole (3ac)



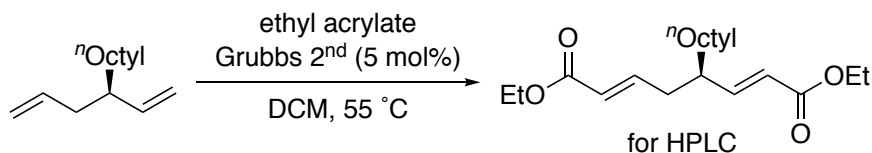
The product **3ac** was purified by flash chromatography on silica gel (5% Et₂O/hexane) (31.5 mg, 0.14 mmol, 97% isolated yield from **2c**). Colorless Oil. IR (neat) 686, 809, 859, 910, 992, 1038, 1188, 1243, 1440, 1488, 1503, 1639, 2916, 3076 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 2.06 (m, 1H), 2.16 (m, 1H), 2.33 (dtt, J = 14.8, 8.0, 6.8 Hz, 1H), 2.51 (dd, J = 13.2, 7.2 Hz, 1H), 2.62 (dd, J = 13.6, 6.8 Hz, 1H), 4.87–5.03 (m, 4H), 5.64 (ddd, J = 17.2, 10.4, 8.0 Hz, 1H), 5.76 (ddt, J = 17.2, 9.6, 7.2 Hz, 1H), 5.91 (s, 2H), 6.58 (d, J = 8.4 Hz, 1H), 6.64 (s, 1H), 6.71 (d, J = 8.4 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 38.3, 40.5, 45.2, 100.7, 107.8, 109.5, 114.7, 116.1, 122.0, 134.1, 136.7, 141.5, 145.5, 147.3. HRMS–EI (m/z): [M]⁺ calcd for C₁₄H₁₆O₂, 216.11503; found, 216.11437. [α]_D²⁵ –4.1 (c 0.9, CHCl₃). The ee value (86% ee) was determined by chiral HPLC analysis of diester derivative obtained by the metathesis between **3ac** and ethyl acrylate in the presence of Grubbs 2nd catalyst [CHIRALCEL[®] AD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 97:3, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 42.4 min for *R* isomer and 44.1 min for *S* isomer]. The absolute configuration of **3ac** was assigned by consideration of the stereochemical pathway.



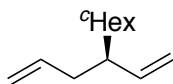
(*R*)-4-Vinyl-1-dodecene (**3ad**)



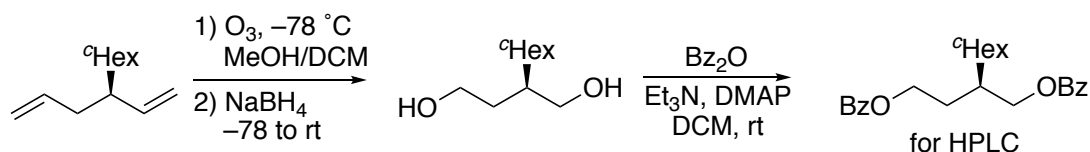
The product **3ad** was purified by flash chromatography on silica gel (hexane) (24.7 mg, 0.12 mmol, 85% isolated yield from **2d**). **3ad** was consistent with the the literature data.⁶ [α]_D²⁶ +4.9 (c 1.0, CHCl₃). The ee value (84% ee) was determined by chiral HPLC analysis of diester derivative obtained by the metathesis between **3ad** and ethyl acrylate in the presence of Hoveyda–Grubbs 2nd catalyst [CHIRALCEL[®] AD-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 = 16.3 min for *S* isomer and 17.3 min for *R* isomer]. The absolute configuration of **3ad** was assigned by consideration of the stereochemical pathway.



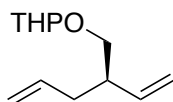
(*R*)-Hexa-1,5-dien-3-ylcyclohexane (3ae)



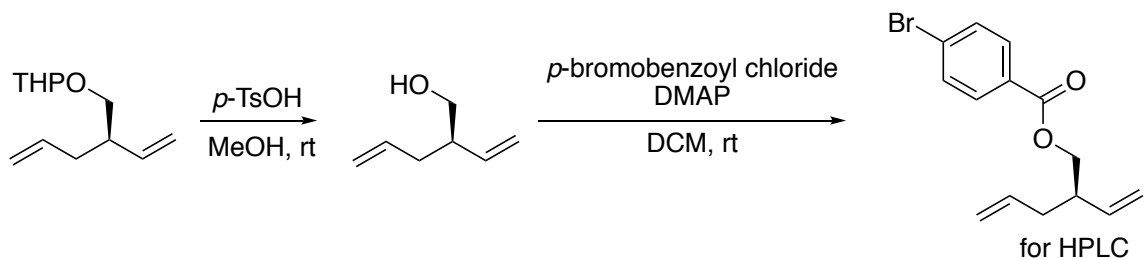
The product **3ae** was purified by flash chromatography on silica gel (pentane) (14.6 mg, 0.09 mmol, 59% isolated yield from **2e**). **3ae** was consistent with the the literature data.^{5a} $[\alpha]_D^{24} +3.7$ (c 0.58, CHCl_3). The ee value (80% ee) was determined by chiral HPLC analysis of the dibenzoate derivative obtained by ozonolytic cleavage, reduction with NaBH_4 followed by dibenzoylation from **3ae** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 25.5 min for *S* isomer and 31.4 min for *R* isomer].



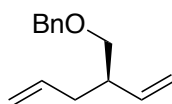
(*R*)-2-{[2-Vinyl-4-penten-1-yl]oxy}tetrahydro-2H-pyran (3af) (Doastereomeric ratio 1:1)



The product **3af** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (24.3 mg, 0.12 mmol, 83% isolated yield from **2f**). Colorless Oil. IR (neat) 680, 756, 815, 869, 907, 976, 992, 1030, 1077, 1121, 1201, 1352, 1441, 1641, 2870, 2941, 3077 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.48–1.62 (m, 4H), 1.69 (m, 1H), 1.82 (m, 1H), 2.12 (dt, J = 8.0, 7.2, 6.8 Hz, 1H), 2.31 (m, 1H), 2.42 (m, 1H), 3.33 (m, 1H), 3.50 (m, 1H), 3.68 (m, 1H), 3.85 (m, 1H), 4.58 (t, J = 3.2 Hz, 1H), 4.98–5.10 (m, 4H), 5.67–5.84 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 19.4 ($\times 2\text{C}$), 25.4 ($\times 2\text{C}$), 30.6 ($\times 2\text{C}$), 35.8 ($\times 2\text{C}$), 43.3, 43.4, 62.0 ($\times 2\text{C}$), 70.2 ($\times 2\text{C}$), 98.7, 98.8, 115.4 ($\times 2\text{C}$), 116.0 ($\times 2\text{C}$), 136.5, 136.5, 139.4, 139.5. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2\text{Na}$, 219.13555; found, 219.13553. $[\alpha]_D^{27} -9.7$ (c 0.93, CHCl_3). The ee value (90% ee) was determined by chiral HPLC analysis of **3al** obtained by deprotection followed by benzoylation from **3af** [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, 0.7 mL/min, 40 $^\circ\text{C}$, 250 nm UV detector, retention time = 65.9 min for *S* isomer and 68.1 min for *R* isomer]. The absolute configuration of **3af** was assigned by consideration of the stereochemical pathway.

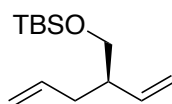


(*R*)-{[(2-Vinyl-4-penten-1-yl)oxy]methyl}benzene (3ag)

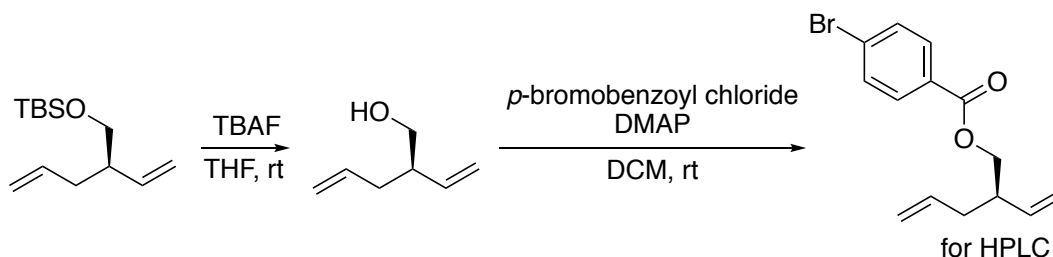


The product **3ag** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (22.8 mg, 0.11 mmol, 75% isolated yield from **2g**). Colorless Oil. IR (neat) 695, 733, 911, 992, 1098, 1361, 1454, 1496, 1640, 2854, 2978, 3030, 3076 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 2.11 (m, 1H), 2.29 (m, 1H), 2.45 (m, 1H), 3.41 (d, $J = 6.4$ Hz, 2H), 4.51 (s, 2H), 5.00 (dd, $J = 16.0, 8.0$ Hz, 2H), 5.07 (dd, $J = 16.0, 11.2$ Hz, 2H), 5.67–5.81 (m, 2H), 7.24–7.36 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3) δ 35.7, 43.5, 73.0, 73.0, 115.5, 116.0, 127.4, 127.5, 128.3, 136.4, 138.5, 139.4. HRMS–APCI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{O}$, 203.14304; found, 203.14299. $[\alpha]_{\text{D}}^{27} -7.3$ (c 0.99, CHCl_3). The ee value (85% ee) was determined by chiral HPLC analysis of **3ag** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99.5:0.5, 0.25 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 9.9 min for *R* isomer and 11.1 min for *S* isomer]. The absolute configuration of **3ae** was assigned by consideration of the stereochemical pathway.

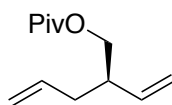
(*R*)-*tert*-Butyldimethyl[(2-vinylpent-4-en-1-yl)oxy]silane (3ah)



The product **3ah** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (26.6 mg, 0.12 mmol, 78% isolated yield from **2h**). **3ah** was consistent with the the literature data.^{5a} $[\alpha]_{\text{D}}^{26} -3.6$ (c 0.61, CHCl_3). The ee value (97% ee) was determined by chiral HPLC analysis of **3al** obtained by deprotection followed by benzylation from **3ah** [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, 0.7 mL/min, 40 $^\circ\text{C}$, 250 nm UV detector, retention time = 65.9 min for *S* isomer and 68.1 min for *R* isomer].

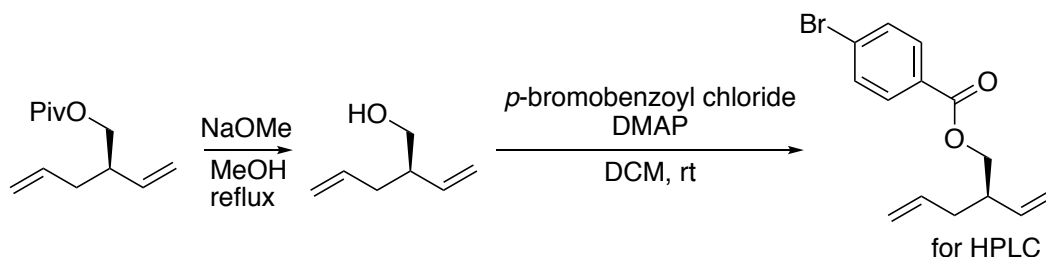


(*R*)-2-Vinyl-4-penten-1-yl Pivalate (3ai)

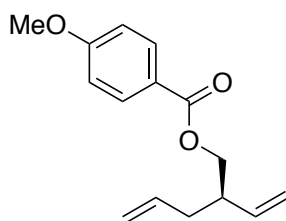


The product **3ai** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (20.6 mg, 0.11 mmol, 70% isolated yield from **2i**). Colorless Oil. IR (neat) 687, 757, 914, 992, 1034, 1148, 1282, 1365, 1397, 1480, 1642, 1729, 2976, 3079 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.19 (s, 9H), 2.10–2.26 (m, 2H), 2.48 (dt, J

= 7.2, 7.2, 6.4 Hz, 1H), 4.01 (d, J = 6.4 Hz, 2H), 5.02–5.09 (m, 4H), 5.62–5.81 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 27.1, 35.5, 38.8, 42.6, 66.1, 116.2, 116.6, 135.6, 138.3, 178.3. HRMS–APCI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{12}\text{H}_{21}\text{O}_2$, 197.15361; found, 197.15386. $[\alpha]_{\text{D}}^{27}$ –4.6 (c 0.50, CHCl_3). The ee value (91% ee) was determined by chiral HPLC analysis of **3ai** obtained by deprotection followed by benzylation from **3ai** [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, 0.7 mL/min, 40 °C, 250 nm UV detector, retention time = 65.9 min for *S* isomer and 68.1 min for *R* isomer]. The absolute configuration of **3ai** was assigned by consideration of the stereochemical pathway.

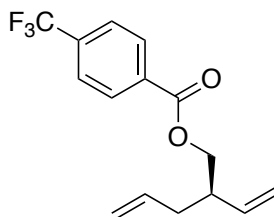


(*R*)-2-Vinyl-4-penten-1-yl 4-Methoxybenzoate (**3aj**)

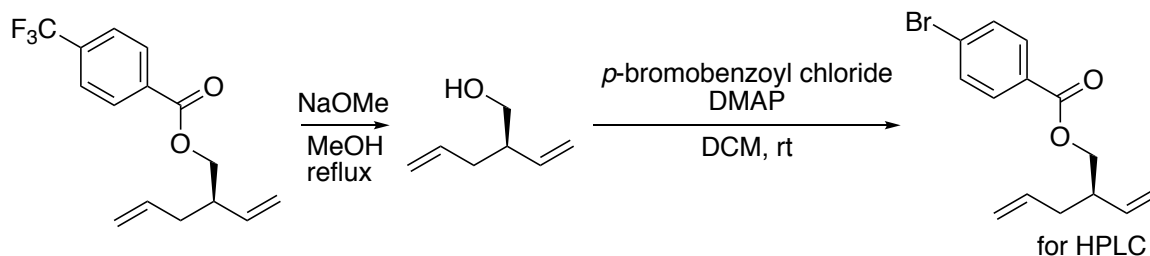


The product **3aj** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (31.2 mg, 0.13 mmol, 85% isolated yield from **2j**). Colorless Oil. IR (neat) 695, 768, 846, 914, 1029, 1099, 1165, 1251, 1420, 1510, 1605, 1709, 2840, 2937, 3078 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 2.22 (m, 1H), 2.31 (m, 1H), 2.61 (dt, J = 7.2, 7.2, 6.4 Hz, 1H), 3.85 (s, 3H), 4.21–4.29 (m, 2H), 5.03–5.16 (m, 4H), 5.71–5.85 (m, 2H), 6.91 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 35.7, 42.6, 55.4, 66.6, 113.5, 116.4, 116.7, 122.7, 131.5, 135.6, 138.4, 163.3, 166.2. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3\text{Na}$, 269.11482; found, 269.11457. $[\alpha]_{\text{D}}^{27}$ –5.2 (c 1.3, CHCl_3). The ee value (92% ee) was determined by chiral HPLC analysis of **3aj** [CHIRALCEL[®] OJ-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 31.1 min for *S* isomer and 34.0 min for *R* isomer]. The absolute configuration of **3aj** was assigned by consideration of the stereochemical pathway.

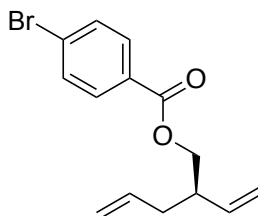
(*R*)-2-Vinyl-4-penten-1-yl 4-(Trifluoromethyl)benzoate (3ak)



The product **3ak** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (25.9 mg, 0.09 mmol, 61% isolated yield from **2k**). Colorless Oil. IR (neat) 703, 774, 861, 916, 1017, 1065, 1099, 1128, 1167, 1270, 1324, 1412, 1723, 2982, 3081 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 2.15–2.34 (m, 2H), 2.64 (dtt, $J = 7.2, 7.2, 6.8$ Hz, 1H), 4.27–4.36 (m, 2H), 5.05–5.17 (m, 4H), 5.70–5.85 (m, 2H), 7.70 (d, $J = 8.0$ Hz, 2H), 8.14 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 35.6, 42.5, 67.4, 116.7, 116.9, 123.6 (q, $J = 277.8$ Hz), 125.3 (q, $J = 3.8$ Hz), 129.9, 133.5, 134.3 (q, $J = 32.4$ Hz), 135.3, 138.1, 165.2. HRMS–ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{16}\text{O}_2\text{F}_3$, 285.11024; found, 285.11026. $[\alpha]_{\text{D}}^{27} -0.26$ (c 0.85, CHCl_3). The ee value (90% ee) was determined by chiral HPLC analysis of **3al** obtained by deprotection followed by benzylation from **3ak** [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, 0.7 mL/min, 40 $^\circ\text{C}$, 250 nm UV detector, retention time = 64.9 min for *S* isomer and 67.1 min for *R* isomer]. The absolute configuration of **3ak** was assigned by consideration of the stereochemical pathway.



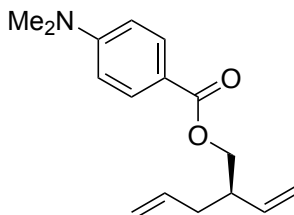
(*R*)-2-Vinyl-4-penten-1-yl 4-Bromobenzoate (3al)



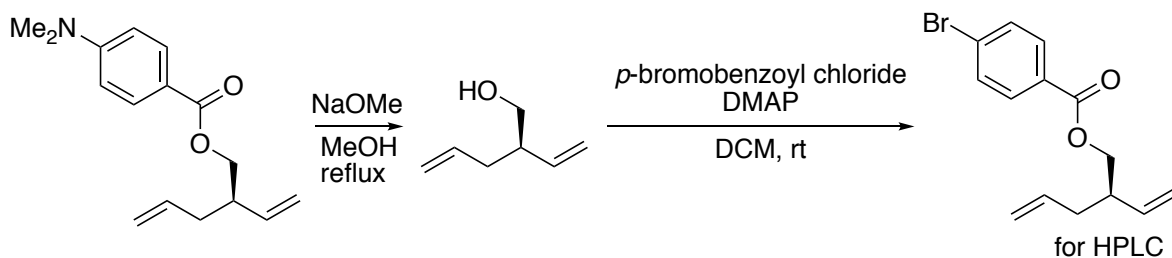
The product **3al** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (28.8 mg, 0.10 mmol, 65% isolated yield from **2l**). Colorless Oil. IR (neat) 682, 754, 846, 914, 1011, 1100, 1173, 1264, 1397, 1484, 1590, 1718, 2979, 3078 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 2.14–2.33 (m, 2H), 2.61 (dtt, $J = 6.8, 6.8, 6.4$ Hz, 1H), 4.23–4.31 (m, 2H), 5.04–5.16 (m, 4H), 5.68–5.84 (m, 2H), 7.57 (d, $J = 8.8$ Hz, 2H), 7.88 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 35.6, 42.5, 67.1, 116.6, 116.8, 128.0, 129.2, 131.0, 131.7, 135.4, 138.2,

165.7. HRMS–APCI (m/z): $[M+H]^+$ calcd for $C_{14}H_{16}O_2Br$, 295.03282; found, 295.03280. $[\alpha]_D^{27} -1.8$ (c 1.3, $CHCl_3$). The ee value (90% ee) was determined by chiral HPLC analysis of **3al** [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, 0.7 mL/min, 40 °C, 250 nm UV detector, retention time = 65.9 min for *S* isomer and 68.1 min for *R* isomer]. The absolute configuration of **3al** was assigned by consideration of the stereochemical pathway.

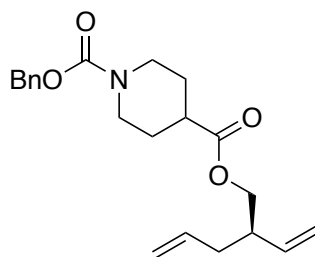
(*R*)-2-Vinyl-4-penten-1-yl 4-(Dimethylamino)benzoate (3am)



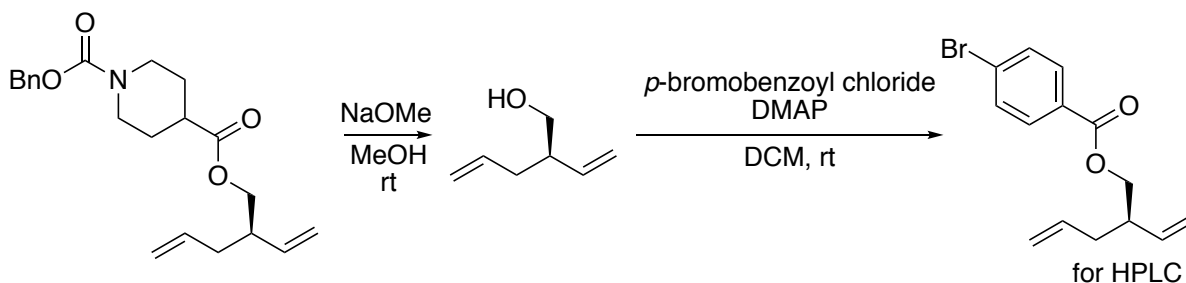
The product **3am** was purified by flash chromatography on silica gel (0–5% EtOAc/hexane) (34.0 mg, 0.13 mmol, 87% isolated yield from **2m**). Colorless Oil. IR (neat) 697, 768, 828, 912, 945, 992, 1101, 1180, 1271, 1365, 1444, 1525, 1605, 1698, 2897, 3077 cm^{-1} . ^1H NMR (400 MHz, $CDCl_3$) δ 2.19 (m, 1H), 2.32 (m, 1H), 2.60 (dt, J = 7.2, 7.2, 6.8 Hz, 1H), 3.03 (s, 6H), 4.18–4.26 (m, 2H), 5.02–5.15 (m, 4H), 5.71–5.85 (m, 2H), 6.64 (d, J = 8.8 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.7, 40.0, 42.7, 66.1, 110.6, 116.2, 116.5, 117.1, 131.2, 135.8, 138.6, 153.2, 166.8. HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{16}H_{22}O_2N$, 260.16451; found, 260.16428. $[\alpha]_D^{27} -13$ (c 0.98, $CHCl_3$). The ee value (91% ee) was determined by chiral HPLC analysis of **3al** obtained by deprotection followed by benzylation from **3am** [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, 0.7 mL/min, 40 °C, 250 nm UV detector, retention time = 65.9 min for *S* isomer and 68.1 min for *R* isomer]. The absolute configuration of **3am** was assigned by consideration of the stereochemical pathway.



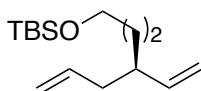
(R)-1-Benzyl 4-(2-Vinyl-4-penten-1-yl)piperidine-1,4-dicarboxylate (3ap)



The product **3ap** was purified by flash chromatography on silica gel (5–10% EtOAc/hexane) (43.0 mg, 0.12 mmol, 80% isolated yield from **2p**). Colorless Oil. IR (neat) 696, 750, 915, 1036, 1172, 1220, 1428, 1696, 1731, 2861, 2953 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.60–1.69 (m, 2H), 1.87–1.90 (m, 2H), 2.08–2.23 (m, 2H), 2.43–2.51 (m, 2H), 2.93 (t, $J = 11.6$ Hz, 2H), 4.01–4.08 (m, 2H), 4.01–4.15 (brs, 2H), 5.01–5.10 (m, 4H), 5.12 (s, 2H), 5.64 (ddd, $J = 18.4, 10.8, 8.0$ Hz, 1H), 5.73 (m, 1H), 7.28–7.38 (m, 5H). ^{13}C NMR (100 MHz, CDCl_3) δ 27.8, 35.5, 40.9, 42.5, 43.2, 66.4, 67.0, 116.4, 116.7, 127.8, 127.9, 128.4, 135.3, 136.7, 138.2, 155.1, 174.1. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{21}\text{H}_{27}\text{O}_4\text{NNa}$, 380.18323; found, 380.18340. $[\alpha]_{\text{D}}^{26} -1.9$ (c 1.2, CHCl_3). The ee value (90% ee) was determined by chiral HPLC analysis of **3al** obtained by deprotection followed by benzylation from **3ap** [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, 0.7 mL/min, 40 $^\circ\text{C}$, 250 nm UV detector, retention time = 65.9 min for *S* isomer and 68.1 min for *R* isomer]. The absolute configuration of **3ap** was assigned by consideration of the stereochemical pathway.

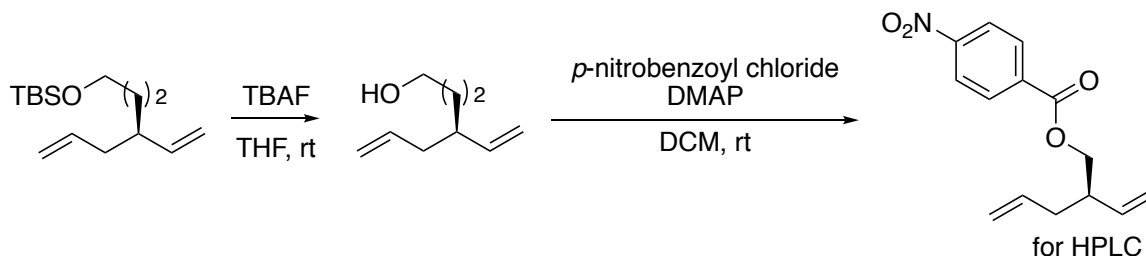


(R)-tert-Butyldimethyl[(4-vinyl-6-hepten-1-yl)oxy]silane (3aq)

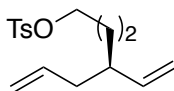


The product **3aq** was purified by flash chromatography on silica gel (0–1% EtOAc/hexane) (29.8 mg, 0.12 mmol, 78% isolated yield from **2q**). Colorless Oil. IR (neat) 660, 773, 833, 910, 993, 1097, 1254, 1463, 1472, 1641, 2857, 2929, 3078 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.25 (m, 1H), 1.40–1.60 (m, 3H), 2.01–2.17 (m, 3H), 3.58 (t, $J = 6.4$ Hz, 2H), 4.93–5.02 (m, 4H), 5.58 (ddd, $J = 18.4, 10.8, 8.0$ Hz, 1H), 5.75 (ddt, $J = 17.2, 10.0, 6.8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ –5.2, 18.3, 25.9, 30.2, 30.3, 39.5, 43.4, 63.2, 114.3, 115.6, 137.0, 142.5. HRMS–ESI (m/z): $[\text{M}-\text{CH}_3]^+$ calcd for $\text{C}_{14}\text{H}_{27}\text{OSi}$, 239.18312; found, 239.18356. $[\alpha]_{\text{D}}^{26} +4.5$ (c 1.3, CHCl_3). The ee value (96% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate

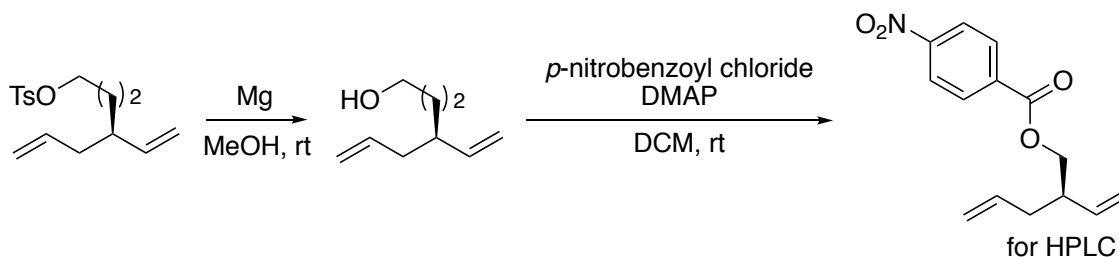
derivative obtained by desilylation followed by benzylation from **3a_q** [CHIRALCEL[®] OJ-3 column, 4.6 mm × 250 mm/OJ-H column, 4.6 mm × 250 mm, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 44.5 min for *R* isomer and 46.7 min for *S* isomer]. The absolute configuration of **3a_q** was assigned by consideration of the stereochemical pathway.



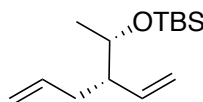
(*R*)-4-Vinyl-6-hepten-1-yl 4-Methylbenzenesulfonate (**3ar**)



The product **3ar** was purified by flash chromatography on silica gel (0–5% EtOAc/hexane) (38.7 mg, 0.13 mmol, 88% isolated yield from **2r**). Colorless Oil. IR (neat) 661, 736, 813, 908, 1097, 1174, 1357, 1598, 1640, 2922, 3075 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 1.21 (m, 1H), 1.43 (m, 1H), 1.56 (m, 1H), 1.68 (m, 1H), 1.92–2.10 (m, 3H), 2.45 (s, 3H), 4.00 (t, *J* = 6.4 Hz, 2H), 4.88–4.99 (m, 4H), 5.48 (ddd, *J* = 18.4, 10.8, 8 Hz, 1H), 5.69 (ddt, *J* = 16.4, 9.6, 7.2 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 21.6, 26.5, 29.6, 39.4, 43.1, 70.6, 115.1, 116.0, 127.8, 129.7, 133.2, 136.4, 141.5, 144.6. HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₁₆H₂₂O₃NaS, 317.11819; found, 317.11780. [α]_D²⁶ +8.0 (*c* 0.63, CHCl₃). The ee value (92% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by detosylation followed by benzylation from **3ar** [CHIRALCEL[®] OJ-3 column, 4.6 mm × 250 mm/OJ-H column, 4.6 mm × 250 mm, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 44.5 min for *R* isomer and 46.7 min for *S* isomer]. The absolute configuration of **3ar** was assigned by consideration of the stereochemical pathway.



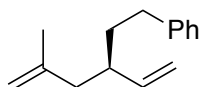
tert-Butyldimethyl[(2*S*,3*S*)-3-vinyl-5-hexen-2-yl]oxy]silane (**3as**)



The product **3as** was purified by flash chromatography on silica gel (0–2% EtOAc/hexane) (22.2 mg, 0.09

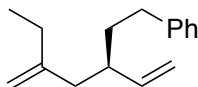
mmol, 61% isolated yield from **2s**). Colorless Oil. IR (neat) 664, 772, 830, 910, 994, 1072, 1254, 1361, 1374, 1463, 1472, 1641, 2858, 2887, 2930, 2957, 3078 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.08 (d, J = 6.4 Hz, 3H), 1.98–2.12 (m, 2H), 2.34 (m, 1H), 3.70 (quintet, J = 6.4 Hz, 1H), 4.95–5.08 (m, 4H), 5.59–5.88 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ –4.8, –4.3, 17.9, 20.8, 25.7, 34.5, 51.7, 70.5, 115.2, 115.8, 137.4, 139.1. HRMS–APCI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{14}\text{H}_{29}\text{OSi}$, 241.19822; found, 241.19826. $[\alpha]_{\text{D}}^{25}$ +34 (c 0.37, CHCl_3). The d.r. (90:10) was determined by ^1H NMR analysis of the crude product. The absolute configuration of **3as** was assigned by consideration of the stereochemical pathway.

(*R*)-(5-Methyl-3-vinyl-5-hexen-1-yl)benzene (3ba)



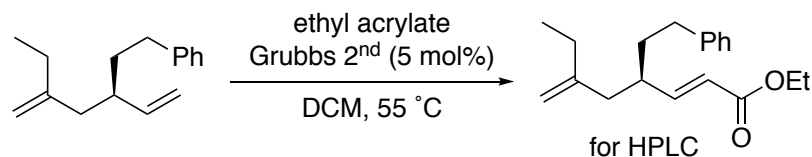
The product **3ba** was purified by flash chromatography on silica gel (hexane) (23.1 mg, 0.12 mmol, 77% isolated yield from (*Z*)-**2a**). Colorless Oil. IR (neat) 697, 745, 886, 910, 994, 1454, 1496, 1641, 2856, 2919, 2969, 3027, 3074 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.50 (m, 1H), 1.65 (s, 3H), 1.72 (m, 1H), 2.00–2.13 (m, 2H), 2.23 (m, 1H), 2.51 (m, 1H), 2.68 (m, 1H), 4.64 (s, 1H), 4.73 (s, 1H), 5.00 (d, J = 18.4 Hz, 1H), 5.03 (d, J = 10.8 Hz, 1H), 5.61 (ddd, J = 18.4, 10.8, 8.0 Hz, 1H), 7.14–7.19 (m, 3H), 7.23–7.28 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 22.3, 33.3, 36.0, 41.3, 43.8, 111.8, 114.5, 125.6, 128.2, 128.4, 142.4, 142.6, 143.9. HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{20}$, 200.15650; found, 200.15633. $[\alpha]_{\text{D}}^{26}$ +2.0 (c 1.3, CHCl_3). The ee value (95% ee) was determined by chiral HPLC analysis of **3ba** [CHIRALCEL[®] OJ-3 column, 4.6 mm $\times$ 250 mm/OJ-H column, hexane, 0.3 mL/min, 40 $^{\circ}\text{C}$, 220 nm UV detector, retention time = 35.1 min for *S* isomer and 36.8 min for *R* isomer]. The absolute configuration of **3ba** was assigned by consideration of the stereochemical pathway.

(*R*)-(5-Methylene-3-vinylheptyl)benzene (3ca)

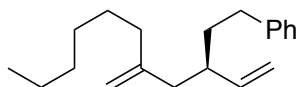


The product **3ca** was purified by flash chromatography on silica gel (hexane) (16.1 mg, 0.07 mmol, 50% isolated yield from (*Z*)-**2a**). Colorless Oil. IR (neat) 697, 744, 888, 910, 994, 1454, 1496, 1644, 2856, 2920, 2966, 3027, 3077 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 0.99 (t, J = 7.2 Hz, 3H), 1.49 (m, 1H), 1.73 (m, 1H), 1.92–2.27 (m, 5H), 2.51 (m, 1H), 2.68 (m, 1H), 4.67 (s, 1H), 4.74 (s, 1H), 4.99 (d, J = 16.8 Hz, 1H), 5.03 (d, J = 10.0 Hz, 1H), 5.61 (ddd, J = 16.8, 10.0, 8.4 Hz, 1H), 7.15–7.20 (m, 3H), 7.25–7.28 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 12.1, 28.3, 33.4, 36.0, 41.4, 42.3, 109.5, 114.5, 125.5, 128.2, 128.3, 142.5, 142.6, 149.2. HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{16}\text{H}_{22}$, 214.17215; found, 214.17134. $[\alpha]_{\text{D}}^{28}$ +3.1 (c 0.4, CHCl_3). The ee value (80% ee) was determined by chiral HPLC analysis of ester derivative obtained by the metathesis between **3ca** and ethyl acrylate in the presence of Grubbs 2nd catalyst [CHIRALCEL[®] AD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 $^{\circ}\text{C}$, 220 nm UV detector, retention time = 9.7 min for *S* isomer and

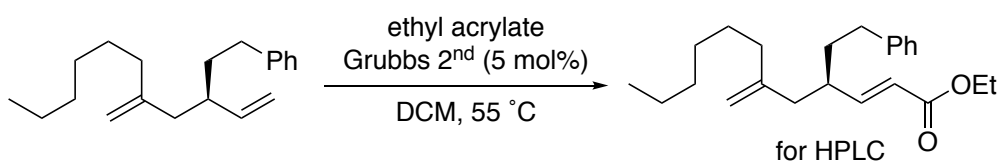
10.1 min for *R* isomer]. The absolute configuration of **3ca** was assigned by consideration of the stereochemical pathway.



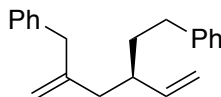
(*R*)-(5-Methylene-3-vinylundecyl)benzene (3da)



The product **3da** was purified by flash chromatography on silica gel (hexane) (35.3 mg, 0.13 mmol, 87% isolated yield from (*Z*)-**2a**). Colorless Oil. IR (neat) 697, 744, 889, 910, 993, 1454, 1496, 1642, 2856, 2925, 3027, 3074 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 0.88 (t, $J = 7.2$ Hz, 3H), 1.21–1.54 (m, 9H), 1.72 (m, 1H), 1.92 (t, $J = 8.4$ Hz, 2H), 2.00–2.10 (m, 2H), 2.20 (m, 1H), 2.51 (m, 1H), 2.68 (m, 1H), 4.66 (s, 1H), 4.73 (s, 1H), 4.99 (d, $J = 17.2$ Hz, 1H), 5.03 (d, $J = 10.4$ Hz, 1H), 5.61 (ddd, $J = 17.6, 10.8, 8.8$ Hz, 1H), 7.15–7.19 (m, 3H), 7.24–7.29 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 14.1, 22.6, 27.5, 29.0, 31.7, 33.3, 35.6, 36.0, 41.3, 42.1, 110.5, 114.5, 125.5, 128.2, 128.4, 142.6, 142.6, 147.8. HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{20}\text{H}_{30}$, 270.23475; found, 270.23412. $[\alpha]_{\text{D}}^{26} +4.3$ (c 1.0, CHCl_3). The ee value (80% ee) was determined by chiral HPLC analysis of ester derivative obtained by the metathesis between **3da** and ethyl acrylate in the presence of Grubbs 2nd catalyst [CHIRALCEL[®] AD-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 = 9.6 min for *S* isomer and 10.1 min for *R* isomer]. The absolute configuration of **3da** was assigned by consideration of the stereochemical pathway.



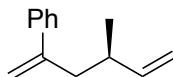
(*R*)-(2-Methylene-4-vinylhexane-1,6-diyl)dibenzene (3ea)



The product **3ea** was purified by flash chromatography on silica gel (0–1% Et₂O/hexane) (24.7 mg, 0.08 mmol, 59% isolated yield from (*Z*)-**2a**). Colorless Oil. IR (neat) 519, 696, 737, 892, 994, 1030, 1453, 1494, 1602, 1642, 2855, 2919, 2969, 3026, 3063 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.48 (m, 1H), 1.69 (m, 1H), 1.95–2.13 (m, 2H), 2.34 (m, 1H), 2.46 (m, 1H), 2.64 (m, 1H), 3.24 (s, 2H), 4.73 (s, 1H), 4.78 (s, 1H), 4.99 (d, $J = 17.6$ Hz, 1H), 5.04 (d, $J = 10.0$ Hz, 1H), 5.58 (ddd, $J = 17.2, 10.0, 8.8$ Hz, 1H), 7.10–7.21 (m, 6H), 7.24–7.28 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3) δ 33.2, 36.0, 41.2, 41.4, 42.6, 113.1, 114.7, 125.6, 126.0, 128.2, 128.2, 128.4,

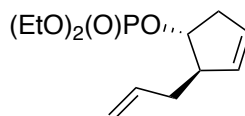
129.0, 139.0, 142.3, 142.5, 146.8. HRMS–EI (m/z): $[M]^+$ calcd for $C_{21}H_{24}$, 276.18780; found, 276.18691. $[\alpha]_D^{26} +2.3$ (c 2.0, $CHCl_3$). The ee value (82% ee) was determined by chiral HPLC analysis of **3ea** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm/OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 38.0 min for *S* isomer and 56.9 min for *R* isomer]. The absolute configuration of **3ea** was assigned by consideration of the stereochemical pathway.

(*R*)-(4-Methyl-1,5-hexadien-2-yl)benzene (3ft)



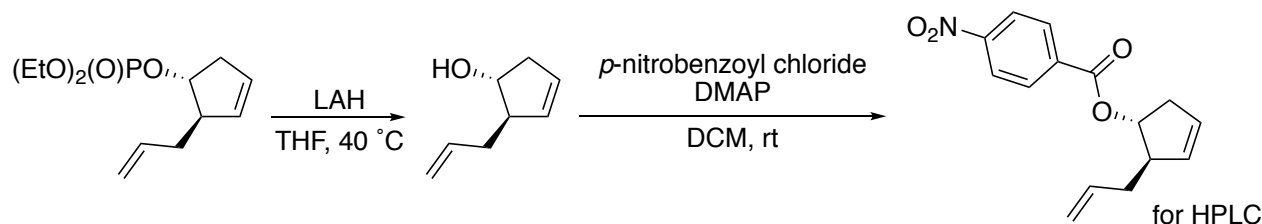
The product **3ft** was purified by flash chromatography on silica gel (hexane) (23.0 mg, 0.13 mmol, 89% isolated yield from **2t**). The isolated branched product (**3ft**) was contaminated with a trace amount of the linear product. Colorless Oil. IR (neat) 702, 758, 776, 895, 993, 1372, 1417, 1444, 1494, 1627, 2925, 2960, 3081 cm^{-1} . ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, J = 6.8 Hz, 3H), 2.24 (dtq, J = 7.2, 7.2, 6.8 Hz, 1H), 2.40 (dd, J = 10.8, 8.0 Hz, 1H), 2.59 (dd, J = 12.8, 6.8 Hz, 1H), 4.87 (d, J = 1.2 Hz, 1H), 4.91 (d, J = 0.8 Hz, 1H), 5.03 (d, J = 1.2 Hz, 1H), 5.27 (d, J = 1.6 Hz, 1H), 5.75 (ddd, J = 17.2, 9.6, 7.2 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 7.31 (dd, J = 7.2, 6.8 Hz, 2H), 7.38 (d, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 35.6, 42.8, 112.4, 113.9, 126.3, 127.2, 128.2, 141.2, 144.0, 147.0. HRMS–APCI (m/z): $[M+H]^+$ calcd for $C_{13}H_{17}$, 173.13248; found, 173.13256. $[\alpha]_D^{26} -9.7$ (c 0.87, $CHCl_3$). The ee value (83% ee) was determined by chiral HPLC analysis of **3ft** [CHIRALCEL[®] OJ-3 column, 4.6 mm $\times$ 250 mm/OJ-H column, hexane, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 18.9 min for *R* isomer and 20.0 min for *S* isomer]. The absolute configuration of **3ft** was assigned by consideration of the stereochemical pathway.

(1*R*,2*R*)-2-Allyl-3-cyclopenten-1-yl Diethyl Phosphate (3au)

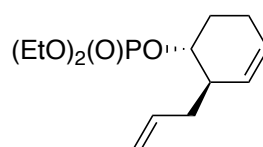


The product **3au** was purified by flash chromatography on silica gel (20–50% EtOAc/hexane) (25.1 mg, 0.10 mmol, 64% isolated yield from **2u**). Colorless Oil. IR (neat) 673, 732, 851, 1020, 1139, 1251, 1370, 1456, 1642, 2979 cm^{-1} . ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (td, J = 7.6, 1.6 Hz, 6H), 2.10 (dt, J = 14.4, 6.8 Hz, 1H), 2.22 (dt, J = 14.4, 6.8 Hz, 1H), 2.52 (dd, J = 16.8, 3.2 Hz, 1H), 2.75 (dd, J = 16.8, 3.2 Hz, 1H), 2.89 (m, 1H), 4.10 (quint doublet, 7.2, 2.8 Hz, 4H), 4.70 (ddd, J = 9.6, 6.4, 3.2 Hz, 1H), 5.03 (dd, J = 10.0, 1.2 Hz, 1H), 5.07 (dd, J = 18.0, 1.6 Hz, 1H), 5.65–5.69 (m, 2H), 5.79 (ddt, J = 17.2, 10.4, 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (d, J = 6.6 Hz), 36.7, 39.7, 39.8, 52.4 (d, J = 5.7 Hz), 63.5 (d, J = 5.7 Hz), 82.2 (d, J = 6.6 Hz), 116.5, 127.6, 132.0, 135.8. HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{12}H_{21}O_4NaP$, 283.10697; found, 283.10703. $[\alpha]_D^{26} -76$ (c 0.55, $CHCl_3$). The ee value (77% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative

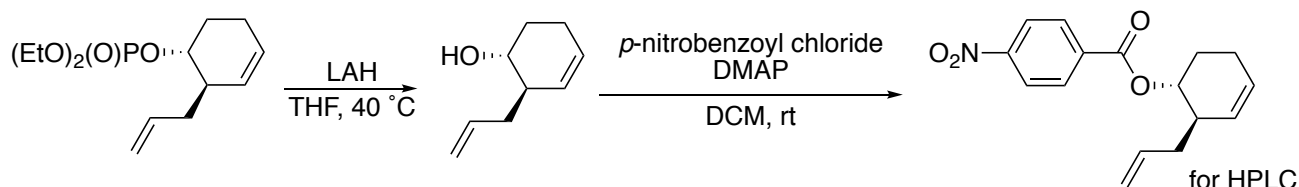
obtained by dephosphorylation followed by benzylation from **3au** [CHIRALCEL[®] OJ-3 column, 4.6 mm × 250 mm, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 20.4 min for *S,S* isomer and 22.0 min for *R,R* isomer].



(1*R*,2*R*)-2-Allyl-3-cyclohexen-1-yl Diethyl Phosphate (**3av**)



The product **3av** was purified by flash chromatography on silica gel (20–50% EtOAc/hexane) (21.3 mg, 0.08 mmol, 52% isolated yield from **2v**). Colorless Oil. IR (neat) 695, 728, 801, 968, 1005, 1166, 1260, 1393, 1442, 1640, 2932, 2981 cm^{-1} . ^1H NMR (400 MHz, CDCl_3) δ 1.34 (t, J = 6.8, 6H), 1.81 (m, 1H), 2.04–2.21 (m, 4H), 2.33–2.41 (m, 2H), 4.11 (quint doublet, J = 7.2, 4.4 Hz, 4H), 4.32 (ddd, J = 10.0, 6.8, 3.2 Hz, 1H), 5.02–5.12 (m, 2H), 5.51 (m, 1H), 5.65–5.69 (m, 1H), 5.78 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3) δ 16.1 (d, J = 6.6 Hz), 23.4, 27.8, 36.6, 41.4 (d, J = 6.7 Hz), 63.5 (d, J = 5.7 Hz), 77.8 (d, J = 6.7 Hz), 117.0, 126.5, 127.4, 135.5. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{23}\text{O}_4\text{NaP}$, 297.12262; found, 297.12226. $[\alpha]_{\text{D}}^{26}$ –14 (c 0.80, CHCl_3). The ee value (66% ee) was determined by chiral HPLC analysis of the *p*-nitrobenzoate derivative obtained by dephosphorylation followed by benzylation from **3av** [CHIRALCEL[®] OJ-3 column, 4.6 mm × 250 mm, hexane/2-propanol = 99:1, 0.5 mL/min, 40 °C, 250 nm UV detector, retention time = 19.5 min for *S,S* isomer and 20.8 min for *R,R* isomer]. The absolute configuration of **3av** was assigned by consideration of the stereochemical pathway.



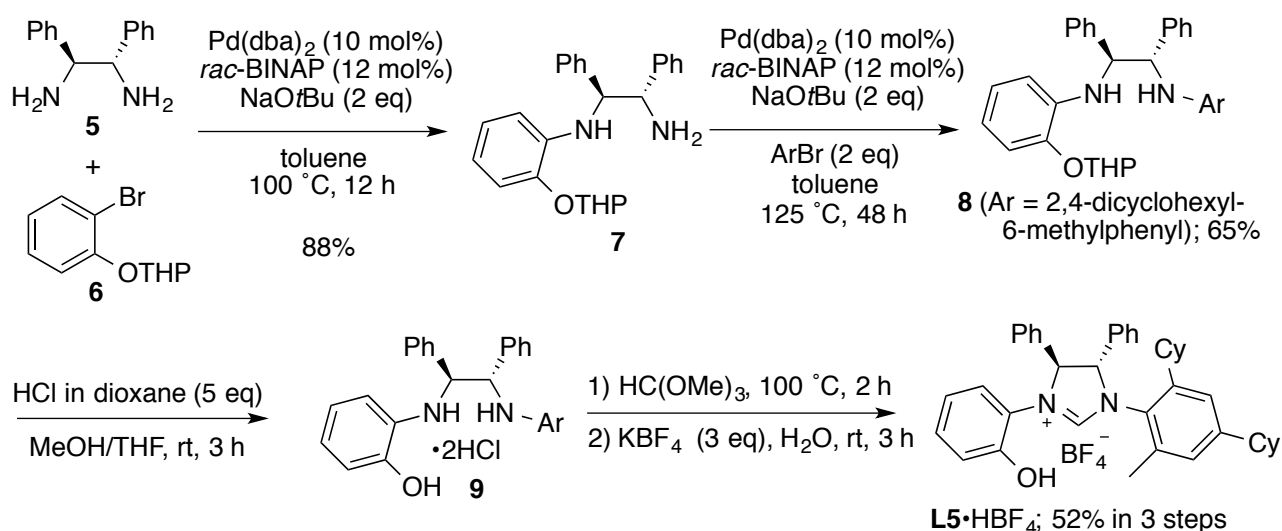
Synthesis of Phenol-NHC Chiral Ligand (**L5**• HBF_4).

To a solution of $\text{Pd}(\text{dba})_2$ (288 mg, 0.50 mmol), *rac*-BINAP (374 mg, 0.60 mmol) and NaOtBu (961 mg, 10.0 mmol) in toluene (30 mL) was added (1*S*,2*S*)-(–)-1,2-diphenylethylenediamine (**5**) (1.06 g, 5.0 mmol) and a solution of arylbromide **6** (1.29 g, 5.0 mmol) in toluene (40 mL). After being stirred at 100 °C for 12 h, the reaction mixture was filtered through a pad of celite, and the celite was washed with CH_2Cl_2 . Solvent was

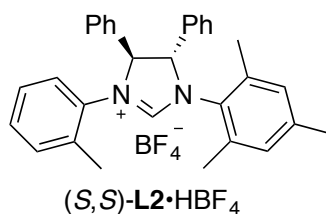
removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 5–45% EtOAc/hexane) to yield the coupling product **7**^{11a} (1.71 g, 88%) as a orange solid.

To a solution of Pd(dba)₂ (288 mg, 0.5 mmol), *rac*-BINAP (374 mg, 0.6 mmol) and NaOtBu (961 mg, 10 mmol) in toluene (20 mL) was added amine **7** (1.94 g, 5.0 mmol), and a solution of 2-bromo-3,5-dicyclohexyltoluene²⁵ [3.94 g, 10 mmol, containing 4-bromo-3,5-dicyclohexyltoluene (15%)]. 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 CH₂Cl₂. Solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 0–5% EtOAc/hexane) to yield the coupling product **8** (2.09 g, 65%) as a pale yellow solid.

To a solution of **8** (2.09 g, 3.25 mmol) in MeOH/THF (7.4 mL/9.0 mL) was added HCl (4.0 M in dioxane, 4.0 mL, 16.2 mmol) at room temperature. After being stirred at room temperature for 3 h, the solvent was removed under reduced pressure, and the residue was triturated with hexane. The pale orange solid was collected with a Kiriyaama-funnel, washed with hexane, and was dried in vacuum to give **9** as a orange powder. The solid was treated with trimethylorthoformate (6.59 mL, 60.3 mmol). After being stirred at 100 °C for 2 h, the reaction mixture was concentrated under reduced pressure. The crude imidazolium salt **L5**•HCl was triturated with hexane in an ultrasonic cleaning bath for ca. 20 min. During this time, the desired salt precipitated as a pale orange solid, which was collected with a Kiriyaama-funnel, washed with hexane, and was concentrated. The residue (1.54 g) was treated with NH₄BF₄ (1.03 mg, 9.9 mmol) in water (12.4 mL) and the mixture was stirred at room temperature for 3 h. The water suspension was extracted with CH₂Cl₂ (two times). The combined CH₂Cl₂ extract was dried and concentrated, and was triturated with hexane in an ultrasonic cleaning bath for ca. 5 min. The obtained solid was purified by flush column chromatography (silica gel, 0–10% MeOH/CHCl₃ and was triturated with hexane in an ultrasonic cleaning bath for ca. 10 min. The orange solid was collected with a Kiriyaama-funnel, washed with hexane, and was dried in vacuum at 60 °C for 12 h to give **L5**•HBF₄ (1.12 g, 1.71 mmol) in 52% yield in 3 steps. White solid. M.p. 147.6–150.7 °C. IR (neat) 699, 755, 1057, 1269, 1449, 1620, 2852, 2926, 3348 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆) δ -0.18 and -0.16 (rotamers) (m, 1H), 0.94–2.62 (m, 24H), 4.99, 5.01 and 5.53 (rotamers) (dm, *J* = 9.6 Hz, 1H), 6.42, 6.47, 6.60 and 6.63 (rotamers) (dm, *J* = 9.6 Hz, 1H), 6.69–6.83 (m, 4H), 6.95–7.61 (m, 12H), 9.33, 9.39, 9.42, 9.51 and 9.54 (rotamers) (s, 1H), 10.91 and 10.97 (rotamers) (br s, 1H), Signal for the five rotamers were given. ¹³C NMR (100 MHz, DMSO-*d*₆) δ 17.8, 18.4, 20.2, 20.5, 20.9, 22.0, 22.3, 23.2, 25.2, 25.4, 26.0, 26.2, 26.3, 28.3, 29.5, 29.7, 30.9, 31.6, 31.9, 33.2, 33.5, 33.6, 34.7, 38.1, 38.4, 38.8, 43.4, 55.8, 68.4, 70.5, 70.8, 71.6, 74.4, 74.8, 77.4, 77.9, 116.6, 119.3, 122.1, 123.7, 124.0, 124.5, 125.0, 125.8, 126.3, 126.8, 127.2, 127.6, 128.9, 129.3, 129.5, 129.6, 129.9, 130.2, 131.7, 132.3, 132.7, 132.8, 135.4, 135.5, 136.0, 136.3, 140.3, 144.7, 144.8, 145.1, 145.6, 145.7, 145.9, 148.4, 149.6, 149.7, 151.3, 151.7, 152.0, 159.3, 159.6 (only observed peaks). HRMS–ESI (*m/z*): [M–BF₄]⁺ calcd for C₄₀H₄₅ON₂, 569.35264; found, 569.35268. [α]_D²⁶ –210 (*c* 0.50, CHCl₃).



(4*S*,5*S*)-1-Mesityl-4,5-diphenyl-3-(*o*-tolyl)-4,5-dihydro-1*H*-imidazol-3-ium Tetrafluoroborate [L2**·HBF₄]**



White Solid. M.p. 114.5–117.8 °C. IR (neat) 699, 760, 1051, 1225, 1265, 1456, 1617, 3064 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 1.91 (s, 3H), 2.20 (s, 3H), 2.53 (s, 3H), 2.59 (s, 3H), 5.65 (d, *J* = 10.4 Hz, 1H), 6.12 (d, *J* = 10.0 Hz, 1H), 6.71 (s, 1H), 6.93 (s, 1H), 7.16–7.52 (m, 14H), 8.49 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 18.1, 18.5, 18.8, 20.8, 73.6, 75.6, 127.8, 127.9, 128.6, 128.9, 129.4, 129.7, 130.0, 130.2, 130.3, 130.6, 131.6, 131.8, 132.7, 133.0, 133.9, 134.6, 135.8, 140.3, 157.8. HRMS–ESI (*m/z*): [*M*–BF₄]⁺ calcd for C₃₁H₃₁N₂, 431.24818; found, 431.24823. [*α*]_D²⁶ –370 (*c* 1.1, CHCl₃).

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Chapter 3

Copper-Catalyzed Enantioselective Allylic Cross-Coupling between an Allenylboronate and Primary Allylic Phosphates with a Phenol/NHC Chiral Ligand

Introduction

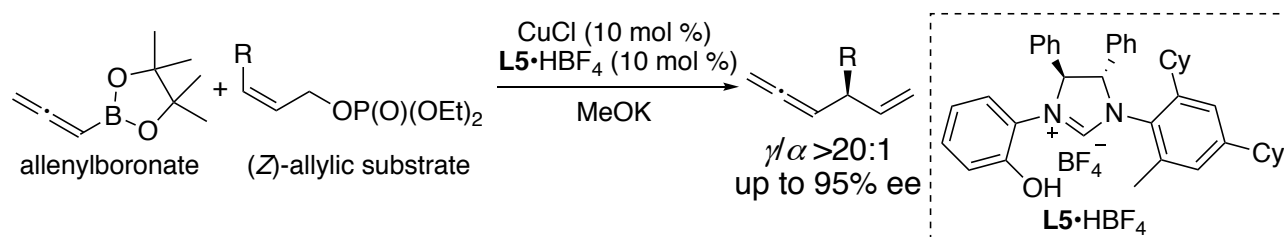
Copper-catalyzed asymmetric allylic substitution (AAS) is an important method for C–C bond formation in organic synthesis.¹ This reaction affords the coupling product with a new stereogenic center and a new olefin. Especially, the organoboron reagents have been applied actively to this reaction due to their broad availability and good functional group compatibility.² Thus, a lot of research groups have developed the copper-catalyzed AAS reactions with various organoboron reagents.^{2,3}

N-heterocyclic carbene (NHC) ligands are useful for transition-metal-catalyzed molecular transforms.⁴ Application of chiral NHC ligands to copper-catalyzed AAS reactions has also actively studied. As a pioneering work, Hayashi group reported the AAS with arylboronic acid esters as organoboron nucleophiles in copper catalysis with chiral NHC ligand bearing an alkoxo functional group.^{3a} Since this report, chiral NHC ligands bearing a functionalized tether group⁵ have been used in copper-catalyzed AAS reactions with the organoboron reagents.^{2,3}

The author's laboratory synthesized chiral NHC ligands bearing a phenolic hydroxy group at the *ortho* position of one of the two *N*-aryl groups and extensively applied the NHCs to the copper-catalyzed AAS.⁶ The phenol group of the chiral NHC ligands may act as a covalent ligand on copper atom. Moreover, the steric effect is tunable with the substituents of the other *N*-aryl group. Using the chiral Phenol–NHC ligands, we developed the copper-catalyzed enantioselective C–C bond formation reactions; direct C–H allylation^{6a,b} and reductive coupling^{6e} afforded the products with high regio- and enantioselectivities.

The author disclosed that the copper-catalyzed enantioselective allyl–allyl cross-coupling reaction between allylboronates and various (*Z*)-acyclic and cyclic allylic phosphates proceeded effectively using the chiral phenol–NHC ligand, in Chap. 2.^{6c,d} The new C–C bond formation occurred with the exceptional S_N2'-type regioselectivity and high enantioselectivity. The broad functional group compatibility is an attractive feature of this protocol. This work demonstrated the utility of this class of chiral ligands for enantioselective copper catalysis with organoboron reagents. Based on this knowledge, herein, the author describes the application of the chiral phenol–NHC ligand to the enantioselective allylic cross-coupling reaction with allenylboronate (Scheme 1).⁷ Previously, Hoveyda and co-workers reported the copper-catalyzed AAS with an allenylboronate using the chiral NHC ligand bearing a weakly coordinative sulfonate group at the tether position.^{3c} They shows only the use of (*E*)-substrates in this report. On the other hand, the Phenol–NHCs are useful ligands on copper-catalyzed AAS with (*Z*)-allylic substrates. Hence, the author broadened the scope of copper-catalyzed AAS reaction of organoboron reagents.

Scheme 1. Copper-catalyzed enantioselective allylic allenylation with a phenol–NHC chiral ligand



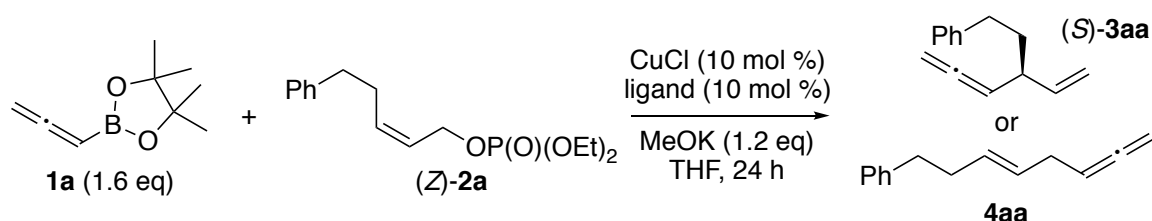
Results and Discussion

First, the author checked the performance of the Phenol-NHC chiral ligand in the reaction between allenylboronate **1a** and (Z)-allylic phosphate **2a**. As a result, the ideal coupling reaction proceeded in the presence of a catalytic amount of CuCl (10 mol%) and a chiral ligand **L1**·HBF₄^{6a} (10 mol%) with a stoichiometric amount of base, MeOK (1.2 eq), in THF at room temperature. The product **3aa** was obtained in 78% yield with good regioselectivity [γ/α (**3aa:4aa**) 95:5] and moderate enantioselectivity (62% ee) (Table 1, entry 1). The effect of the phenolic hydroxy group on the chiral ligand was assessed in entries 2–4. When the C₂-symmetric NHC ligand [(S,S)-**L2**·HBF₄]⁸ gave nearly racemic **3aa** as a minor product and α -regioselective product **4aa** as a major component in good yield (entry 2). Sterically similar chiral NHC ligands bearing 2-methylphenyl (**L3**) or 2-methoxyphenyl (**L4**) groups instead of the phenol group in **L1** are also ineffective for regio- and enantioselectivities (γ/α 75:25, 31% ee and γ/α 84:16, 40% ee, respectively) (entries 3 and 4). These results indicate that the hydroxy group in **L1** has a key role in this copper catalyst system.

Next, the steric effect of non-functionalized *N*-aryl group was investigated at low temperature (–20 °C). When the reaction was conducted at –20 °C, the enantiomeric excess of the product was improved to a good level in the reaction with **L1**·HBF₄ (76% ee) (entry 5). Slightly higher enantioselectivity was obtained by changing the mesityl group of **L1** to bulkier 2,4-diCy-6-Me-C₆H₂ group **L5**^{4c,d} affording the product in 87% yield, 79% ee, γ/α >20:1 (entry 6). The installation of naphthol group instead of phenol group to the NHC ligand, **L6**·HBF₄ and **L7**·HBF₄,^{4b} did not lead to improvement of the enantioselectivity (entries 7 and 8).

The absolute configuration of **3aa** [$[\alpha]_{\text{D}}^{26} +29.8$ (*c* 0.48, CHCl₃) {lit^{3c}, (S) isomer, 90% ee, $[\alpha]_{\text{D}}^{22} +44.0$ (*c* 0.73 CHCl₃)}] was determined by comparison of the specific rotations with the values reported previously.

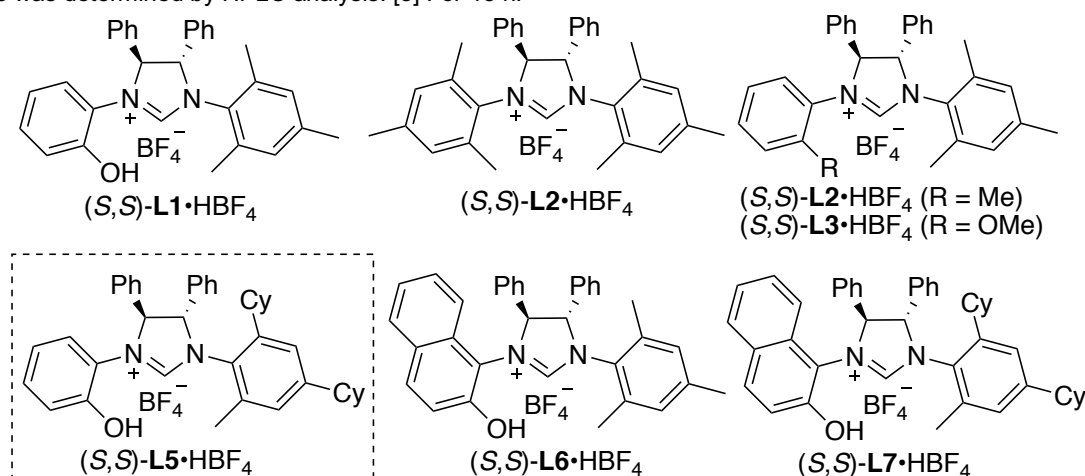
Table 1. Ligand effects in reaction between **1a** and (Z)-**2a**^[a]



entry	ligand	temp.(°C)	yield (%) ^[b]	γ/α (3aa/4aa) ^[c]	ee (%) ^[d]
1 ^[e]	L1 ·HBF ₄	25	78	95:5	62
2 ^[e]	L2 ·HBF ₄	25	81	35:65	7
3 ^[e]	L3 ·HBF ₄	25	79	75:25	31
4 ^[e]	L4 ·HBF ₄	25	82	84:16	40
5	L1 ·HBF ₄	-20	53	>20:1	76
6	L5 ·HBF ₄	-20	87	95:5	79
7	L6 ·HBF ₄	-20	77	>20:1	72
8	L7 ·HBF ₄	-20	76	>20:1	73

[a] MeOK (0.18 mmol), THF (0.6 mL). [b] Yield of isolated product. [c] Determined by ¹H NMR analysis of the crude product.

[d] The ee was determined by HPLC analysis. [e] For 13 h.



The author investigated the effect of the bases on yield and selectivities in this copper catalysis (Table 2). Although the reactions with alkoxide bases, other than MeOK, also proceeded with good regioselectivity, the product yield and enantioselectivity decreased. When MeONa was used, the coupling product was obtained with slightly decreased enantioselectivity (58 ee) in moderate yield (66%) (entry 2). Changing MeOK to MeOLi, the reactivity dropped significantly; the greater solubility of LiCl or LiOP(O)(OEt)₂ is considered as a reason for the low reactivity, because they may form inactive copper species through ionic interactions. The size of the alkoxide moiety on the base also affected the reaction efficiency. Use of a sterically more demanding base, *t*BuOK, instead of MeOK gave a strong impact on yield and enantioselectivity (entry 4). A dependency on bases in the reaction is similar to the tendency observed in the case of the reaction with allylboronates (cf. Chap. 2, Table 3, entries 1 and 4–6).^{4c,d} Presumably, the trialkoxyboron, ROBpin, may participate as a Lewis acid which activate the phosphate leaving group (see Figure 2). Weak bases (AcOK, KF, K₂CO₃) were not effective; coupling reactions did not occur (entries 5–7).

The effect of solvents is also summarized in Table 2. In ether solvents, methyl *tert*-butyl ether (MTBE) or

cyclopentyl methyl ether (CPME), the enantioselectivities were improved (72% ee and 78% ee, respectively), but the yield of the products decreased (entries 8 and 9). Next, the author checked the reaction in non-ether solvents. The reaction in toluene proceeded with good regioselectivity (γ/α 96:4) and enantioselectivity (72% ee) in satisfied yield (77%). On the other hand, dichloromethane (DCM), *N,N*-dimethylformamide (DMF) and acetonitrile (MeCN) were not effective (entries 11–13). Then, by changing **L1** to **L5** and lowering the reaction temperature in toluene, the enantioselectivity reached to 90% ee with excellent regioselectivity (γ/α >20:1) (entry 14).

The author also checked the reaction with the other leaving groups; the phosphate group gave the best result compared to chloride, carbonate and acetate as leaving groups (data is not shown).

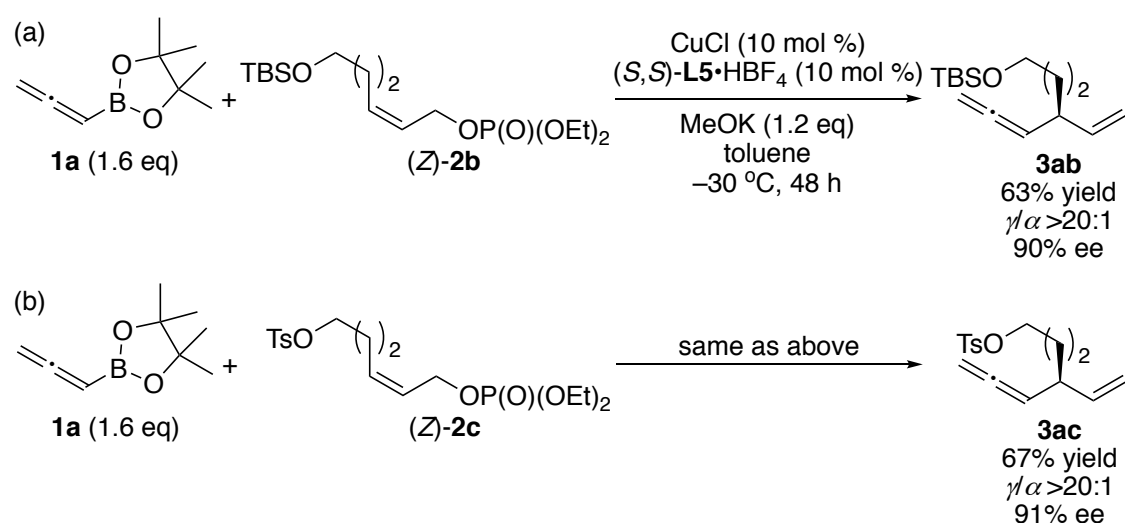
Table 2. Effect of bases and solvents^[a]

entry	base	solvent	yield (%) ^[b]	γ/α (3aa:4aa) ^[c]	ee (%) ^[d]
1 ^[e]	MeOK	THF	78	95:5	62
2	MeONa	THF	66	98:2	58
3	MeOLi	THF	18	96:4	32
4	<i>t</i> BuOK	THF	48	93:7	12
5	AcOK	THF	0	—	—
6	KF	THF	0	—	—
7	K ₂ CO ₃	THF	0	—	—
8	MeOK	MTBE	26	>99:1	72
9	MeOK	CPME	25	96:4	78
10	MeOK	toluene	77	96:4	72
11	MeOK	DCM	62	86:14	64
12	MeOK	DMF	31	63:37	12
13	MeOK	MeCN	0	—	—
14 ^[f]	MeOK	toluene	58	>20:1	90

[a] Conditions: **1a** (0.24 mmol), (*Z*)-**2** (0.15 mmol), CuCl/(*S,S*)-**L1**·HBF₄ (10 mol%), base (0.18 mmol), THF (0.6 mL), 25 °C for 13 h. [b] Yield of isolated product. [c] Determined by ¹H NMR of crude product. [d] The ee was determined by HPLC. [e] Table 1, entry 1. [f] **L5**·HBF₄ (10 mol%), −30 °C for 48 h.

A range of allylic phosphates can be used in this copper catalysis (Scheme 2 and Table 3). Since the nucleophile of the reaction is mildly reactive organoboron reagents, broad functional compatibility is observed. The coupling reaction of the allylic phosphate containing silyl ether **2b** proceeded in moderate yield (63%) with excellent regioselectivity (γ/α >20:1) and high enantioselectivity (90% ee) (Scheme 2a). *p*-Toluenesulfonate group on the γ -substituent of allylic phosphate **2c** was tolerated; the corresponding product **3ac** was formed in high enantiocontrol (91% ee) (Scheme 2b).

Scheme 2. Reaction of allylic phosphates containing functional groups



Because the functional group of the (Z)-allylic phosphates is compatible with the Phenol–NHC/Cu complex catalyst system, various allylic phosphates derived from *cis*-2-butene-1,4-diol are broadly assessed in this method (Table 3). For example, ethereal groups, such as THP ether (**2d**) and silyl ether (**2e**), are tolerated to afford the corresponding products with high γ -regio- and enantioselectivity (**3ad**: 64% yield, $\gamma/\alpha > 20:1$, 90% ee; **3ae**: 53% yield, $\gamma/\alpha > 20:1$, 95% ee) (entries 1 and 2). Similarly, various allylic substrates having an ester group can be used. Although these substrates have two potential leaving groups, a phosphate group and an ester group, at different allylic positions, the coupling reactions proceeded exclusively at γ to the phosphate leaving group (entries 3–8). Allylic phosphate **2f** reacts with allenylboronate under the chiral copper catalyst, and produced the γ -substituted enantioenriched product ($\gamma/\alpha > 20:1$, 90% ee) without decomposition of pivalate group (entry 3). Methoxy (**2g**) and trifluoromethyl (**2h**) groups on the aromatic ring of the benzoate groups do not give a significant effect to regio- and enantioselectivities (entry 4: $\gamma/\alpha > 20:1$, 86% ee; entry 5: $\gamma/\alpha > 20:1$, 87% ee). The allylic phosphates with bromo (**2i**) and dimethylamino (**2j**) substituents can be used; the corresponding products were formed with good enantioselectivity (90% ee, 87% ee, respectively) (entry 6 and 7). A carbamate group (**2k**) was also compatible in this reaction (entry 8).

Table 3. Scope of allylic phosphates^[a]

entry	phosphate	product	temp (°C)	yield (%) ^[b]	ee (%) ^[d]
1	R = THP (2d)	3ad	−20	64	90
2	R = TBS (2e)	3ae	−30	53	95
3	R = Piv (2f)	3af	−20	45	90
	 2g-j	 3ag-aj			
4	R' = OMe (2g)	3ag	−20	47	86
5	R' = CF ₃ (2h)	3ah	−20	60	87
6	R' = Br (2i)	3ai	−30	58	90
7	R' = NMe ₂ (2j)	3aj	−20	62	87
8	 2k	 3ak	−20	75	82

[a] Conditions: **1a** (0.24 mmol), (*Z*)-**2** (0.15 mmol), CuCl/**L5** (10 mol%), MeOK (0.18 mmol), toluene (0.6 mL) for 48 h. [b] Yield of isolated product. [c] Constitutional isomer ratio $\gamma/\alpha > 20:1$ (determined by ¹H NMR analysis of the crude product). [d] The ee was determined by HPLC analysis.

To gain insight into the mechanism of the copper-catalyzed AAS with an allenylboronate, the author performed the reaction of (*E*)-**2a** or secondary allylic phosphate **2a'**, which is a constitutional isomer of (*Z*)-**2a**. The selectivities in these reactions were changed greatly. First, reaction between **1a** and (*E*)-**2a** was observed under the optimized conditions described in Table 1, entry 7. While the reaction afforded the linear α -substitution product **4aa** as major product and (*S*)-**3aa** (80% ee) as a minor product, which is the antipode of

the product derived from (*Z*)-**2a** (Eq. 1). Similarly, the reaction of secondary allylic phosphate **2a'** under the same conditions gave comparable results, giving linear **4aa** as the major product (Eq. 2). Considering these results, the reaction of allenylboronate may proceed on the mechanism similar to the copper-catalyzed AAS reaction with allylboronates;^{4c} allylcopper(III) species, which can produce the two regioisomers via allylic 1,3-migration, is assumed to be formed in the reaction (Figure 1).

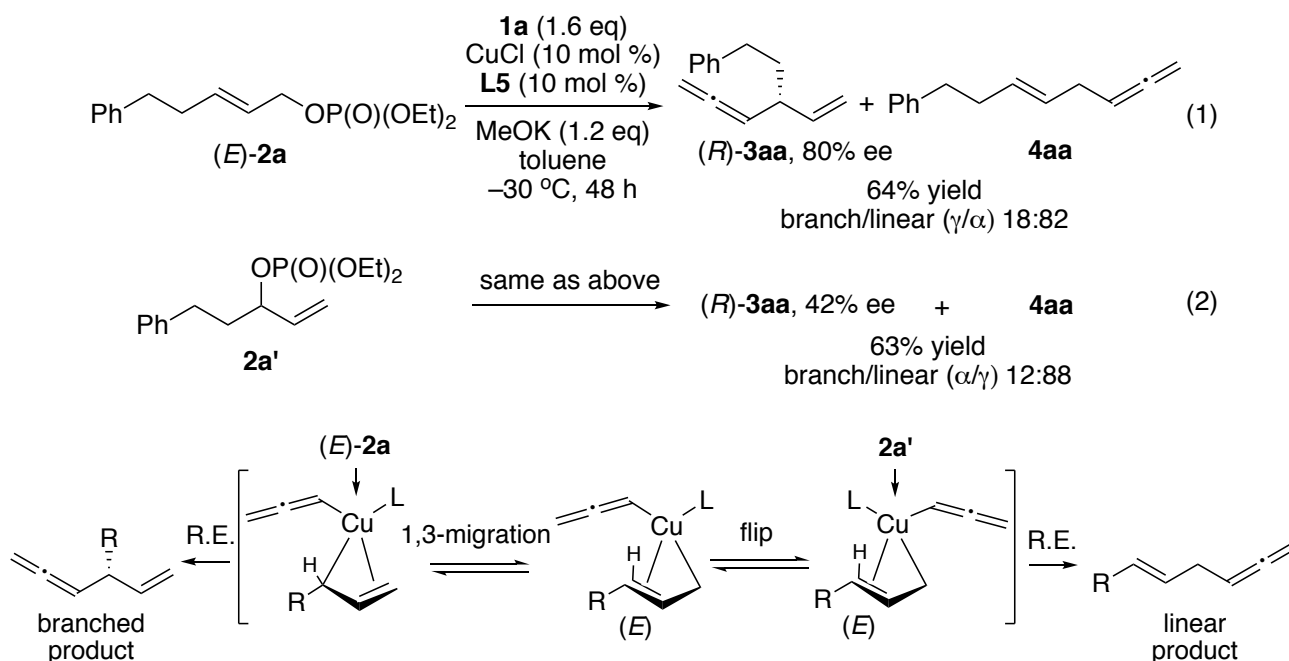


Figure 1. Allylcopper(III) species

Based on previous reports^{4c} and these results, a plausible catalytic cycle for the copper-catalyzed enantioselective AAS with an allenylboronate using **L5**·HBF₄ ligand is shown in Figure 2. An alkoxycopper(I) complex (**I**), the chiral NHC coordinates to Cu center as an anionic bidentate ligand, derived from CuCl, **L5**·HBF₄, and MeOK, reacts with an allenylboronate (**II**) to produce the potassium phenoxo(allyl)cuprate (**III**) via transmetalation. **III** is coordinated with allylic phosphate **2** to deliver a π -complex (**IV**). In this intermediate, the MeOBpin may have a role as a Lewis acid and activate the phosphate leaving group. On π -complex (**IV**), oxidative addition occurs to form (π -en- σ -yl)copper(III) complex (**V**), followed by facile reductive elimination of **V** affords the branched γ -substitution product **3**, and a catalytic cycle restarts from alkoxycopper(I) complex **I**. According to the results of Eqs. 1 and 2, reductive elimination step may occur faster than allylic 1,3-Cu-migration to form **V'** for greatly steric repulsion as 1,3-allylic strain in the reaction of (*Z*)-allylic substrates.⁹

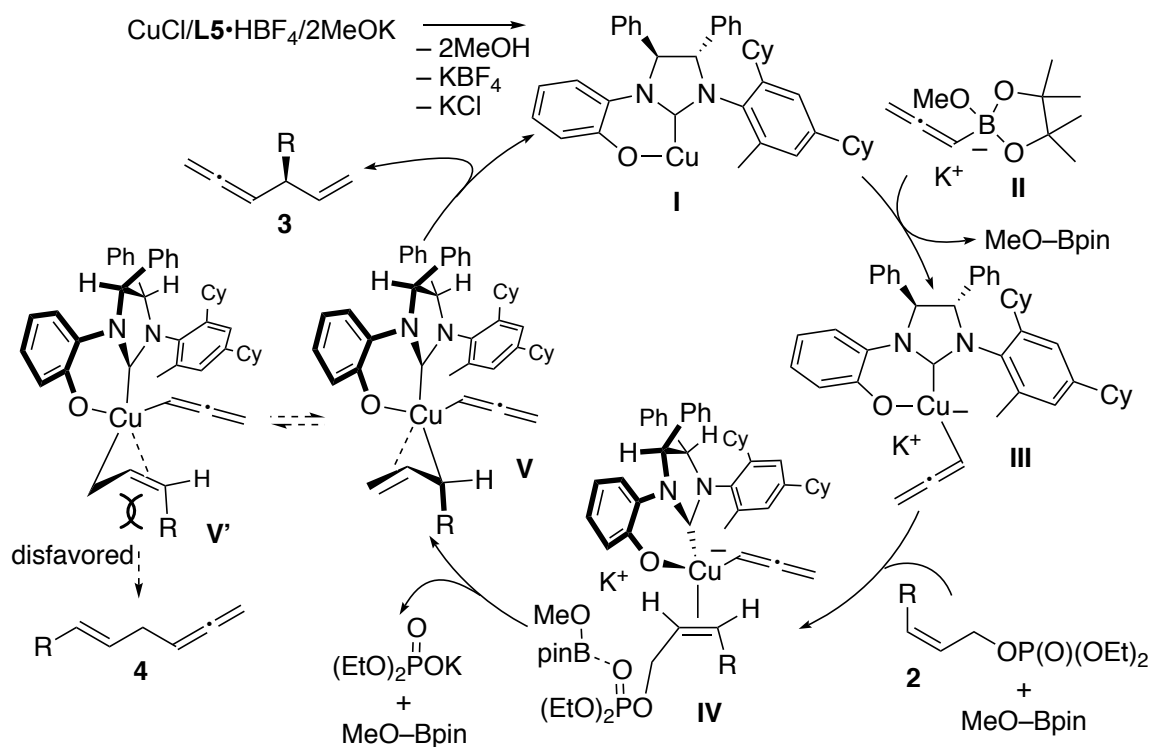


Figure 2. Plausible catalytic cycle

Conclusion

The author demonstrated that a Phenol–NHC chiral ligand is useful in copper-catalyzed AAS reaction with an allenylboronate. The reaction afforded the coupling products containing a tertiary stereogenic center with high regio- and enantioselectivity. By the chiral Cu/L5 catalyst system, the scope was expanded to not only (*E*)-allylic phosphate but also (*Z*)-substrates. Various (*Z*)-allylic phosphates derived from *cis*-2-butene-1,4-diol, which is a commercially available and inexpensive compound, can be used in this reaction. This work suggests that the other organoboron reagents can be applied to copper-catalyzed AAS with a Phenol–NHC chiral ligand.

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 128 MHz for ^{11}B 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. Silica gel (Kanto Chemical Co., Silica gel 60 N, spherical, neutral) was used for column chromatography. IR spectra were measured with a Perkin-Elmer Spectrum One. 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, CHCl_3 , 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. CuCl , and MeOK were purchased from Aldrich Chemical Co., stored under nitrogen, and used as received. Toluene was purchased from Kanto Chemical Co., and stored under argon. 2-Allenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1a**) was obtained from commercial suppliers. Allylic phosphates **2a-k** and **2a'** are found in the literature.^{6a,c,d} NHC ligands **L1–L7** are found in the literature.^{6a–d}

Preparation of Allylic Phosphates

Preparation of 2a-k and 2a'.^{6a,c,d} **2a** was prepared through the phosphorylation of the corresponding allylic alcohol obtained by Lindlar reduction of the known propargylic alcohols. **2b**, **2c**, (*E*)-**2a** and **2a'** were prepared through the phosphorylation of the corresponding allylic alcohols. **2d–k** were prepared through the monoprotection of commercial available *cis*-2-butene-1,4-diol followed by phosphorylation.

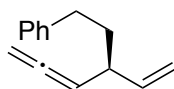
The phosphorylation of (*Z*)-5-phenyl-2-penten-1-ol to **2a** is representative. To a solution of (*Z*)-5-phenyl-2-penten-1-ol (4.9 g, 30 mmol) in pyridine (60 mL), $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$ (5.2 mL, 36 mmol) and DMAP (183 mg, 1.5 mmol) were sequentially added at 0 °C. After being stirred at rt for 12 h, the reaction mixture was diluted with EtOAc (100 mL) and was treated with H_2O (10 mL). The resulting mixture was washed with saturated CuSO_4 aq. (30 mL $\times$ 3) and brine, and was dried over anhydrous MgSO_4 , filtered, and evaporated under reduced pressure. The residue was purified through flash column chromatography on silica gel (10–45% EtOAc /hexane) to provide (*Z*)-diethyl 5-phenyl-2-penten-1-yl phosphate (**2a**) in 64% yield (5.8 g, 19.4 mmol).

Procedure for the Copper-Catalyzed Enantioselective Allylic Substitution with Allenylboronate

The reaction in Table 1, entry 7 is representative. CuCl (1.5 mg, 0.015 mmol), **L5**•HBF₄ (9.8 mg, 0.015 mmol) and MeOK (12.6 mg, 0.18 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. Toluene (0.6 mL) was added to the vial, and then the mixture was stirred at room temperature for 15 min. Next, 2-allenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1a**) (42.8 μ L, 0.24 mmol) was added. Finally, allylic phosphate **2a** (44.7 mg, 0.15 mmol) was added at -30°C . After 48 h stirring at -30°C , the reaction was quenched with saturated NH₄Cl aq. and extracted with diethyl ether (1 mL $\times$ 3). The combined organic layer was 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 (hexane) to give **3aa** (15.6 mg, 0.08 mmol) in 56% yield.

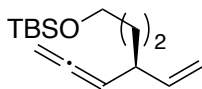
Characterization Data for Coupling Products

(*S*)-(3-vinyl-4,5-hexadien-1-yl)benzene (**3aa**)

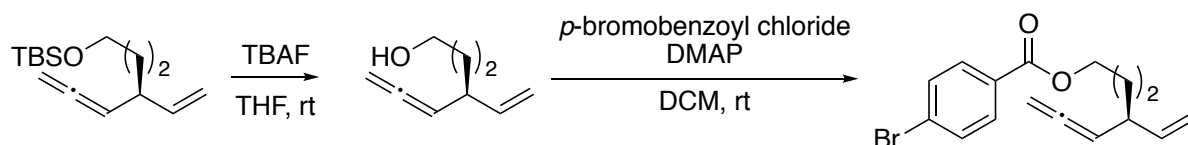


The product **3aa** was purified by flash chromatography on silica gel (hexane) (16.3 mg, 0.08 mmol, 58% isolated yield from (*Z*)-**2a**). Colorless Oil. **3aa** was consistent with the literature data.^{3c} The ee value (90% ee) was determined by chiral HPLC analysis of **3aa** [CHIRALCEL[®] OD-H column, 4.6 mm $\times$ 220 mm / OD-H column, 4.6 mm $\times$ 220 mm, Daicel Chemical Industries, hexane, 0.3 mL/min, 40 $^{\circ}\text{C}$, 220 nm UV detector, retention time = 26.2 min for *R* isomer and 27.5 min for *S* isomer].

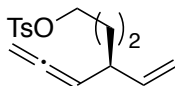
(*S*)-*tert*-butyldimethyl{(4-vinyl-5,6-heptadien-1-yl)oxy}silane (**3ab**)



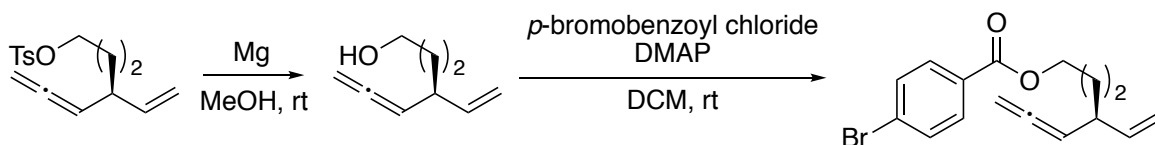
The product **3ab** was purified by flash chromatography on silica gel (0–1% Et₂O/hexane) (24.1 mg, 0.09 mmol, 63% isolated yield from **2b**). Colorless Oil. ¹H NMR (400 MHz, CDCl₃) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.42–1.59 (m, 4H), 2.70 (m, 1H), 3.62 (t, *J* = 6.4 Hz, 2H), 4.71 (dd, *J* = 6.8, 2.4 Hz, 2H), 4.99–5.09 (m, 3H), 5.71 (ddd, *J* = 17.2, 10.0, 7.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ -5.2 , 18.3, 25.9, 30.3, 30.8, 42.7, 63.0, 75.6, 93.2, 114.1, 141.1, 207.8. [α]_D²⁸ +36.2 (*c* 0.84, CHCl₃). The ee value (90% ee) was determined by chiral HPLC analysis of the *p*-bromobenzoate derivative obtained by deprotection followed by benzylation from **3ab** [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, 0.5 mL/min, 40 $^{\circ}\text{C}$, 220 nm UV detector, retention time = 25.5 min for *S* isomer and 27.4 min for *R* isomer]. The absolute configuration of **3ab** was assigned by consideration of the stereochemical pathway.



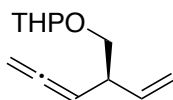
(S)-4-vinyl-5,6-heptadien-1-yl 4-methylbenzenesulfonate (3ac)



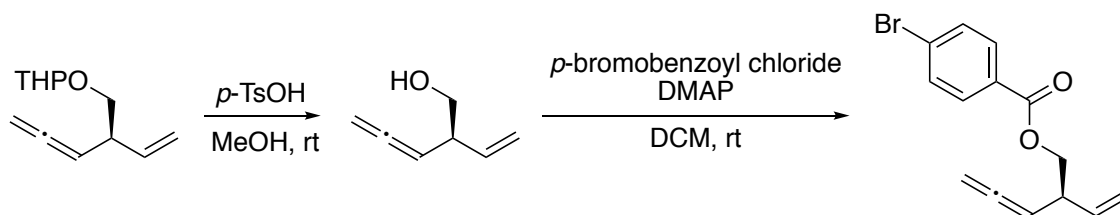
The product **3ac** was purified by flash chromatography on silica gel (0–5% Et₂O/hexane) (29.4 mg, 0.10 mmol, 67% isolated yield from **2c**). Colorless Oil. ¹H NMR (400 MHz, CDCl₃) δ 1.37–1.51 (m, 2H), 1.68 (tt, *J* = 7.2, 6.8 Hz, 2H), 2.45 (s, 1H), 2.61 (m, 1H), 4.02 (t, *J* = 6.8 Hz, 2H), 4.66–4.74 (m, 2H), 4.97–5.04 (m, 3H), 5.62 (ddd, 1H, *J* = 14.8, 10.0, 7.6 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 21.6, 26.5, 30.0, 42.3, 70.4, 76.0, 92.5, 114.7, 127.8, 129.8, 133.0, 140.3, 144.6, 207.8. [α]_D²⁸ +28.5 (*c* 0.62, CHCl₃). The ee value (91% ee) was determined by chiral HPLC analysis of the *p*-bromobenzoate derivative obtained by deprotection followed by benzylation from **3ac** [CHIRALCEL[®] OD-3 column, 4.6 mm × 250 mm/ 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 = 25.5 min for *S* isomer and 27.4 min for *R* isomer]. The absolute configuration of **3ac** was assigned by consideration of the stereochemical pathway.



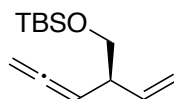
2-[(S)-2-vinyl-3,4-pentadien-1-yl]oxy]tetrahydro-2H-pyran (3ad) (Diastereomeric ratio 1:1)



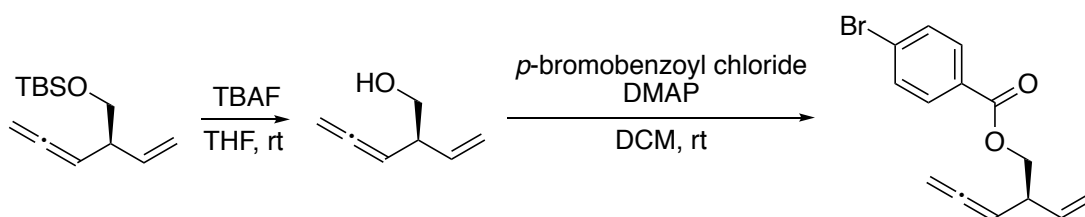
The product **3ad** was purified by flash chromatography on silica gel (0–2% Et₂O /hexane) (18.9 mg, 0.09 mmol, 64% isolated yield from **2d**). ¹H NMR (400 MHz, CDCl₃) δ 1.50–1.62 (m, 4H), 1.69 (m, 1H), 1.81 (m, 1H), 3.07 (m, 1H), 3.42 (m, 1H), 3.50 (m, 1H), 3.74 (m, 1H), 3.86 (m, 1H), 4.61 (m, 1H), 4.74 (dd, *J* = 6.8, 2.8 Hz, 2H), 5.09–5.22 (m, 3H), 5.82 (ddd, *J* = 17.6, 10.0, 7.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 19.3, 25.4, 30.5, 30.5, 42.7, 42.8, 62.0, 70.2, 70.3, 75.9, 90.2, 98.7, 115.8, 138.0, 208.3. [α]_D²⁸ +44.5 (*c* 0.43, CHCl₃). The ee value (90% ee) was determined by chiral HPLC analysis of the *p*-bromobenzoate derivative obtained by deprotection followed by benzylation from **3ad** [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 = 14.7 min for *R* isomer and 15.2 min for *S* isomer]. The absolute configuration of **3ad** was assigned by consideration of the stereochemical pathway.



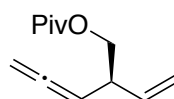
(*S*)-tert-butyldimethyl{(2-vinyl-3,4-pentadien-1-yl)oxy}silane (3ae**)**



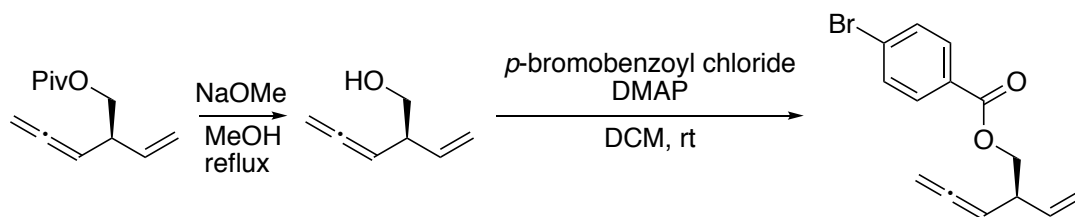
The product **3ae** was purified by flash chromatography on silica gel (0–1% Et₂O/hexane) (17.9 mg, 0.07 mmol, 53% isolated yield from **2e**). ¹H NMR (400 MHz, CDCl₃) δ 0.49 (s, 6H), 0.89 (s, 9H), 2.92 (m, 1H), 3.55–3.62 (m, 2H), 4.72 (dd, *J* = 6.8, 2.8 Hz, 2H), 5.08–5.19 (m, 3H), 5.79 (ddd, *J* = 17.6, 10.4, 7.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ –5.3, 18.3, 25.8, 45.5, 66.3, 75.5, 90.1, 115.8, 138.0, 208.3. [α]_D²⁷ +19.9 (*c* 0.56, CHCl₃). The ee value (95% ee) was determined by chiral HPLC analysis of the **3ai** obtained by deprotection followed by benzylation from **3ae** [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 = 14.7 min for *R* isomer and 15.2 min for *S* isomer]. The absolute configuration of **3ae** was assigned by consideration of the stereochemical pathway.



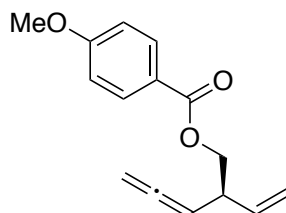
(*S*)-2-vinyl-3,4-pentadien-1-yl pivalate (3af**)**



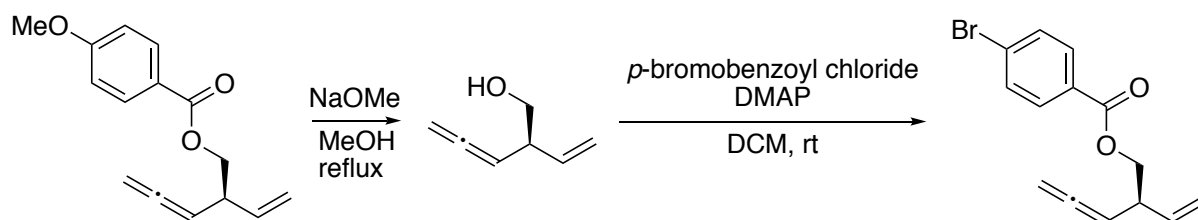
The product **3af** was purified by flash chromatography on silica gel (0–2% Et₂O /hexane) (13.3 mg, 0.06 mmol, 45% isolated yield from **2f**). Colorless Oil. ¹H NMR (400 MHz, CDCl₃) δ 1.19 (s, 9H), 3.11 (m, 1H), 4.07 (d, *J* = 7.2 Hz, 2H), 4.76 (dd, *J* = 6.8, 2.8 Hz, 2H), 5.08–5.18 (m, 3H), 5.75 (ddd, *J* = 17.2, 10.0, 7.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 27.2, 38.8, 42.3, 66.1, 76.4, 89.5, 116.7, 136.9, 178.4, 208.4. [α]_D²⁹ +32.9 (*c* 0.59, CHCl₃). The ee value (90% ee) was determined by chiral HPLC analysis of the **3ai** obtained by deprotection followed by benzylation from **3af** [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 = 14.7 min for *R* isomer and 15.2 min for *S* isomer]. The absolute configuration of **3af** was assigned by consideration of the stereochemical pathway.



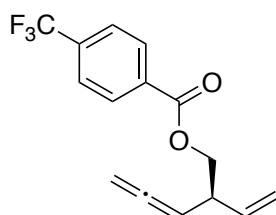
(*S*)-2-vinyl-3,4-pentadien-1-yl 4-methoxybenzoate (3ag**)**



The product **3ag** was purified by flash chromatography on silica gel (0–2% Et₂O /hexane) (17.4 mg, 0.07 mmol, 47% isolated yield from **2g**). Colorless Oil. ¹H NMR (400 MHz, CDCl₃) δ 3.24 (m, 1H), 3.86 (s, 3H), 4.28–4.31 (m, 2H), 4.75–4.80 (m, 2H), 5.13–5.24 (m, 3H), 5.84 (ddd, *J* = 17.6, 10.8, 7.6 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 8.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 42.1, 55.4, 66.4, 76.4, 89.4, 113.5, 116.7, 122.6, 131.5, 136.9, 163.3, 166.1, 208.4. [α]_D²⁹ +19.9 (*c* 0.56, CHCl₃). The ee value (86% ee) was determined by chiral HPLC analysis of the **3ai** obtained by deprotection followed by benzylation from **3ag** [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 = 14.7 min for *R* isomer and 15.2 min for *S* isomer]. The absolute configuration of **3ag** was assigned by consideration of the stereochemical pathway.

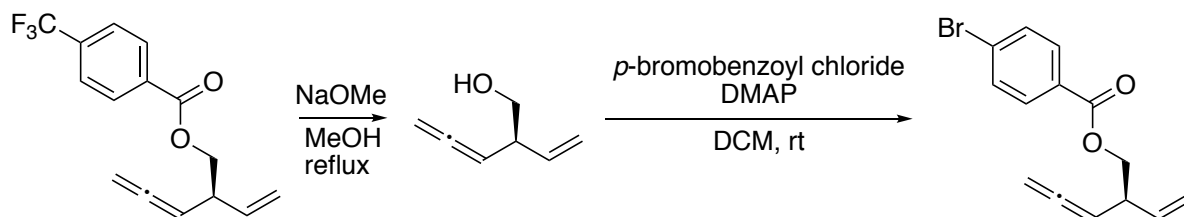


(*S*)-2-vinyl-3,4-pentadien-1-yl 4-(trifluoromethyl)benzoate (3ah**)**

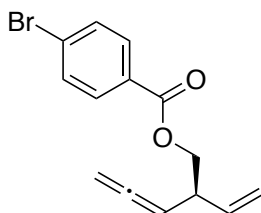


The product **3ah** was purified by flash chromatography on silica gel (0–2% Et₂O /hexane) (25.7 mg, 0.09 mmol, 87% isolated yield from **2h**). ¹H NMR (400 MHz, CDCl₃) δ 3.27 (m, 1H), 4.32–4.42 (m, 2H), 4.75–4.83

(m, 2H), 5.17–5.25 (m, 3H), 5.83 (ddd, $J = 17.6, 10.0, 7.6$ Hz, 1H), 7.71 (d, $J = 8.0$ Hz, 2H), 8.14 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 15.2, 42.0, 65.8, 67.1, 89.2, 117.0. 123.5 (q, $J = 270.7$ Hz), 125.4, 129.9, 133.3, 135.5 (d, $J = 31.4$ Hz). $[\alpha]_{\text{D}}^{29} +32.0$ (c 0.60, CHCl_3). The ee value (87% ee) was determined by chiral HPLC analysis of the **3ai** obtained by deprotection followed by benzylation from **3ah** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 14.7 min for *R* isomer and 15.2 min for *S* isomer]. The absolute configuration of **3ah** was assigned by consideration of the stereochemical pathway.

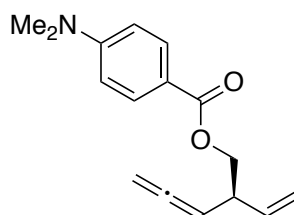


(*S*)-2-vinyl-3,4-pentadien-1-yl 4-bromobenzoate (3ai**)**

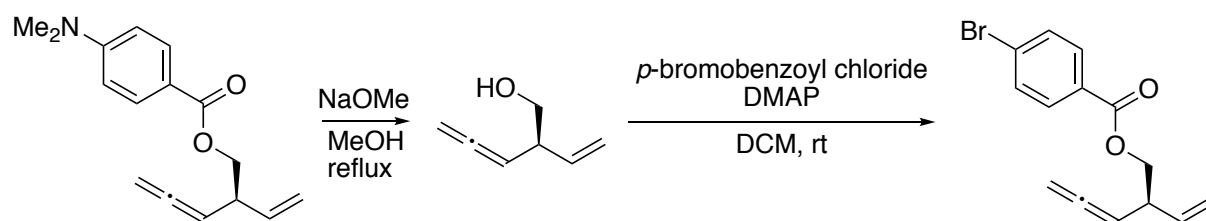


The product **3ai** was purified by flash chromatography on silica gel (0–2% Et_2O /hexane) (25.8 mg, 0.08 mmol, 58% isolated yield from **2i**). Colorless Oil. ^1H NMR (400 MHz, CDCl_3) δ 3.24 (m, 1H), 4.27–4.36 (m, 2H), 4.71–4.82 (m, 2H), 5.14–5.23 (m, 3H), 5.82 (ddd, $J = 17.6, 10.4, 7.6$ Hz, 1H), 7.58 (d, $J = 8.0$ Hz, 2H), 7.88 (d, $J = 8.0$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 42.0, 66.8, 76.5, 89.2, 116.9, 128.0, 129.0, 131.0, 131.7, 136.6, 165.6, 208.3. $[\alpha]_{\text{D}}^{28} +29.0$ (c 0.78, CHCl_3). The ee value (91% ee) was determined by chiral HPLC analysis of **3ai** [CHIRALCEL[®] OD-3 column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 99:1, 0.5 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 14.7 min for *R* isomer and 15.2 min for *S* isomer]. The absolute configuration of **3ai** was assigned by consideration of the stereochemical pathway.

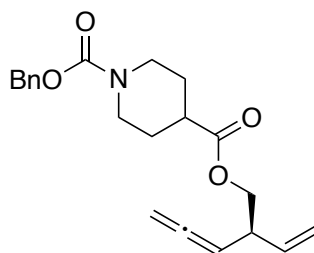
(*S*)-2-vinyl-3,4-pentadien-1-yl 4-(dimethylamino)benzoate (3aj**)**



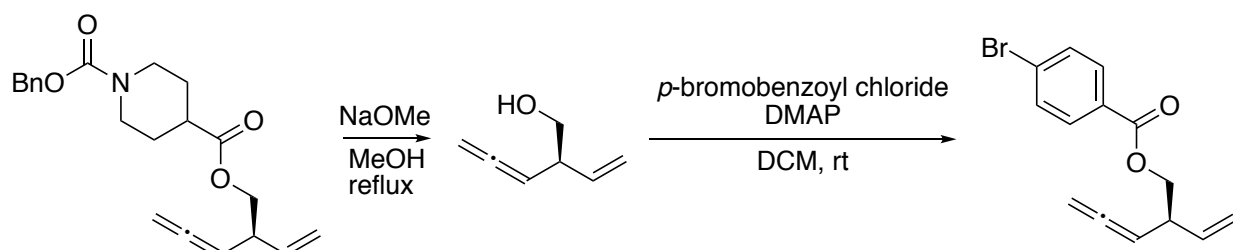
The product **3aj** was purified by flash chromatography on silica gel (0–5% Et₂O /hexane) (24.1 mg, 0.09 mmol, 62% isolated yield from **2j**). Colorless Oil. ¹H NMR (400 MHz, CDCl₃) δ 3.04 (s, 6H), 3.23 (m, 1H), 4.23–4.31 (m, 2H), 4.71–4.83 (m, 2H), 5.13–5.23 (m, 3H), 5.85 (ddd, *J* = 17.6, 10.8, 8.0 Hz, 1H), 6.64 (d, *J* = 7.2 Hz, 2H), 7.90 (d, *J* = 7.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 39.9, 40.1, 42.6, 66.0, 76.3, 89.5, 110.6, 116.5, 116.9, 131.2, 137.1, 153.2, 166.7, 208.4. [α]_D²⁹ +18.1 (*c* 0.67, CHCl₃). The ee value (87% ee) was determined by chiral HPLC analysis of the **3ai** obtained by deprotection followed by benzylation from **3aj** [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 = 14.7 min for *R* isomer and 15.2 min for *S* isomer]. The absolute configuration of **3aj** was assigned by consideration of the stereochemical pathway.



(*S*)-1-benzyl 4-(2-vinylpenta-3,4-dien-1-yl) piperidine-1,4-dicarboxylate (3ak**)**



The product **3ak** was purified by flash chromatography on silica gel (5–15% Et₂O /hexane) (40.4 mg, 0.11 mmol, 75% isolated yield from **2k**). Colorless Oil. ¹H NMR (400 MHz, CDCl₃) δ 1.64–1.66 (m, 2H), 1.83–1.96 (m, 2H), 2.47 (m, 1H), 2.89–3.02 (m, 2H), 3.09 (m, 1H), 4.07–4.14 (m, 4H), 4.75–4.78 (m, 2H), 5.07–5.17 (m, 5H), 5.72 (ddd, *J* = 17.6, 10.0, 7.6 Hz, 1H), 7.29–7.38 (m, 5H). ¹³C NMR (100 MHz, CDCl₃) δ 27.8, 40.8, 41.9, 42.1, 43.0, 43.2, 66.2, 67.0, 76.4, 76.5, 89.1, 116.8, 127.7, 127.8, 127.9, 128.3, 128.4, 136.6, 155.1, 174.1, 208.2. [α]_D²⁹ +22.5 (*c* 0.72, CHCl₃). The ee value (82% ee) was determined by chiral HPLC analysis of the **3ai** obtained by deprotection followed by benzylation from **3ak** [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 = 14.7 min for *R* isomer and 15.2 min for *S* isomer]. The absolute configuration of **3ak** was assigned by consideration of the stereochemical pathway.



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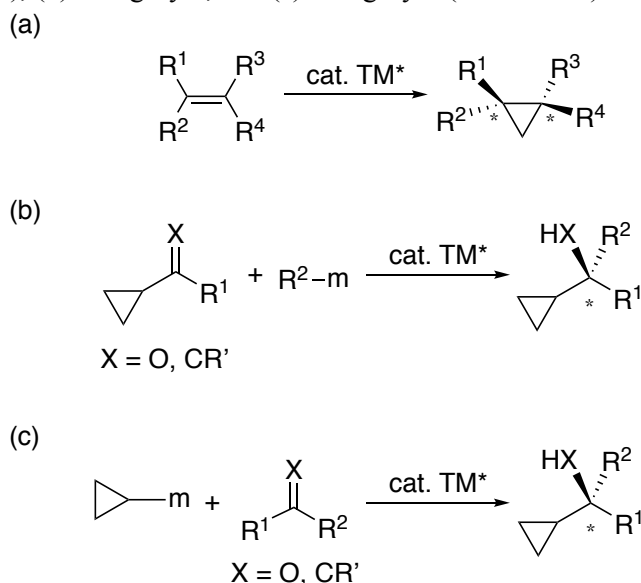
Chapter 4

Copper-Catalyzed Enantioselective Allylic Cyclopropylation with 3-Bromo-1,1-diborylpropane using a Phenol/NHC Chiral Ligand

Introduction

Cyclopropane is a ubiquitous structure motif in natural products, medicines, agrochemicals, and fragrances.¹ The motif is also important as synthetic intermediates due to the unique reactivities derived from its strained natures.² Hence, a catalytic asymmetric reactions for an easy access to chiral organic molecules containing a cyclopropyl unit is highly desirable. In a few decades, various methods to access cyclopropanes have been developed. There are mainly three approaches to synthesize the chiral compounds containing a cyclopropane framework: 1) catalytic asymmetric cyclopropanation of pro-chiral alkenes,³ 2) catalytic asymmetric transformations of pro-chiral molecules with a cyclopropyl substituent,^{4,5} 3) catalytic asymmetric installation of a cyclopropyl group to pro-chiral molecules (Scheme 1a–c). Especially, the author focused on the category 3. Although the third approach is simple and straightforward, highly enantioselective method in this category is relatively rare compared to the other two approaches.^{6–8} 1,2-addition to aldehydes developed by Soai, C(sp³)-C(sp³)-Suzuki cross-coupling developed by Fu (only one entry of cyclopropyl group introduction), and 1,4-addition to Michael-acceptors developed by Nishimura are limited examples. However, these reactions require preparation of organometallic reagents containing cyclopropyl group.

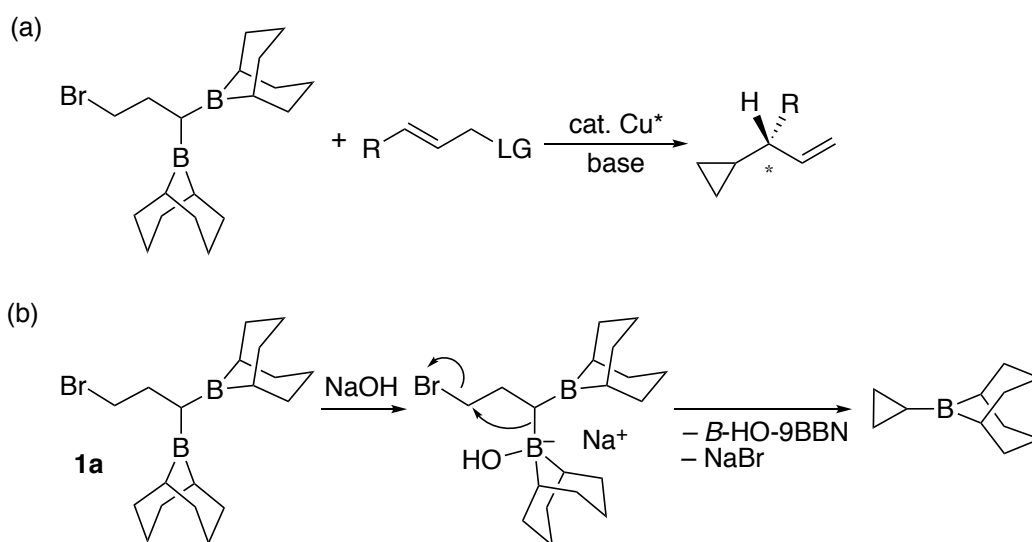
Scheme 1. Three categories for the synthesis of chiral compounds containing a cyclopropane framework: (a) Category 1 (typical example), (b) Category 2, and (c) Category 3 (ref. 6 and 8)



On the other hand, unique reactivity of 1,1-diborylalkanes, composed of characteristic *gem*-boryl structure, has attracted considerable attention. However, in contrast to the increasing number of reports on the use of (pinacolate)boron-based 1,1-diborylalkanes,⁹ analogous 9-borabicyclo[3.3.1]nonane (9-BBN)-based 1,1-diborylalkanes have attracted much less attention in organic synthesis.¹⁰ The author's laboratory recently reported a phosphine-catalyzed *anti*-carboboration of alkynoates with 9-BBN-based 1,1-diborylalkanes to afford multi-substituted- γ -borylallylboranes.¹¹ Herein, the author describes a novel application of 9-BBN-based

1,1-diborylalkanes to a catalytic asymmetric cyclopropylation of pro-chiral molecules (Scheme 2a). On the basis of a report by Brown, which described generation of cyclopropyl-9-BBN from 3-bromo-1,1-diborylpropane **1a** upon base treatment (Scheme 2b),¹² the author utilized **1a** for the one-pot cyclopropylation reaction as a tool to construct a cyclopropane ring, while the utility of cyclopropyl-9-BBN has not been explored except for oxidation to cyclopropanol. This reaction belongs to the category 3 as a method for the preparation of cyclopropane-containing molecules, but it is distinct from the previous examples in that the cyclopropyl nucleophile is generated *in-situ*. Furthermore, this reaction is the first example of the copper-catalyzed enantioselective allylic substitution with non-activated secondary alkylboranes.¹³

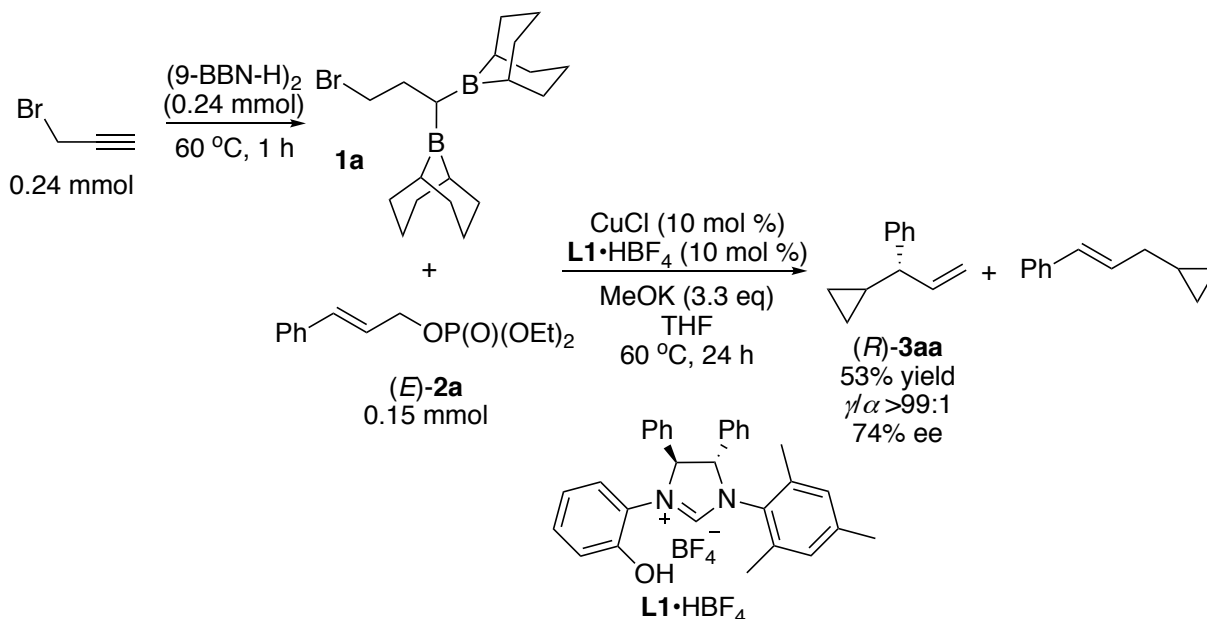
Scheme 2. (a) This work, (b) Generation method for cyclopropyl-9-BBN



Results and Discussion

As a result, the chiral phenol–NHC/Cu catalyzed allylic coupling reaction¹⁴ between allylic phosphate **2a** and 3-bromo-1,1-diborylpropane **1a**,¹² which is prepared via double hydroboration of a propargyl bromide with 9-BBN dimer, proceeded to give the allylcyclopropane **3aa** in good enantioselectivity and excellent γ -selectivity (Scheme 3). The reaction might proceed through in situ generation of cyclopropyl-9-BBN followed by copper-catalyzed AAS, delivering the chiral allylcyclopropane.

Scheme 3. Copper-catalyzed enantioselective allylic cyclopropylation



Based on this result, various reaction conditions were examined. First, the ligand effect was assessed (Table 1). Changing **L1**·HBF₄ to the C₂-symmetric imidazolinium chloride (**L2**·HBF₄),¹⁵ the nearly racemic γ -alkylated product was observed with lower yield (entry 2). To investigate the necessity of the phenolic hydroxy group on the ligand, similar chiral NHC ligands bearing 2-methylphenyl (**L3**) or 2-methoxyphenyl (**L4**) groups were examined (entry 3 and 4). Although the yield and regioselectivity were comparable to the reaction with **L1**/copper complex, the enantioselectivity significantly decreased in these cases. The results imply that the phenolic hydroxy group in **L1** has a key role.

To improve the enantioselectivity, the author explored more effective ligands. Changing the *N*-mesityl group of **L1**·HBF₄ to more sterically hindered group (**L5**) decreased enantiomeric excess (47% ee) (entry 5). Intensive studies on effect of steric bulkiness of the *N*-aryl group gave no good result (data is not shown.). The naphthol–NHC chiral ligands **L6** and **L7**^{14b} were also ineffective (entries 6 and 7). Finally, a bisphosphine ligand, (R)-DTBM-SEGPHOS, was tested in this copper catalyst system, because the ligand was suitable for enantioselective allylic substitution with alkyl-9-BBN reagents in our previous reports.¹⁶ However, no reaction occurred in the cyclopropylation reaction (entry 8). According to these results, further investigation was

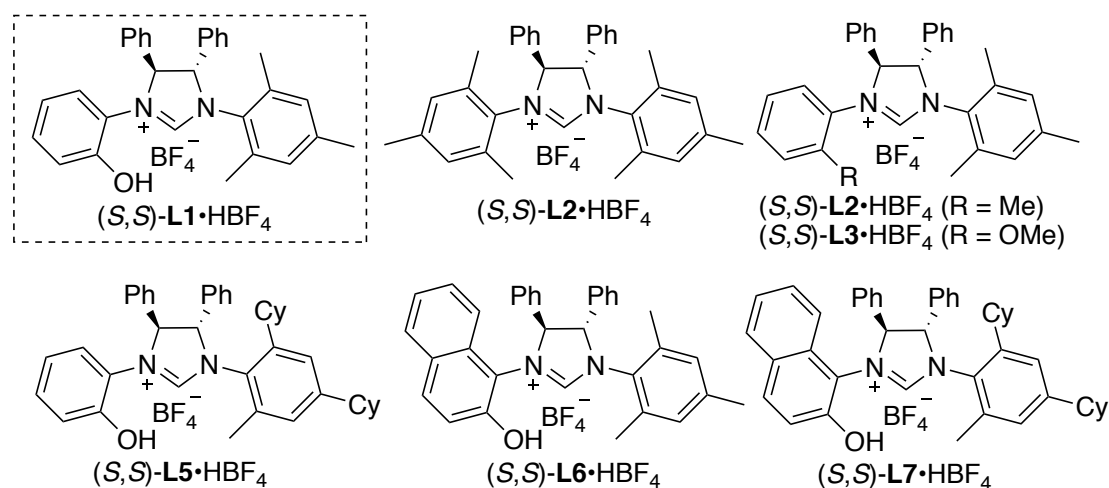
conducted with **L1**·HBF₄ as the most efficient ligand.

The absolute configuration of **3aa** [$[\alpha]_D^{29} +6.0$ (c 0.52, CHCl₃) {lit¹⁷, (*R*) isomer, 99% ee, $[\alpha]_D^{20} +13.7$ (c 1.0 CHCl₃)}] was determined by comparison of the specific rotations with the values reported previously.

Table 1. Ligand effects in reaction between **1a** and (*E*)-**2a**^{a,b}

entry	ligand	yield (%) ^c	ee (%) ^d
1	L1 ·HBF ₄	53	74
2	L2 ·HBF ₄	22	3
3	L3 ·HBF ₄	48	6
4	L4 ·HBF ₄	55	8
5	L5 ·HBF ₄	55	47
6	L6 ·HBF ₄	51	16
7	L7 ·HBF ₄	19	40 ^e
8	(<i>R</i>)-DTBM-SEGPPOS	0	—

[a] MeOK (0.495 mmol), THF (0.6 mL). [b] Constitutional isomer ratio was determined by ¹H NMR analysis of the crude product. [c] Yield of isolated product. [d] The ee was determined by HPLC analysis. [e] Major stereoisomer was (*S*)-**3aa**. THF = tetrahydrofuran.



Results of an examination for leaving groups are shown in Table 2. None of the allylic acetate, allylic carbonate, and allylic halides improved the yield and ee (entries 2-5). A leaving group of a propargyl compound, a precursor of cyclopropyl-9-BBN, was also checked (entry 6–8). While the reaction of propargyl chloride proceeded with slightly decreased enantioselectivity (entry 6), propargylmethanesulfonate and *p*-

toluenesulfonate (-OTs) were totally ineffective (entry 7 and 8).

Table 2. Effect of leaving group^{a,b}

Entry	Leaving group (allylic phosphate 2)	Leaving group (propargyl bromide)	Yield (%) ^c	Ee (%) ^d
1	OP(O)(OEt) ₂	Br	53	74
2	OCOMe	Br	0	–
3	OCO ₂ Me	Br	22	38
4	Cl	Br	48	65
5	Br	Br	17	3
6	OP(O)(OEt) ₂	Cl	53	71
7	OP(O)(OEt) ₂	OMs	0	–
8	OP(O)(OEt) ₂	OTs	0	–

[a] Conditions: **1a** (0.24 mmol), (*E*)-**2** (0.15 mmol), CuCl/(*S,S*)-**L1**·HBF₄ (10 mol%), MeOK (0.495 mmol), THF (0.6 mL), 60 °C for 24 h. [b] Constitutional isomer ratio γ/α >99:1 (determined by ¹H NMR analysis of the crude product). [c] Yield of isolated product. [d] The ee was determined by HPLC.

The nature of the base had a significant impact on yield (Table 3, entry 1–5). The use of MeONa instead of MeOK decreased the product yield (21%) with the similar value of enantiomeric excess (entry 2). No reaction occurred with MeOLi, due to the greater solubility of LiCl, LiBr or LiOP(O)(OEt)₂, which may form inactive Cu species through ionic interactions (entry 3). The structure of the alkoxide moiety of the base also greatly influenced on the reaction. When MeOK was changed to a sterically more demanding base, *t*BuOK, the coupling product was not obtained (entry 4). This result suggests that the *B*-RO-9-BBN may participate in the reaction for activation as Lewis acids. The reaction with K₂CO₃ did not occur (entry 5).

The solvent effect was also summarized in Table 3 (entry 1 and 6–12). Reaction in toluene gave the γ -substituted product with slightly decreased enantioselectivity (76% ee) in moderate yield (44%) (entry 6). Dichloromethane (DCM) was ineffective in the reaction (34% yield, γ/α > 99:1, 64% ee) (entry 7). Polar solvents (*N,N*-dimethylformamide: DMF, acetonitrile: MeCN) were also not suitable (entry 8 and 9). Based on these results, the author focused on the use of ether solvents. In methyl *tert*-butyl ether (MTBE) or cyclopentyl methyl ether (CPME), the reactions proceeded with good enantioselectivity, but the products yields significantly decreased (25% yield; 20% yield, respectively) (entry 10 and 11). Fortunately, the reaction in dioxane afforded a sufficient amount of the product (53% yield) with high enantioselectivity (86% ee) (entry 12).

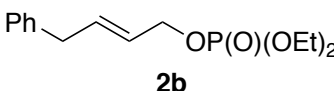
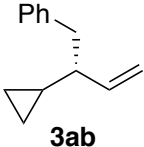
Table 3. Effect of base and solvent^{a,b}

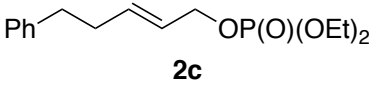
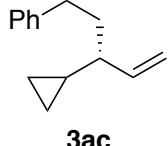
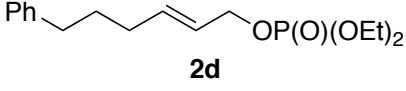
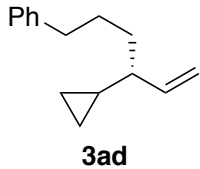
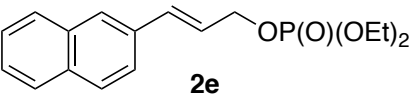
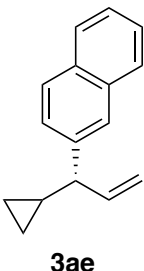
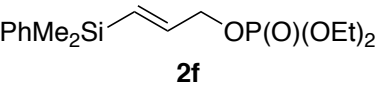
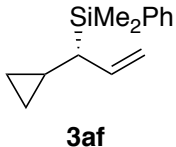
Entry	Base	Solvent	Yield (%) ^c	Ee (%) ^d
1	MeOK	THF	53	74
2	MeONa	THF	21	72
3	MeOLi	THF	0	–
4	<i>t</i> BuOK	THF	0	–
5	K ₂ CO ₃	THF	0	–
6	MeOK	toluene	44	76
7	MeOK	DCM	34	64
8	MeOK	DMF	43	9 ^e
9	MeOK	MeCN	0	–
10	MeOK	MTBE	25	83
11	MeOK	CPME	20	75
12 ^f	MeOK	dioxane	53	86

[a] Conditions: **1a** (0.24 mmol), (*E*)-**2** (0.15 mmol), CuCl/(*S,S*)-**L1**·HBF₄ (10 mol%), MeOK (0.495 mmol), THF (0.6 mL), 60 °C for 24 h. [b] Constitutional isomer ratio γ/α >99:1 (determined by ¹H NMR analysis of the crude product). [c] Yield of isolated product. [d] The ee was determined by HPLC. [e] Major stereoisomer was (*S*)-**3aa**. [f] In dioxane (0.5 mL).

Next, the author investigated the scope of allylic phosphates **2** with the optimized reaction condition (Table 3, entry 12). The γ -substituted allylic phosphates afforded the various allyl cyclopropanes effectively in this Cu catalyst system (Table 4). The phenyl group of (*E*)-**2a** could be replaced with a benzyl group (**2b**); the reaction proceeded with exclusive γ -selectivity and good enantioselectivity (entry 1). Phenylethyl (**2c**) and phenylpropyl (**2d**) groups, longer alkyl chain, are tolerated as the γ -substituent on the allylic phosphates (entry 2 and 3). The reaction of the allylic phosphate substituted with sterically more demanding substituent, naphthyl group, afforded the corresponding product with moderate yield and comparable enantioselectivity (entry 4). A chiral allylsilane containing the cyclopropyl ring adjacent to a stereogenic center was obtained in excellent regio- and enantioselectivities (entry 5).

Table 4. Substrate scope of allylic phosphates^{a,b}

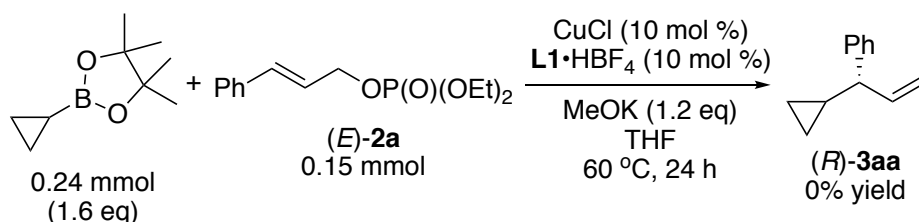
entry	phosphate	product	yield (%) ^c	ee (%) ^d
1	 2b	 3ab	59	87

2	 2c	 3ac	74	82
3	 2d	 3ad	78	82
4	 2e	 3ae	59	87
5	 2f	 3af	74	96

[a] Conditions: **1a** (0.24 mmol), (*E*)-**2** (0.15 mmol), CuCl/(*S,S*)-**L1**·HBF₄ (10 mol%), MeOK (0.495 mmol), dioxane (0.5 mL), 60 °C for 24 h. [b] Constitutional isomer ratio γ/α >99:1 (determined by ¹H NMR analysis of the crude product). [c] Yield of isolated product. [d] The ee was determined by HPLC.

The author performed the reaction of 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as cyclopropyl group source with a γ -substituted (*E*)-cinnamyl phosphate **2a** under the chiral copper catalyst system (Scheme 4).^{15c,d} However, no reaction occurred, and an unreacted cyclopropylboronate was recovered.¹⁸ This result indicates that the transmetalation of cyclopropyl boronic acid ester to copper catalyst seems to be an inefficient process; the use of a readily transferable trialkylborane, cyclopropyl-9-BBN, is important.¹⁹

Scheme 4. Reaction of cyclopropylboronate



Conclusion

The author disclosed the enantioselective cyclopropylation of allylic phosphates by a copper-catalyzed allylic substitution with 3-bromo-1,1-diborylpropane **1a**, that is prepared in situ via hydroboration of a propargyl bromide.

The use of the Phenol–NHC chiral ligand affords enantioenriched coupling products containing cyclopropyl unit, which is widely found in natural products, medicines and agrochemicals, and has a unique reactivity. In addition, the chiral allyl cyclopropanes contain an alkene unit that allows a further transformation. This method is a one-pot synthesis of cyclopropanes from a commercially available propargyl bromide, directly constructing a stereogenic center adjacent to cyclopropyl ring.

This reaction is the first example of the use of a secondary alkylborane as a nucleophile in copper-catalyzed enantioselective allylic alkylation. By the further studies in details, various secondary alkyl units will be introduced in catalytic asymmetric synthesis.

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 128 MHz for ^{11}B 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. Silica gel (Kanto Chemical Co., Silica gel 60 N, spherical, neutral) was used for column chromatography. IR spectra were measured with a Perkin-Elmer Spectrum One. 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, CHCl_3 , 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. CuCl , and MeOK were purchased from Aldrich Chemical Co., stored under nitrogen, and used as received. Dioxane was purchased from Kanto Chemical Co., and stored under nitrogen. Allylic phosphates **2a**, **2c** and **2e–f** are found in the literature.²⁰ NHC ligands **L1–7** are found in the literature.^{10, 11}

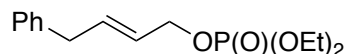
Preparation of Allylic Phosphates

Preparation of 2a–f. **2a–e** were prepared through the phosphorylation of the corresponding allylic alcohols obtained by two-step Horner-Wadsworth-Emmons olefination/DIBAL-H reduction sequence. **2f** was prepared through the phosphorylation of the corresponding allylic alcohols obtained.

The phosphorylation of (*E*)-cinnamyl alcohol to **2a** is representative. To a solution of (*E*)-cinnamyl alcohol (4.0 g, 30 mmol) in pyridine (60 mL), $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$ (5.18 mL, 36 mmol) and DMAP (183 mg, 1.5 mmol) were sequentially added at 0 °C. After being stirred at rt for 1 h, the reaction mixture was diluted with EtOAc (100 mL) and was treated with H_2O (20 mL). The resulting mixture was washed with saturated CuSO_4 aq. (30 mL $\times$ 3) and brine, and was dried over anhydrous MgSO_4 , filtered, and evaporated under reduced pressure. The residue was purified through flash column chromatography on silica gel (10–45% EtOAc /hexane) to provide (*E*)-cinnamyl diethyl phosphate (**2a**) in 76% yield (6.2 g, 22.9 mmol).

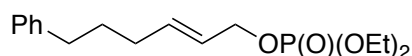
Characterization Data for Allylic Phosphates

(*E*)-diethyl (4-phenyl-2-buten-1-yl) phosphate (2b)



Colorless Oil. ^1H NMR (400 MHz, CDCl_3) δ 1.32 (t, $J = 6.8$ Hz, 6H), 3.40 (d, $J = 6.4$ Hz, 2H), 4.09 (quint, $J = 6.8$ Hz, 4H), 4.51, (t, $J = 7.6$ Hz, 2H), 5.66 (dt, $J = 15.2$, 6.4 Hz, 1H), 5.96 (dt, $J = 15.2$, 6.4 Hz, 1H), 7.16–7.22 (m, 3H), 7.29 (dd, $J = 7.6$, 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 16.0 (d, $J = 6.7$ Hz), 38.4, 63.6 (d, $J = 5.7$ Hz), 67.6 (d, $J = 4.8$ Hz), 125.7 (d, $J = 6.6$ Hz), 126.2, 128.4, 128.5, 134.5, 139.3.

(*E*)-diethyl (6-phenyl-2-hexen-1-yl) phosphate (2d)



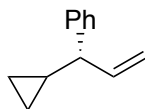
Colorless Oil. ^1H NMR (400 MHz, CDCl_3) δ 1.33 (t, $J = 7.6$ Hz, 6H), 1.72 (tt, $J = 7.6$, 6.8 Hz, 2H), 2.10 (td, $J = 7.6$, 6.8 Hz, 2H), 2.61 (t, $J = 7.6$ Hz, 2H), 4.10 (quint, $J = 7.6$ Hz, 4H), 4.48 (t, $J = 6.4$ Hz, 2H), 5.62 (dt, $J = 14.8$, 6.4 Hz, 1H), 5.79 (dt, $J = 14.8$, 7.6 Hz, 1H), 7.15–7.20 (m, 3H), 7.28 (d, $J = 7.2$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 16.1 (d, $J = 6.6$ Hz), 30.4, 31.5, 35.2, 63.6 (d, $J = 5.7$ Hz), 68.0 (d, $J = 5.8$ Hz), 124.8 (d, $J = 5.8$ Hz), 125.7, 128.2, 128.3, 135.9, 142.0.

Typical Procedure for Copper-Catalyzed Allylic Cyclopropylation of Primary Allylic Phosphates.

The reaction in Table 3, entry 12 is representative. (9-BBN-H) $_2$ (58.6 mg, 0.24 mmol) was 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. Propargyl bromide (0.017 mL, 0.24 mmol) were added to the vial, and then the mixture was stirred at 60 °C for 1 h to prepare a 3-bromo-1,1-diborylpropane **1a**. Meanwhile, CuCl (1.5 mg, 0.015 mmol), **L1** · HBF $_4$ (7.8 mg, 0.015 mmol) and MeOK (34.7 mg, 0.495 mmol) were placed in another vial containing a magnetic stirring bar. This vial was sealed with a Teflon[®]-coated silicon rubber septum and then evacuated and filled with argon. After dioxane (0.2 mL) was added to the vial, the mixture was stirred at 25 °C for 1 h. Next, the alkylborane **1a** was transferred to the vial containing the Cu salt with dioxane (0.1 mL $\times$ 3). Then, (*E*)-**2a** (40.5 mg, 0.15 mmol) was added to the mixture. After 24 h stirring at 60 °C, the mixture was filtered through a short plug of aluminum oxide, which was washed with diethyl ether. After the solvent was removed under reduced pressure, flash chromatography on silica gel (hexane) gave (*R*)-**3aa** (12.7 mg, 0.08 mmol) in 53% yield.

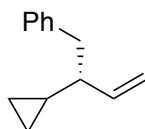
Characterization Data for Coupling Products

(*R*)-(1-cyclopropylallyl)benzene (**3aa**)



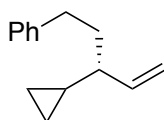
The product **3aa** was purified by flash chromatography on silica gel (hexane) (12.7 mg, 0.08 mmol, 53% isolated yield from (*E*)-**2a**). Colorless Oil. **3aa** was consistent with the literature data.¹⁷ $[\alpha]_D^{29} +6.0$ (c 0.52, CHCl_3). The ee value (86% ee) was determined by chiral HPLC analysis of **3aa** [CHIRALCEL[®] OJ-H column, 4.6 mm $\times$ 220 mm, Daicel Chemical Industries, hexane, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 13.3 min for *S* isomer and 13.9 min for *R* isomer].

(*R*)-(2-cyclopropyl-3-buten-1-yl)benzene (**3ab**)



The product **3ab** was purified by flash chromatography on silica gel (hexane) (15.4 mg, 0.08 mmol, 59% isolated yield from **2b**). Colorless Oil. ¹H NMR (400 MHz, CDCl_3) δ 0.00–0.11 (m, 2H), 0.38–0.47 (m, 2H), 0.69 (m, 1H), 1.61 (tdd, J = 8.0, 7.2, 7.2 Hz, 1H), 2.72 (m, 1H), 2.85 (m, 1H), 4.93 (d, J = 12.8 Hz, 1H), 4.94 (d, J = 17.2 Hz, 1H), 5.74 (ddd, J = 17.2, 12.8, 7.2 Hz, 1H), 7.16 (d, J = 6.4 Hz, 2H), 7.18 (d, J = 8.0 Hz, 1H), 7.25 (dd, J = 8.0, 6.4 Hz, 2H). ¹³C NMR (100 MHz, CDCl_3) δ 3.3, 4.3, 15.2, 41.7, 49.9, 114.1, 125.6, 127.9, 129.3, 140.5, 141.1 $[\alpha]_D^{29} +19.3$ (c 0.39, CHCl_3). The ee value (87% ee) was determined by chiral HPLC analysis of **3ab** [CHIRALCEL[®] OJ-3 column, 2.1 mm $\times$ 250 mm/ OJ-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane, 0.5 mL/min, 25 °C, 220 nm UV detector, retention time = 31.6 min for *S* isomer and 32.6 min for *R* isomer]. The absolute configuration of **3ab** was assigned by consideration of the stereochemical pathway.

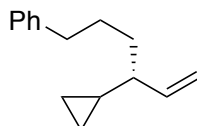
(*R*)-(3-cyclopropyl-4-penten-1-yl)benzene (**3ac**)



The product **3ac** was purified by flash chromatography on silica gel (hexane) (20.9 mg, 0.11 mmol, 74% isolated yield from **2c**). Colorless Oil. ¹H NMR (400 MHz, CDCl_3) δ 0.03–0.15 (m, 2H), 0.38–0.50 (m, 2H), 0.68 (m, 1H), 1.33 (m, 1H), 1.73 (m, 1H), 1.84 (m, 1H), 2.55–2.71 (m, 2H), 5.01 (d, J = 16.8 Hz, 1H), 5.02 (d, J = 10.8 Hz, 1H), 5.76 (ddd, J = 16.8, 10.8, 8.4 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 7.6 Hz, 2H), 7.27 (dd, J = 7.6, 7.2 Hz, 2H). ¹³C NMR (100 MHz, CDCl_3) δ 3.1, 4.2, 15.8, 33.3, 36.7, 48.0, 114.1, 125.4, 125.6,

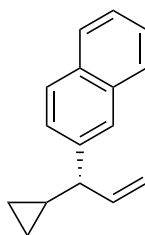
128.2, 128.2, 128.4, 141.9, 142.8. $[\alpha]_D^{29} -2.7$ (c 0.90, CHCl_3). The ee value (82% ee) was determined by chiral HPLC analysis of **3ac** [CHIRALCEL[®] OJ-3 column, 2.1 mm $\times$ 250 mm/ OJ-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane, 25 $^\circ\text{C}$, 220 nm UV detector, retention time = 28.5 min for *R* isomer and 29.7 min for *S* isomer]. The absolute configuration of **3ac** was assigned by consideration of the stereochemical pathway.

(*R*)-(4-cyclopropyl-5-hexen-1-yl)benzene (3ad)



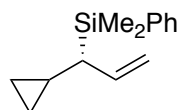
The product **3ad** was purified by flash chromatography on silica gel (hexane) (23.7 mg, 0.11 mmol, 78% isolated yield from **2d**). ^1H NMR (400 MHz, CDCl_3) δ 0.02–0.15 (m, 2H), 0.36–0.48 (m, 2H), 0.62 (m, 1H), 1.28 (m, 1H), 1.44 (m, 1H), 1.52–1.72 (m, 3H), 2.52–2.65 (m, 2H), 4.95 (d, J = 10.8 Hz, 1H), 4.96 (d, J = 17.6 Hz, 1H), 5.69 (ddd, J = 17.6, 10.8, 7.6 Hz, 1H), 7.15–7.18 (m, 3H), 7.27 (dd, J = 8.4, 6.8 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 3.0, 4.2, 15.7, 29.1, 34.6, 36.1, 48.3, 113.6, 125.5, 128.2, 128.3, 142.1, 142.7. $[\alpha]_D^{29} +9.1$ (c 1.0, CHCl_3). The ee value (82% ee) was determined by chiral HPLC analysis of **3ad** [CHIRALCEL[®] OJ-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane, 25 $^\circ\text{C}$, 220 nm UV detector, retention time = 15.8 min for *S* isomer and 18.3 min for *R* isomer]. The absolute configuration of **3ad** was assigned by consideration of the stereochemical pathway.

(*R*)-2-(1-cyclopropylallyl)naphthalene (3ae)

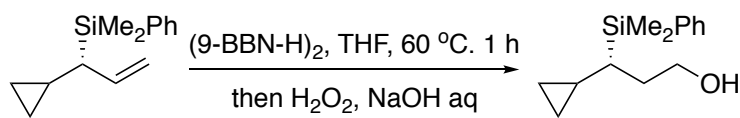


The product **3ae** was purified by flash chromatography on silica gel (hexane) (18.7 mg, 0.08 mmol, 59% isolated yield from **2e**). ^1H NMR (400 MHz, CDCl_3) δ 0.23–0.35 (m, 2H), 0.54 (m, 1H), 0.67 (m, 1H), 1.18 (m, 1H), 2.75 (dd, J = 7.6, 7.2 Hz, 1H), 5.11 (d, J = 10.0 Hz, 1H), 5.14 (d, J = 17.2 Hz, 1H), 6.09 (ddd, J = 17.2, 10.0, 8.4 Hz, 1H), 7.40–7.49 (m, 3H), 7.70 (s, 1H), 7.78–7.81 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3) δ 4.1, 4.7, 15.7, 53.9, 114.5, 125.2, 125.8 (2C), 126.6, 127.5, 127.6, 127.7, 132.2, 133.5, 141.0, 141.5. $[\alpha]_D^{29} -2.5$ (c 0.73, CHCl_3). The ee value (87% ee) was determined by chiral HPLC analysis of **3ae** [CHIRALCEL[®] OJ-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane, 0.5 mL/min, 40 $^\circ\text{C}$, 250 nm UV detector, retention time = 33.6 min for *S* isomer and 34.7 min for *R* isomer]. The absolute configuration of **3ae** was assigned by consideration of the stereochemical pathway.

(*R*)-(1-cyclopropylallyl)dimethyl(phenyl)silane (3af)



The product **3af** was purified by flash chromatography on silica gel (hexane) (24.3 mg, 0.11 mmol, 74% isolated yield from **2f**). Colorless Oil. ^1H NMR (400 MHz, CDCl_3) δ -0.05–0.03 (m, 2H), 0.34 (s, 6H), 0.40–0.49 (m, 2H), 0.73 (m, 1H), 1.07 (dd, J = 10.0, 8.0 Hz, 1H), 4.86–4.90 (m, 2H), 5.75 (ddd, J = 17.6, 12.0, 8.0 Hz, 1H), 7.32–7.36 (m, 3H), 7.52–7.54 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ -4.5, -4.2, 4.3, 5.6, 10.2, 39.0, 112.0, 127.5, 128.8, 134.0, 137.9, 139.1. $[\alpha]_{\text{D}}^{29}$ +5.3 (c 0.72, CHCl_3). The ee value (96% ee) was determined by chiral HPLC analysis of the alcohol obtained by deprotection followed by hydroboration/oxidation from **3af** [CHIRALCEL[®] OD-3 column, 2.1 mm $\times$ 250 mm/ OD-H column, 4.6 mm $\times$ 250 mm/ OD-H column, 4.6 mm $\times$ 250 mm, Daicel Chemical Industries, hexane/2-propanol = 98:2, 0.5 mL/min, 40 $^\circ\text{C}$, 220 nm UV detector, retention time = 69.8 min for *R* isomer and 74.2 min for *S* isomer]. The absolute configuration of **3af** was assigned by consideration of the stereochemical pathway.



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Publication List

- 1) Copper-Catalyzed γ -Selective and Stereospecific Allylic Cross-Coupling with Secondary Alkylboranes
Yuto Yasuda, Kazunori Nagao, Yoshinori Shido, Seiji Mori, Hirohisa Ohmiya, Masaya Sawamura
Chem. Eur. J. **2015**, *21*, 9666-9670.
- 2) Copper-Catalyzed Enantioselective Allyl-Allyl Coupling between Allylic Boronates and Phosphates with a Phenol/N-Heterocyclic Carbene Chiral Ligand
Yuto Yasuda, Hirohisa Ohmiya, Masaya Sawamura
Angew. Chem. Int. Ed. **2016**, *55*, 10816-10820.
- 3) Copper-Catalyzed Enantioselective Coupling between Allylboronates and Phosphates Using a Phenol-Carbene Chiral Ligand: Asymmetric Synthesis of Chiral Branched 1,5-Dienes
Yuto Yasuda, Hirohisa Ohmiya, Masaya Sawamura
Synthesis **2018**, *50*, 2235-2246.

Acknowledgment

The studies described in this thesis have been carried out under the direction of Professor Masaya Sawamura at Graduate School of Chemical Sciences and Engineering, Hokkaido University from April 2013 to March 2019.

The author wishes to express his grateful acknowledgment to Professor Masaya Sawamura for giving opportunities to study in his laboratory and for his kind guidance, constant encouragement, and valuable discussion. He is deeply grateful to Professor Hirohisa Ohmiya for his practical guidance, helpful discussions and considerable suggestions. He also wishes to express his deepest appreciation to Lecturer Yohei Shimizu for elaborated guidance and kind supports. He would like to express his appreciation to Assistant Professor Tomohiro Iwai and Assistant Professor Arteaga Arteaga Fernando for their kind discussions, advices and supports.

The author is much grateful to Professor Hideaki Oikawa, Professor Keiji Tanino and Associate Professor Tatsuo Ishiyama for their accurate advices and considerable suggestions on this thesis.

Moreover, he would like to express his appreciation to Mr. Kazunori Nagao, Saori Shibata, Ayaka Yamazaki, Takashi Asano, Masato Ueno, Shohei Mimura, Koji Imai, Yusuke Ueda, Sho Mizushima and all the members of Sawamura group's for the excellent collaboration, continuous encouragements and the helpful supports.

Financial support from JSPS, Research Fellowship of the Japan Society for the Promotion of Science for Young Scientists, was indispensable, and author deeply appreciates this support.

Finally, he would like to express his gratitude for his family, Mr. Tatsuji Yasuda, Kyoko Yasuda and Naoto Yasuda for warm encouragement and continuous assistance.

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