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Ph D. Thesis

**Development of Ligand-Controlled
Chemo- and Stereoselective
Borylation Reactions with
Copper(I) Complex Catalyst**

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General Introduction

1 Borylation reactions: The history of development

Since organoboron compounds were first synthesized from organozinc reagents by Edward Frankland in 1860, organoboron compounds have been studied about their chemical properties and synthetic utility for organic synthesis.¹ Nowadays, organoboron compounds have been one of the most important synthetic intermediates because a huge amount of transformation reactions of organoboron compounds to various functional groups such as alcohol, amine and halides have been reported (Fig. 1).² The most classical synthetic method for organoboron compounds is nucleophilic substitution between boron electrophiles and organometallic nucleophiles such as organozinc reagents, organolithium reagent and Grignard reagents (Fig. 2).³ Harbert C. Brown reported an innovative borylation reaction in 1956, which is hydroboration of carbon–carbon unsaturated bonds to give the alkylboron compounds (Fig. 3).⁴ The hydroboration of terminal alkenes followed by oxidation of the boryl group to give the corresponding primary alcohols has been recognized as a complementary method for the acid catalyzed hydration of terminal alkenes to give secondary alcohols with Markovnikov's rule.⁵

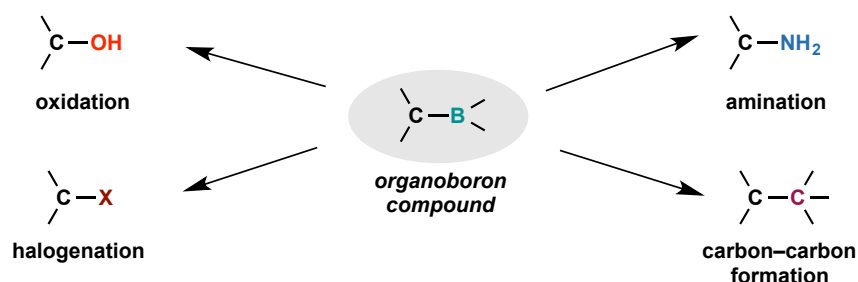


Fig. 1 Functionalization of organoboron compounds.

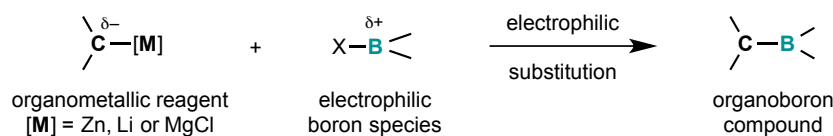


Fig. 2 Electrophilic carbon–boron bond formation with organometallic reagents.

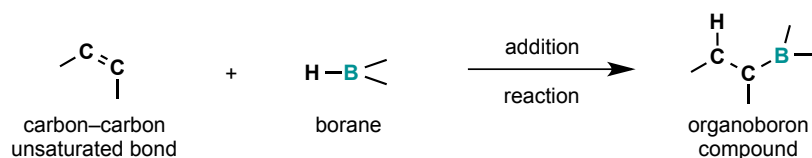


Fig. 3 Hydroboration of carbon–carbon unsaturated bonds.

Chiral organoboron compounds have been recognized as attractive intermediates for organic synthetic chemistry because they can be derivatized to the chiral organic compounds bearing various functional groups through stereospecific transformations.² In 1961, Brown and co-workers reported the first enantioselective borylation reaction through a hydroboration of alkenes using a chiral borane reagent (Fig. 4).⁶ Furthermore, an enantioselective synthesis of chiral organoboron compounds through an asymmetric homologation of achiral organoboron compounds bearing a chiral auxiliary has been developed by Matteson and co-workers in 1980 (Fig. 5).⁷

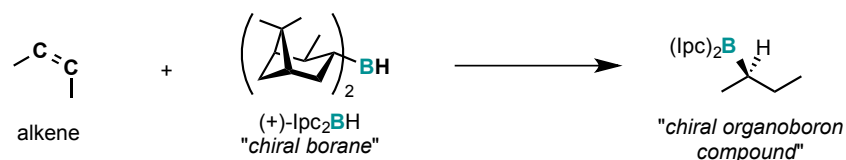


Fig. 4 Enantioselective hydroboration with chiral borane reagents.

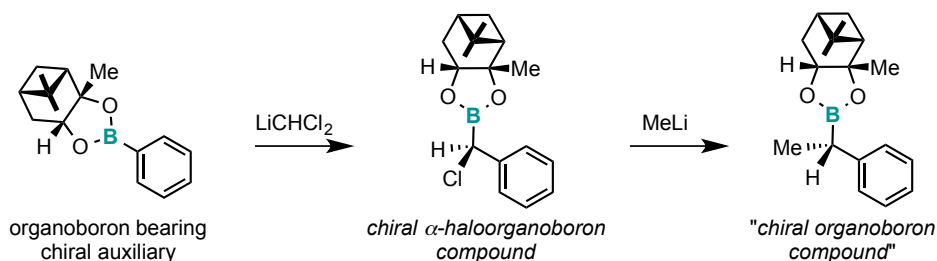


Fig. 5 Enantioselective synthesis of chiral organoboron compounds via homologation with chiral auxiliaries.

In 1981, the first example of catalytic borylation reaction was reported by using a rhodium(I)-catalyst. This reaction system is highly reactive toward unactivated alkenes and can employ the borane reagents such as boronic esters which are inert in non-catalytic hydroboration (Fig. 6).^{8–10} Furthermore, the catalytic enantioselective hydroboration of styrenes using a chiral rhodium-BINAP catalyst was achieved by Hayashi and co-workers in 1989 (Fig. 7).^{11–13} The regioselectivity of this enantioselective hydroboration is controlled by a stabilization of the π -benzyl rhodium intermediate.

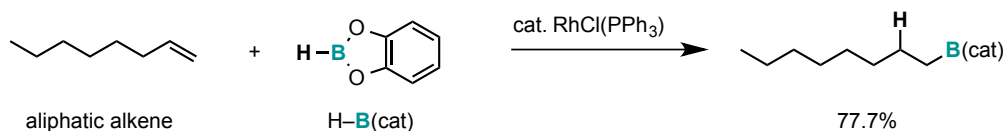


Fig. 6 Transition-metal catalyzed hydroboration of unactivated alkenes.

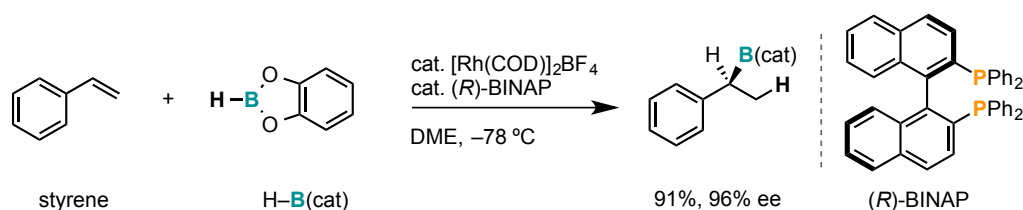


Fig. 7 Transition-metal catalyzed hydroboration of unactivated alkenes

Many examples of transition-metal catalyzed borylation reactions utilizing the high reactivity of diboron reagent for transition-metal complexes have been reported.¹⁴ In 1995, Miyaura and Ishiyama developed a palladium-catalyzed borylation of aryl electrophiles with bis(pinacolato)diboron [B₂(pin)₂] as a diboron reagent (Fig. 8).^{15,16} This reaction has widely been employed for organoboron compound synthesis because of the high functional group tolerance. Furthermore, the conversion of unactivated carbon–hydrogen bonds into carbon–boron bonds what is called C–H borylation reaction was achieved by the noble metal catalyst such as iridium and rhodium complexes (Fig. 9).^{17–21} Since beginning of a new era of catalytic borylation with transition-metal catalysts, a various class of borylation reactions has been developed.

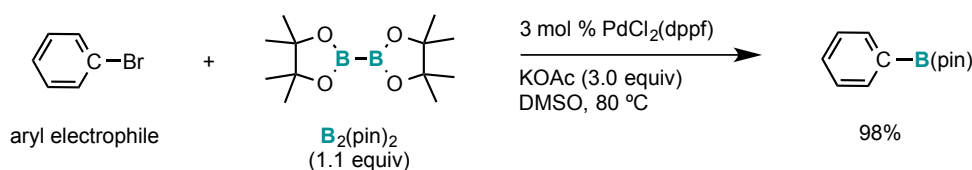


Fig. 8 Palladium-catalyzed borylsubstitution of C(sp²)–X bonds.

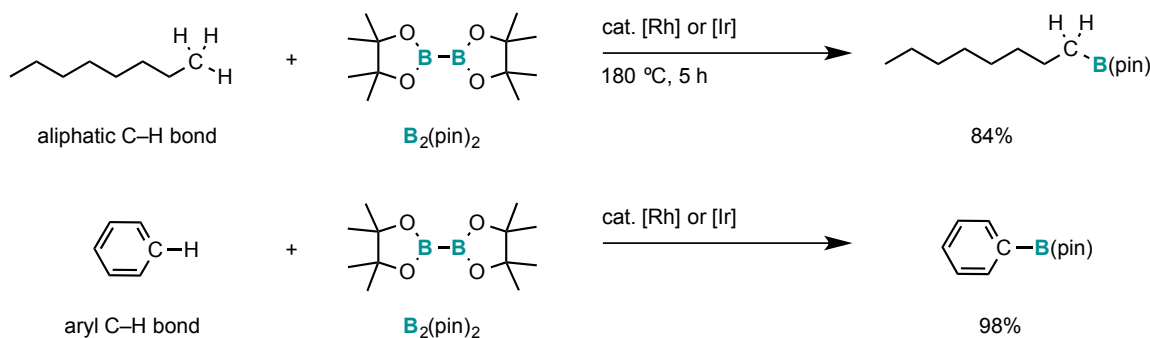


Fig. 9 Unactivated C–H bond borylation of arenes and alkanes.

2 Copper(I)-catalyzed Borylation Reaction with Diboron

In 2000, Hosomi and Ito's group and Miyaura and Ishiyama's group reported a copper(I)-catalyzed borylation of carbon–carbon double bonds with a diboron reagent, respectively (Fig. 10).^{22,23} This borylation reaction proceeds through a borylcopper(I) intermediate which is generated by a reaction between copper(I) species and diboron reagent (Fig. 11). Although, boron compounds generally have

an electrophilicity due to a vacant p-orbital of the boron center, this metal-boryl complex has a unique nucleophilic reactivity and stereoselectivity for borylation reactions. In 2005, Ito and Sawamura reported a regio- and stereospecific allylic borylsubstitution of allyl electrophiles with Xantphos-copper(I) alkoxide catalyst.^{24,25} Furthermore, a chiral bisphosphine ligand (*R,R*)-QuinoxP*, which was developed by Imamoto, enabled an enantioselective allylic borylsubstitution of allyl carbonates (Fig. 12).^{26–28} Whereas, Yun and co-workers reported a methanol-accelerated borylation of alkenes bearing electron withdrawing groups with a copper(I)-catalyst and a chiral phosphine ligand (Fig. 13).^{29–33} In 2009, Hoveyda achieved an enantioselective hydroboration of styrene derivatives with a chiral N-hetero cyclic carbene (NHC) ligand. This hydroboration reaction can be recognized as a complementary regioselectivity to the transition-metal catalyzed hydroboration with borane reagents (Fig. 14).³⁴

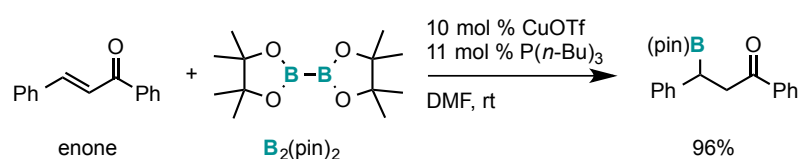


Fig. 10 The first example of copper(I)-catalyzed borylation reaction with diboron reagent.

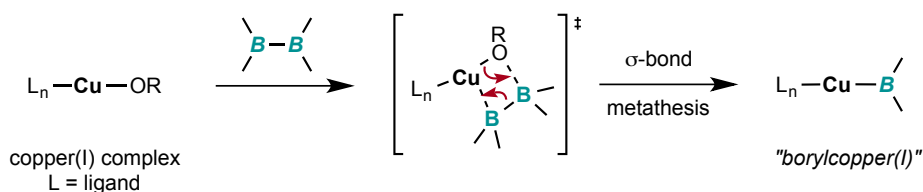


Fig. 11 Generation of borylcopper(I) species through σ -bond metathesis.

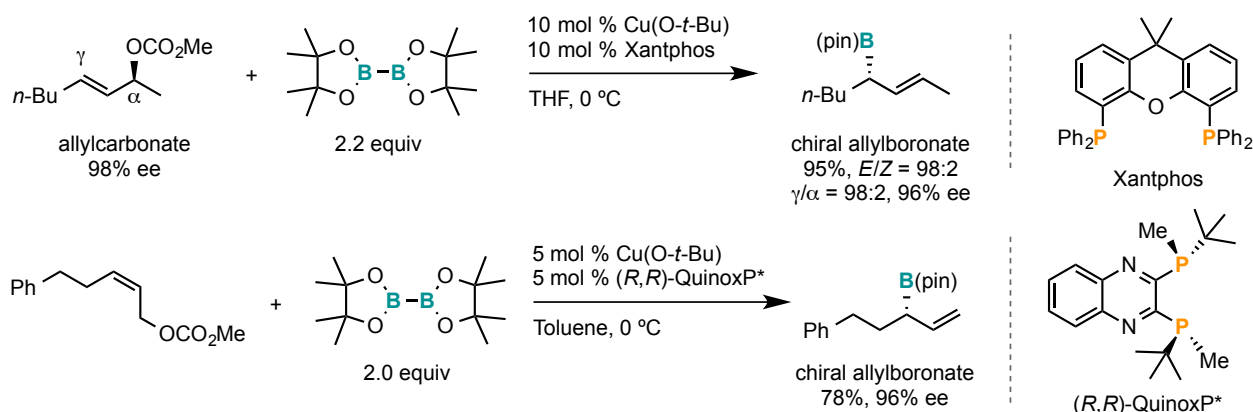


Fig. 12 Copper(I)-catalyzed enantio-specific and selective allylic borylations of allyl electrophiles.

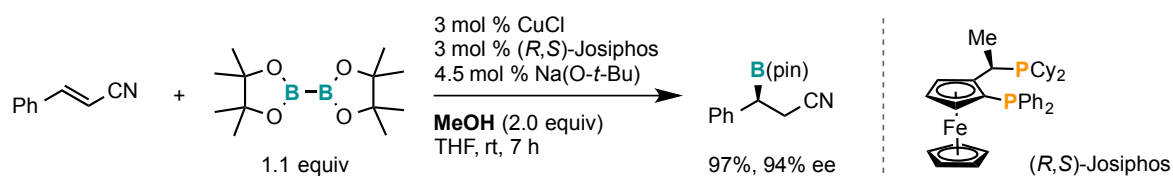


Fig. 13 Alcohol additive-accelerated enantioselective borylation of electrophilic alkenes.

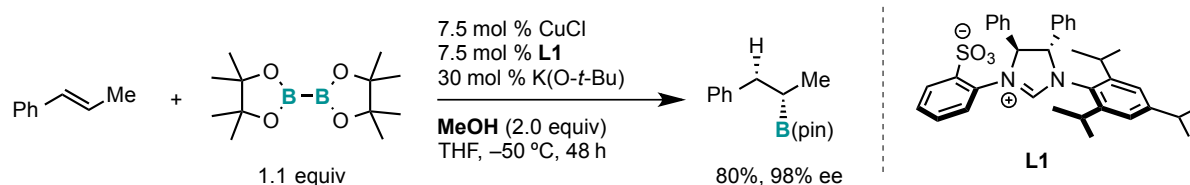


Fig. 14 Enantio- and regioselective hydroboration of styrene derivatives.

3 Structure and Intrinsic Reactivity of Borylcopper(I) Complexes

Isolation and characterization studies of the borylcopper(I) species disclosed their structure and reactivity. The NHC–borylcopper(I) complexes features linear type coordination and reacts with various carbon–carbon unsaturated bonds and electrophiles such as carbonyl compounds and carbon dioxide (CO₂) (Fig. 15).^{35–37} Such nucleophilic reactivity is similar to boryl lithium chemistry which were reported by Yamashita and Nozaki.^{38,39} In 2017, borylcopper(I) complexes with phosphine ligands were isolated and found as stable dimer species or multi-nuclear complexes.⁴⁰ This dimer structure was expected by DFT calculation as a resting state in the borylcopper(I)-mediated catalytic cycle (Fig. 16).⁴¹

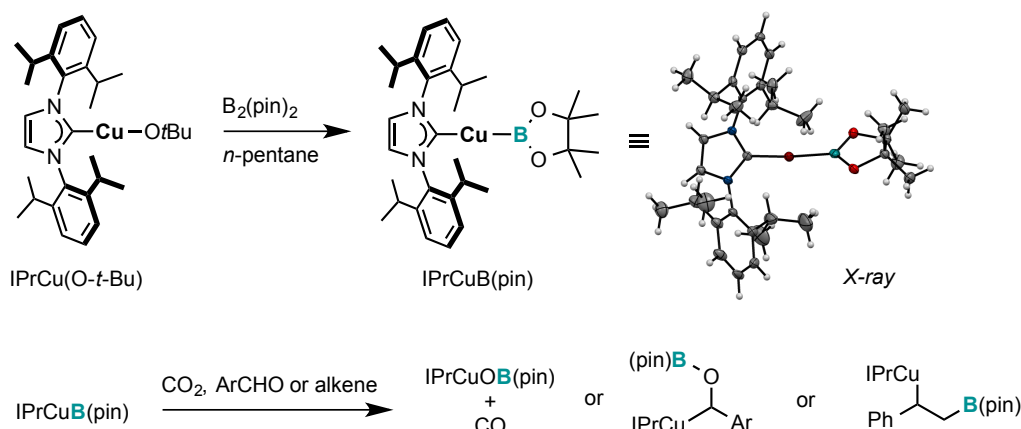


Fig. 15 Structure and reactivity of borylcopper(I) complex with NHC ligand.

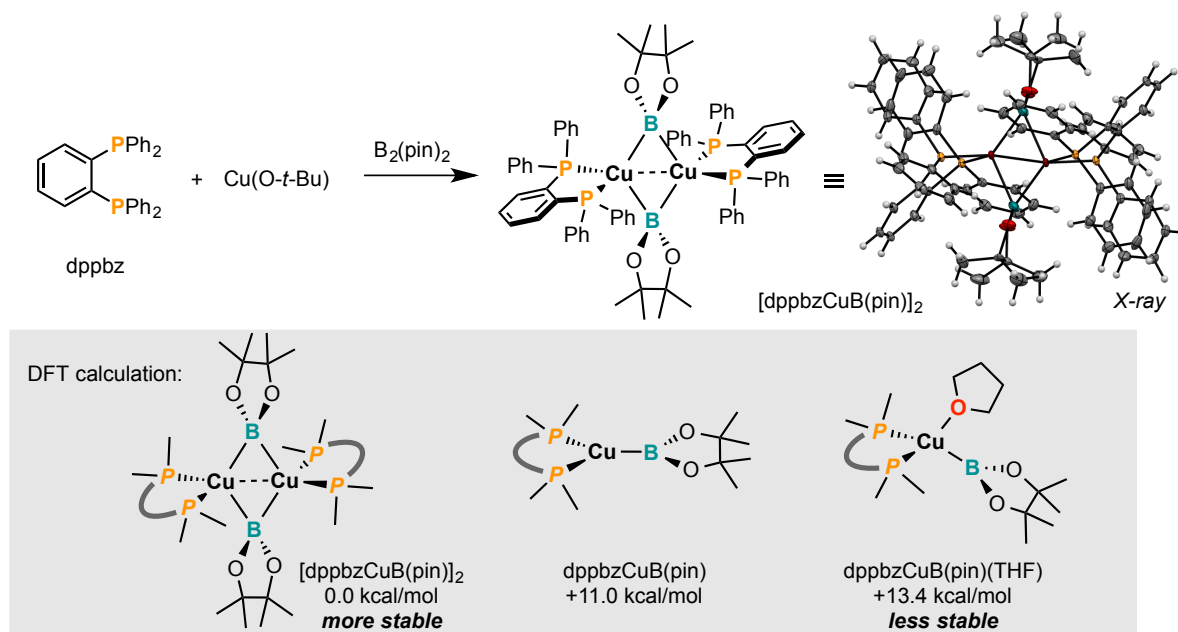


Fig. 16 Isolation and DFT calculation of borylcopper(I) dimer complexes with bisphosphine ligand.

4 Borylation of Carbon–Carbon and Carbon–Heteroatom Multiple Bonds

It has been revealed that the catalytic borylation utilizing borylcopper(I) species can only react with various carbon–carbon unsaturated bonds but also carbon–heteroatom double bonds to generate new carbon–boron bonds with high regio- and stereoselectivity. Hoveyda and co-workers reported that the NHC–copper(I) complex works as a catalyst for branch-selective hydroboration of carbon–carbon triple bonds (Fig. 17).^{42–48} Although the stoichiometric reaction between a NHC–borylcopper(I) complex and an aldehyde gave the organocopper(I) compound (Fig. 15), reaction conditions using a catalytic amount of the NHC–borylcopper(I) complex and a stoichiometric amount of diboron reagent provided the organoboron compounds.³⁶ The reaction mechanism of this reaction, which was investigated by Lin and Marder in 2008, suggested there is a rearrangement of the copper(I) alkoxide intermediate after the borylcupration of carbon–oxygen double bond.⁴⁹ Thus, this rearrangement from the copper(I) alkoxide gives a thermodynamically favored organocopper(I) intermediate in the absence of diboron reagent. On the other hand, the catalytic reaction conditions with a large amount of diboron reagent give the diboration products because the borylcopper(I) complex is regenerated from the copper(I) alkoxide before the rearrangement. Based on the mechanism, the several copper(I)-catalyzed borylations of aldehydes and ketones to give α -hydroxy boronates have been developed (Fig. 18).^{50–55} Furthermore, Ellman and co-workers reported a copper(I)-catalyzed borylation of imines bearing a chiral auxiliary to give the chiral α -amino boronates (Fig. 19).^{56–61}

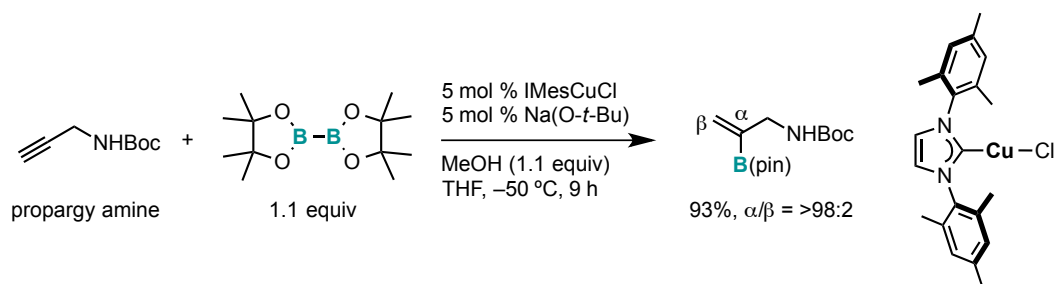


Fig. 17 Regioselective borylation of carbon–carbon triple bonds.

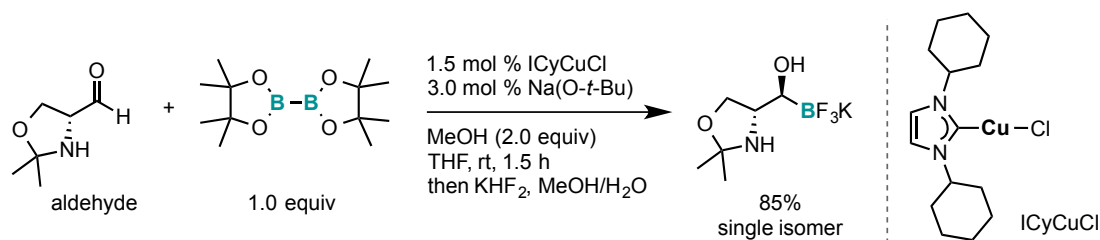


Fig. 18 α -Alkoxy-organoboron compound synthesis through borylation of carbonyl moieties.

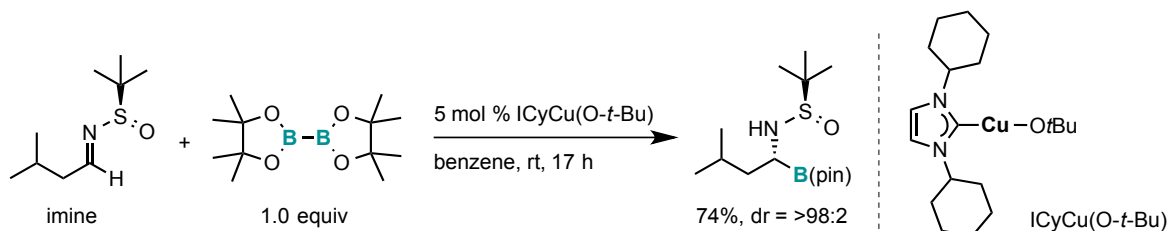


Fig. 19 α -Amino-organoboron compound synthesis through borylation of imines.

5 Intramolecular Borylative Cyclization

The organocopper(I) intermediates in the borylcopper(I)-mediated catalytic borylation reactions can be used to tandem reactions with various electrophiles such as alkyl halides, carbonyl groups and nitrogen electrophiles because the organocopper(I) species has a strong nucleophilicity.⁶² In 2008, Ito and Sawamura reported the first example of enantioselective borylative *endo*-cyclization of allyl electrophiles bearing a silyl group to give the *trans*-1,2-silylboryl cyclopropanes (Fig. 20).⁶³ In the case of this reaction, the α -silyl-alkylcopper(I) intermediate generated through the silicon atom-directed borylcupration of the carbon–carbon double bond reacts with an electrophile moiety at γ -position. This intramolecular reaction can expand to the borylative cyclization of styrene derivatives and 3 to 5 membered ring formation (Fig. 21).^{64,65}

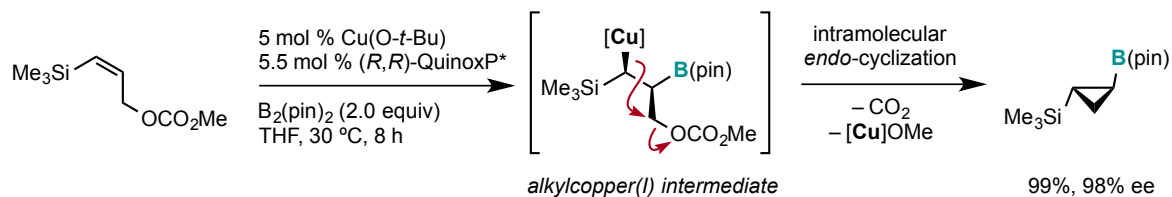


Fig. 20 Enantioselective *endo*-borylative cyclization of alkenyl silanes bearing a leaving group.

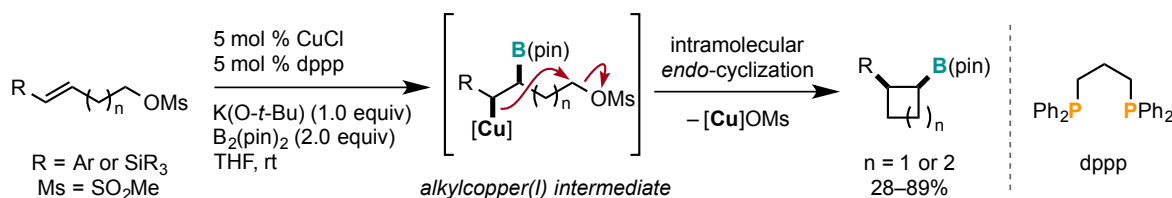


Fig. 21 Stereospecific *endo*-borylative cyclization for cyclobutanes and cyclopropanes.

These reaction systems can also be applicable to the borylative *exo*-cyclization reactions. The copper(I)-catalyzed borylative cyclization of alkyl halides bearing an unactivated alkene moiety gives the cyclization products via the organocopper(I) species (Fig. 22).⁶⁶ Furthermore, some examples of the stereoselective borylative cyclization of alkenes bearing an imine or ketone moiety as electrophilic moiety were reported.^{67–70} The enantioselective *exo*-borylative cyclization of propargyl ethers bearing electrophilic alkene moieties was also achieved by a chiral phosphoramidite **L2** (Fig. 23).⁷¹ The alkynyl silanes bearing an unactivated alkyl halide moiety can be applicable to the *exo*-borylative cyclization system to give the tetrasubstituted silyl-boryl-alkenes (Fig. 24).⁷² Although the borylative cyclization of allenes bearing a leaving group is possible to provide both *exo*- and *endo*-cyclization products due to the isomerization of the allylcopper(I) intermediate, the reaction of the allenes bearing an alkyl halide moiety gave the *exo*-cyclization products with high diastereoselectivity. (Fig. 25).^{73–75}

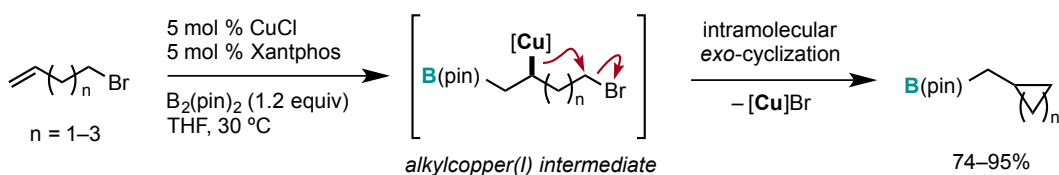


Fig. 22 Intramolecular *exo*-borylative cyclization of unactivated alkenes.

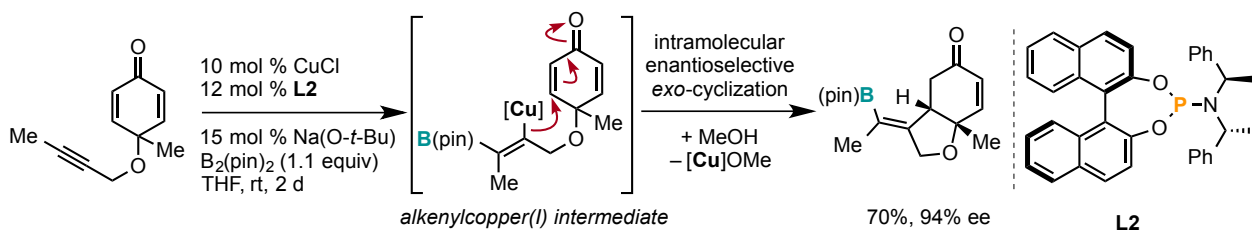


Fig. 23 Enantioselective *exo*-borylative cyclization of propargyl ethers.

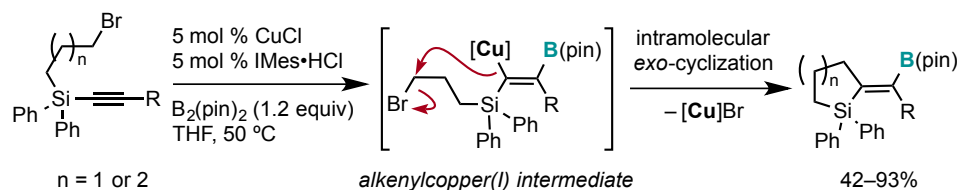


Fig. 24 Intramolecular *exo*-Borylative cyclization of alkynyl silanes.

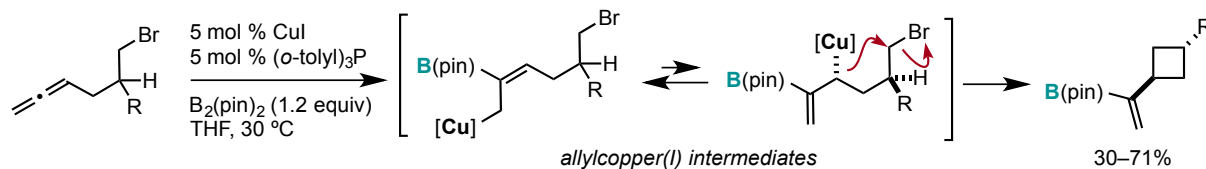


Fig. 25 Intramolecular diastereoselective *exo*-Borylative cyclization of allenes.

6 Three-Component Intermolecular Carboboration with Carbon Electrophiles

Considerable effort for the development of intermolecular multi-component borylation reactions utilizing the organocopper(I) intermediates has been devoted. In 2012, Tortosa and co-workers reported a copper(I)-catalyzed stereoselective three-component coupling reaction of alkynes, diboron reagent and carbon electrophiles (Fig. 26).^{76–81} Moreover, the organocopper(I) intermediates generated from the borylcupration can react with carbon dioxide to provide the boracarboxylation products.^{82–84} Hoveyda and Procter achieved that enantioselective carboboration reactions of carbon–carbon unsaturated bonds with diboron reagent and various carbon electrophiles such as aldehydes, ketones and imines to give the organoboron compounds bearing adjacent stereocenters (Fig. 27).^{85–92} Activated acyl electrophiles such as acyl halides can be employed for carboboration reactions to give the corresponding ketones or aldehyde products.^{91,93–95} Furthermore, highly regioselective carboboration reactions of allenes through a coupling with allyl electrophiles and the boryl group were reported by Hoveyda and Tsuji, respectively (Fig. 28).^{96,97} Such multi-component reactions provide the corresponding highly functionalized carbon chains.^{98–100} The copper(I)/palladium(0) cooperative catalyst systems for a transmetalation between organocopper(I) intermediates and electrophilic palladium(II) complexes made the carboboration reactions more efficient.^{101–105} The ligand-controlled regiodivergent carboboration of unactivated alkenes and alkynes were reported by Fu and co-workers (Fig. 29).^{106,107}

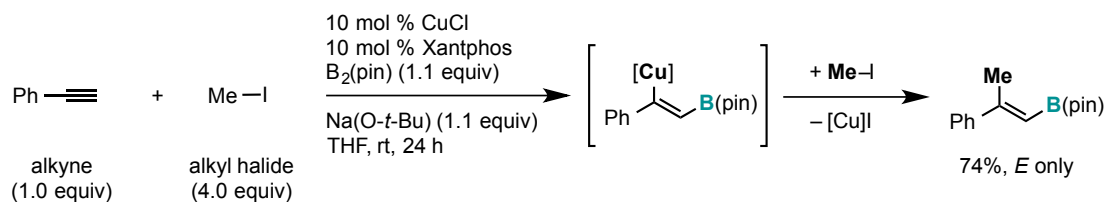


Fig. 26 Intermolecular carboboration of alkynes with alkyl electrophiles.

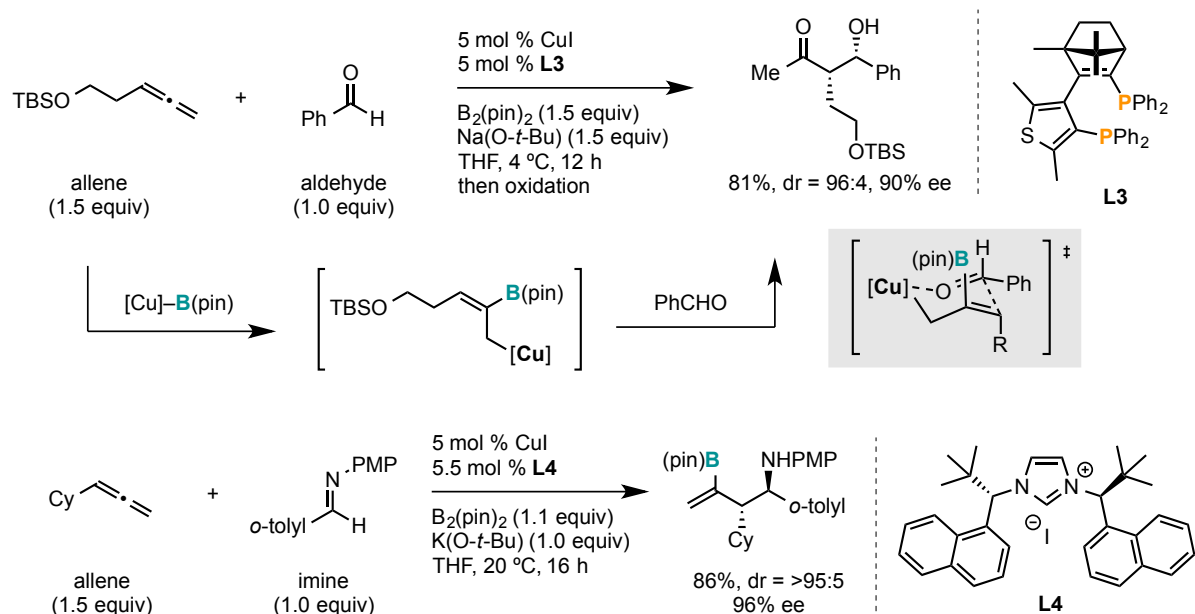


Fig. 27 Enantio- and diastereoselective carboboration with aldehydes and imines.

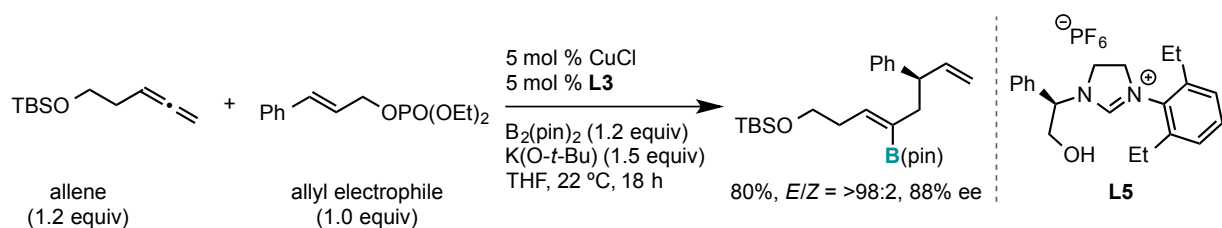


Fig. 28 Enantio-, regioselective carboboration with allyl electrophiles.

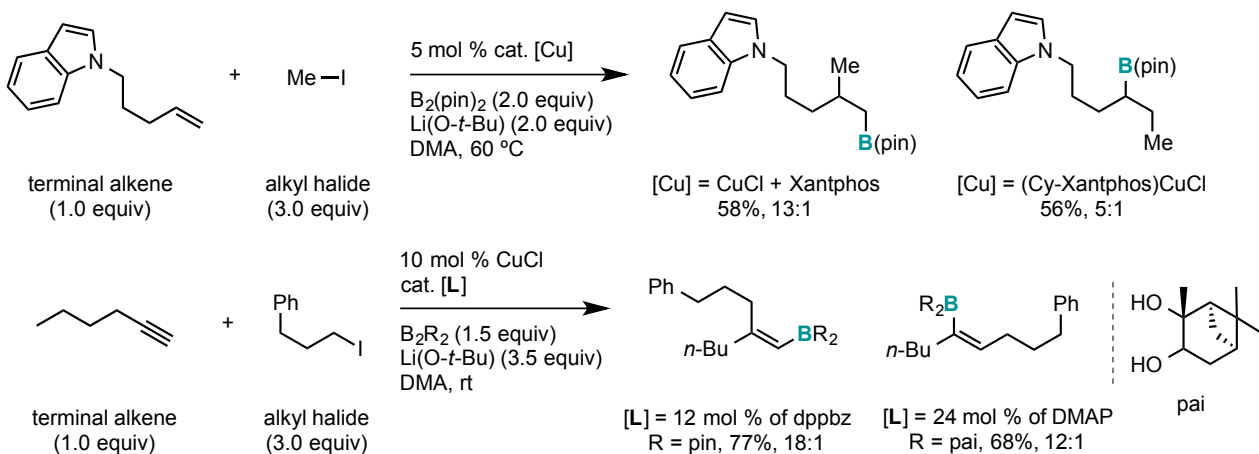


Fig. 29 Ligand-controlling regioselectivity of carboboration of unactivated alkenes and alkynes.

7 Three-Component Borylation Reactions with Other Electrophiles

The functionalization of the alkylcopper(I) intermediates not only allow the carbon electrophiles but also be applicable to other electrophiles bearing hetero atoms such as stannane, nitrogen and

oxygen electrophiles to give the corresponding stannylboration products, aminoboration products and oxyboration products. In 2012, the borylation of the alkenyl copper(I) intermediates without base additive to give the corresponding diboration products was reported.¹⁰⁸ The borylation reaction with the stannane electrophiles provided stannylboration products (Fig. 30).¹⁰⁹ The aminoboration of alkenes have been achieved by using hydroxyamine derivatives as nitrogen electrophiles (Fig. 31).^{110–114} The reaction of aliphatic terminal alkenes using tetramethyl piperidine *N*-oxide (TEMPO) gave the oxyboration products. The carbon–oxygen bond formation of the alkylcopper(I) intermediates in this reaction would proceed via radical mechanism due to the radical reactivity of TMEPO. Furthermore, the regioselectivity of this reaction can be controlled by the appropriate ligands on the copper(I) center. The reaction with the Xantphos derivative ligand gave the products bearing the boryl group attaching the terminal carbon of alkenes. In contrast, the reaction with the NHC-Copper(I) complex gave the secondary alkylboronate products (Fig. 32).¹¹⁵

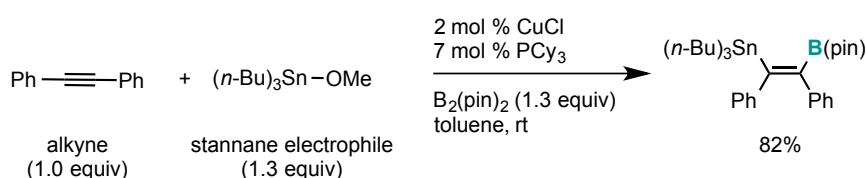


Fig. 30 Copper(I)-catalyzed stannylboration of alkynes.

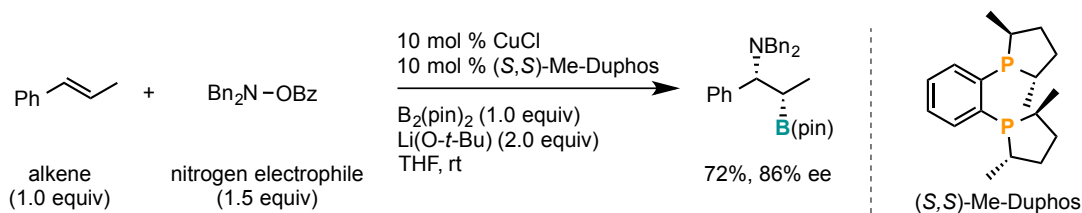


Fig. 31 Copper(I)-catalyzed aminoboration of alkenes.

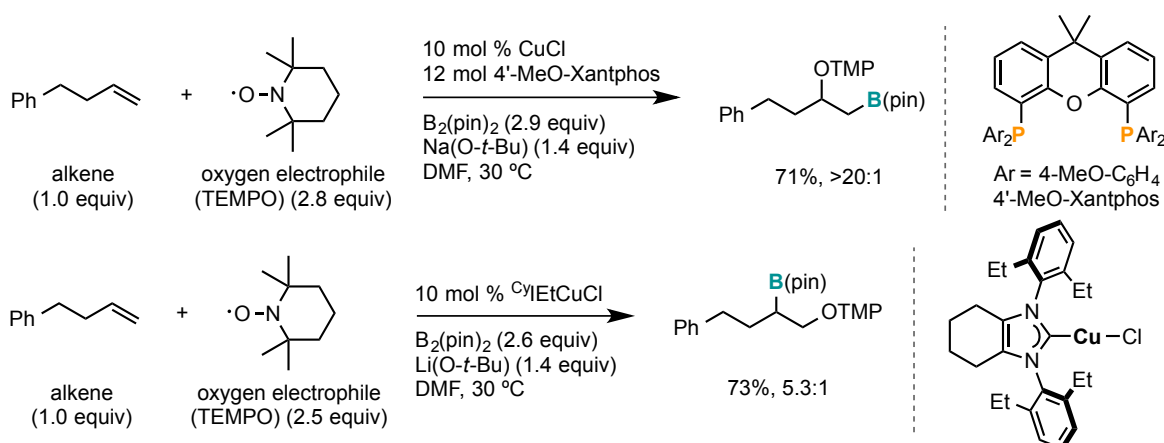


Fig. 32 Ligand-controlling regioselectivity of oxyboration of unactivated alkenes.

8 Borylstubstitution Reactions of Carbon Electrophiles

In 2009, Marder and Lin developed a copper(I)-catalyzed borylstubstitution reaction of aryl halides with diboron reagent and alkoxide base (Fig. 33).¹¹⁶ In this study, the DFT calculation indicated that mono phosphine ligand has higher reactivity for this reaction than NHC ligand. Although the borylstubstitution of aryl electrophiles was developed, the catalyst for boryl substitution of unactivated alkyl electrophiles had not been discovered. In 2012, Ito and Liu reported that copper(I)/phosphine ligand systems react with unactivated alkyl halides to give the corresponding borylstubstitution products, respectively (Fig. 34).^{117,118} As mechanistic studies, the borylstubstitution of the enantioenriched alkyl halide and the radical clock experiment suggested that this reaction proceeds through the radical intermediate.

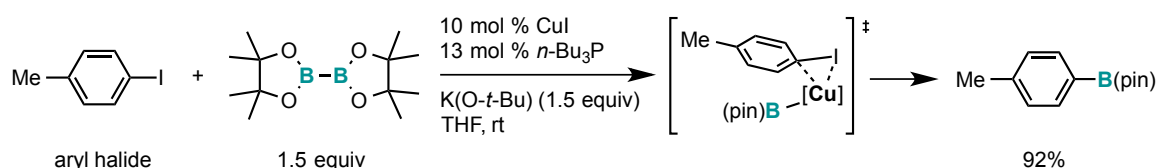


Fig. 33 Borylstubstitution of aryl halides by Copper(I)/diboron catalyst system.

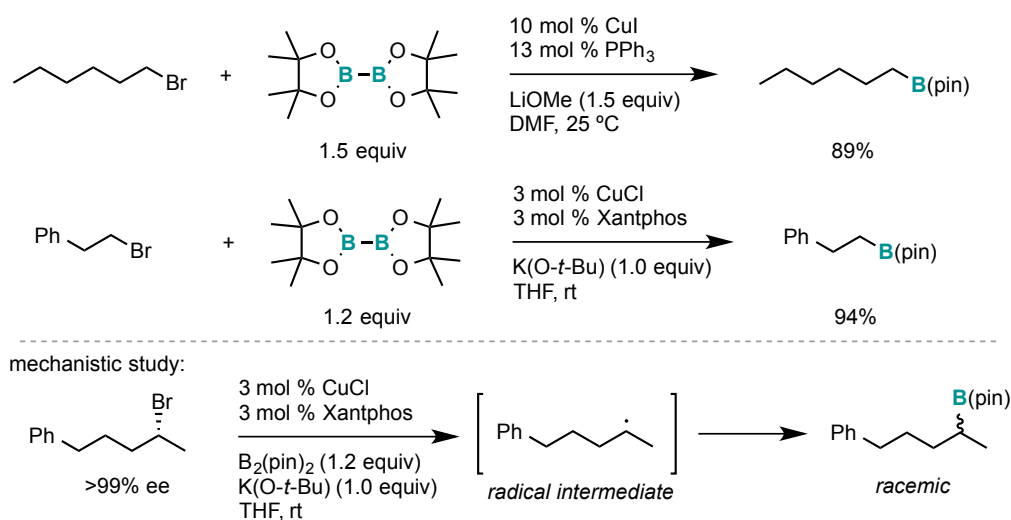


Fig. 34 Borylstubstitution of unactivated alkyl halides via radical intermediate.

1.9 Overview

As described above, borylation reactions by the copper(I)-catalyst and diboron reagent have been recognized as powerful methods for the organoboron compound synthesis because they can react with various substrates such as carbon–carbon, carbon–hetero atom unsaturated bonds and organic halides. The reactions catalyzed by borylcopper(I) species can be categorized into two reaction-type: (i) addition-type reaction which proceeds via borylcupration of unsaturated bonds, (ii) substitution-type reactivity which proceeds via a metathesis mechanism or radical mechanism (Fig. 34).^{119–122}

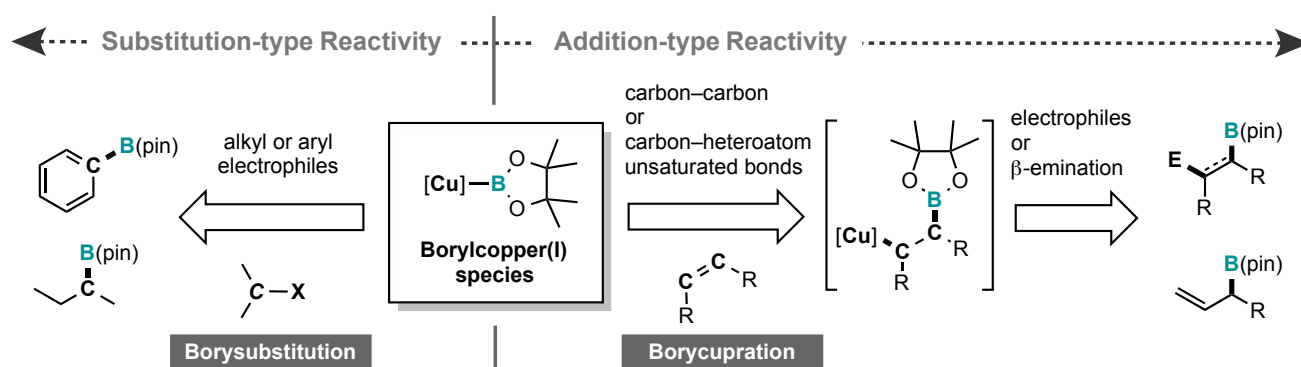


Fig. 34 Typical reactivities of borylcopper(I) species.

In this thesis, the author focused on a variety of reactivity of copper(I)-catalyzed borylation reactions and controlling them by the ligands to develop the unprecedented borylation reactions. To develop new class of borylation reactions, the investigation was conducted for revealing ligand effects on: (i) the chemoselectivity between borylcupration of alkenes and borylsubstitution of alkyl halides, (ii) regioselectivity of borylcupration of terminal alkenes, (iii) enantioselectivity of borylation of terminal alkenes (Fig. 35).

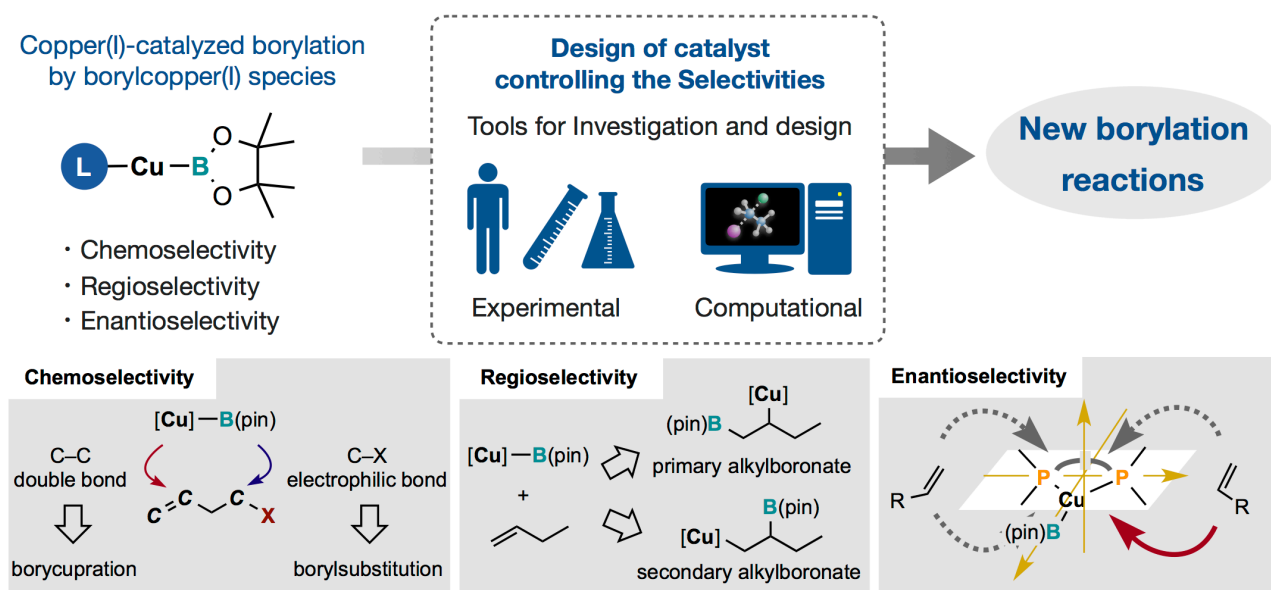


Fig. 35 Research concept for development of new type of borylation reactions by borylcopper(I) species.

Chapter 1 and 2 describe the investigation and application of ligand-controlled chemoselective borylation reactions between the addition-type reaction of carbon–carbon unsaturated bonds and the radical mediated boryl substitution reaction of carbon–halogen bonds. The author found that reaction selectivity in the copper(I)-catalyzed borylation toward alkyl halides bearing an alkene moiety to give the borylative cyclization products or boryl substitution products depends on the ligand, whether it is mainly monophosphine or bisphosphine ligand.^{66,117,118} In other words, the chemoselectivity between the borylcupration reaction and radical reaction in the copper(I)/diboron catalyst system can be

controlled by the appropriate ligand (Chapter 1, Fig. 36).¹²³

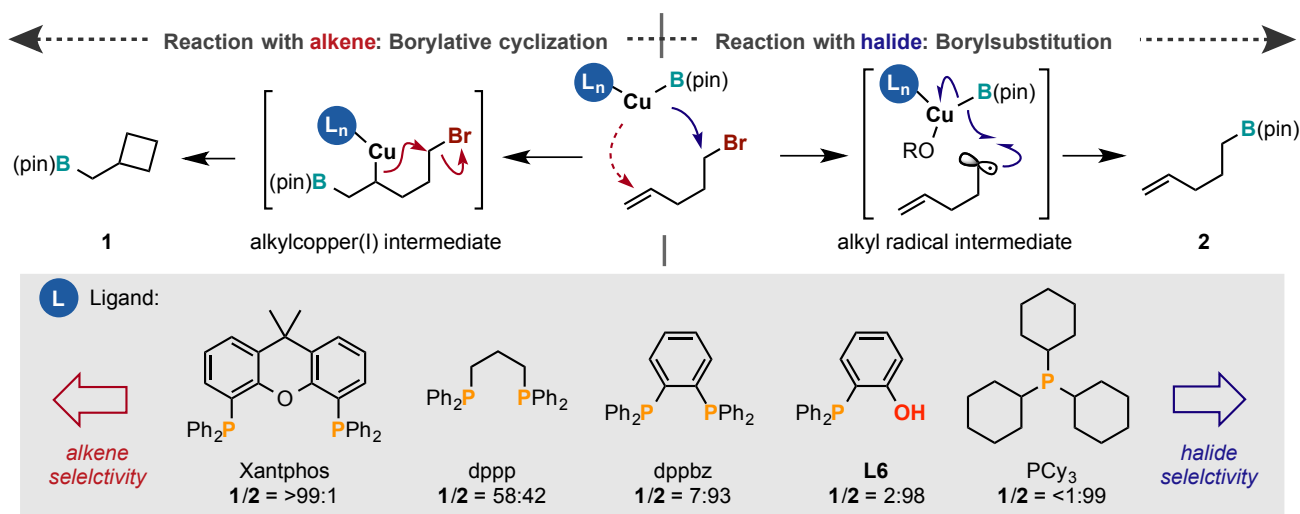


Fig. 36 Ligand-controlled chemoselective borylation of alkyl halides bearing terminal alkene moieties.

Furthermore, the stereoselective borylative radical cyclization to give the corresponding alkylboronates bearing heterocyclic structures was newly developed by the ligand-controlled chemoselective catalytic system (Chapter 2, Fig. 37).^{124,125}

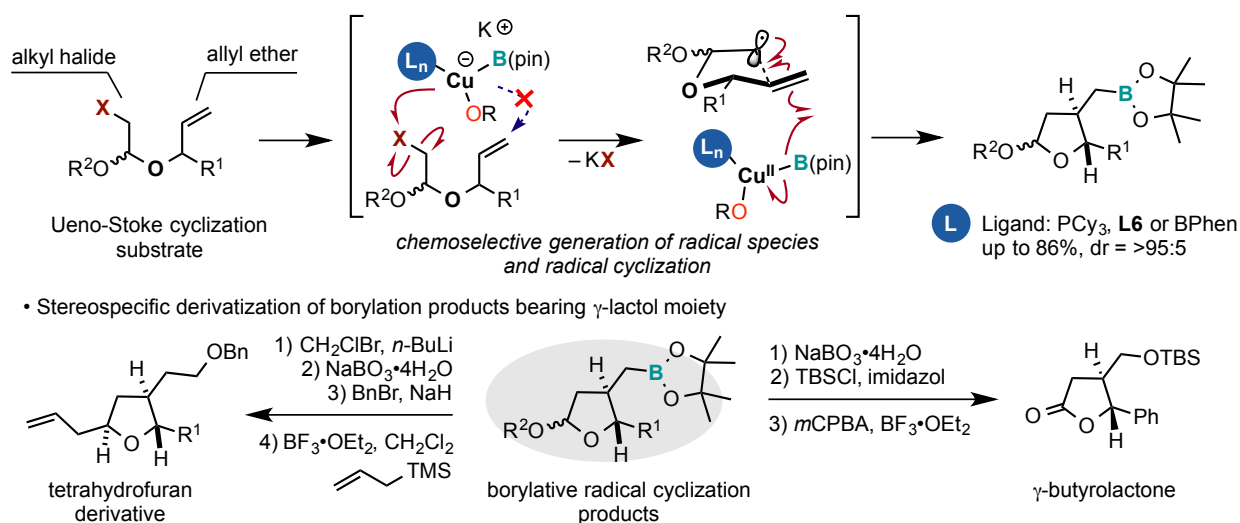


Fig. 37 Ligand-controlled chemoselectivity enabled borylative radical cyclization.

Chapter 3 and 4 describe the investigation of regio- and enantioselectivity on a copper(I)-catalyzed hydroboration of aliphatic terminal alkenes with diboron reagent. In general, hydroboration reactions of aliphatic terminal alkenes with borane reagents give the corresponding primary alkylboron compounds.⁵ This regioselectivity is called as *anti*-Markovnikov regioselectivity. On the other hand, the hydroboration of unactivated aliphatic terminal alkenes providing the secondary alkylboron compounds with Markovnikov regioselectivity have not been developed. Previously, the copper(I)/diboron catalytic system mediated hydroboration reaction of aliphatic terminal alkenes with

anti-Markovnikov regioselectivity have been achieved by using Xantphos as a ligand.⁶⁶ The ligand investigation for the copper(I)-catalyzed hydroboration of aliphatic terminal alkenes revealed that the regioselectivity depends on the ligand. The Markovnikov hydroboration of aliphatic terminal alkenes to give the racemic secondary alkylboronates was achieved by using the highly bulky bisphosphine ligand L7 (Chapter 3, Fig. 38).¹²⁶

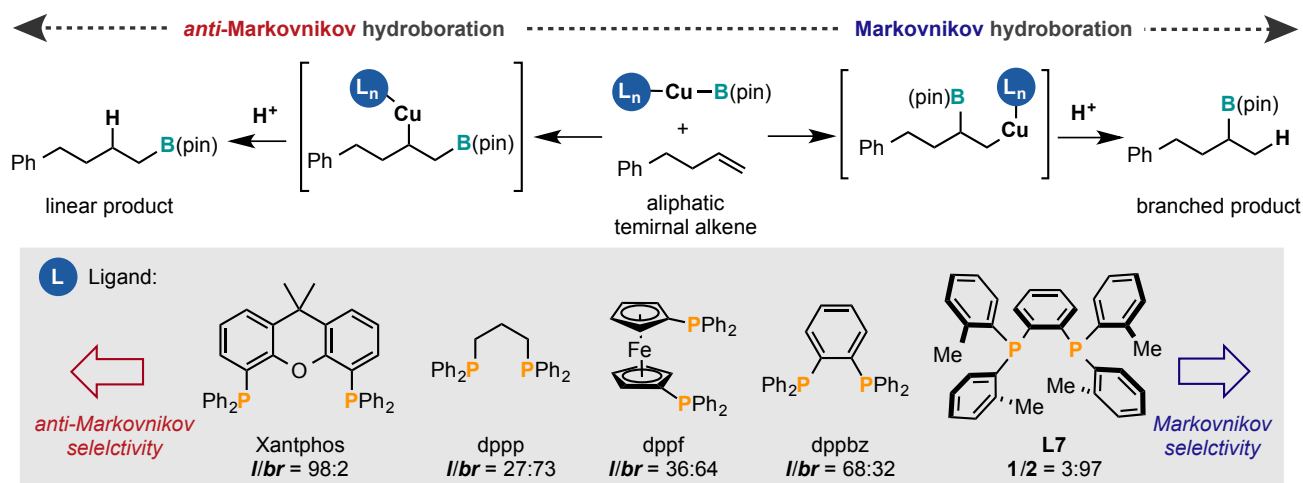


Fig. 38 Ligand-controlled regioselective hydroboration of aliphatic terminal alkenes.

The enantio- and regioselective reaction of aliphatic terminal alkenes have been recognized as one of the most difficult molecular transformation due to their small steric demanding and unpolarized carbon–carbon double bond. It is anticipated that the enantioselective Markovnikov hydroboration of aliphatic terminal alkenes to give the versatile chiral alkylboron compounds will be a powerful method for enantioselective functionalization of aliphatic terminal alkenes. In order to achieve the enantioselective Markovnikov hydroboration of aliphatic terminal alkenes, the author developed a novel chiral ligand design method based on the combination of computational and experimental evaluation. This computational study-assisted chiral ligand design indicated the optimized P-chirogenic three-hindered quadrant bisphosphine ligand to give the chiral secondary alkylboronates with excellent enantioselectivity (up to 99% ee) (Chapter 4, Fig. 39).¹²⁷

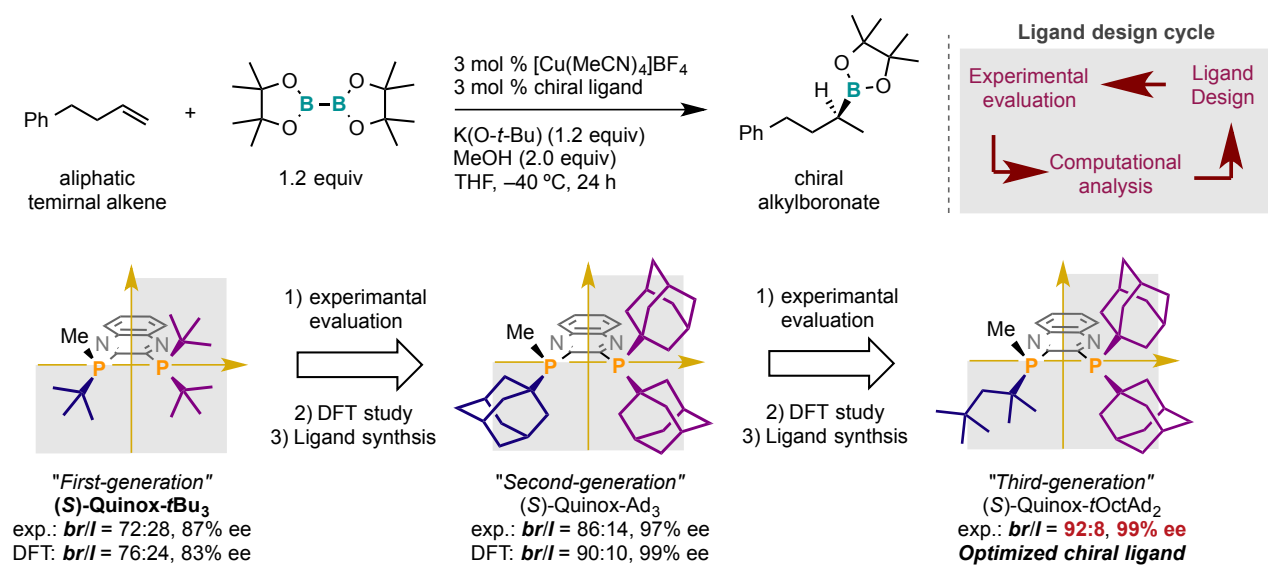


Fig. 39 Rational chiral ligand design enabled enantioselective Markovnikov hydroboration of aliphatic terminal alkenes.

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Chapter 1

Copper(I)-Catalyzed Chemoselective Borylation Reaction of Alkyl Halides Bearing Alkene Moieties

Abstract Copper(I)-catalyzed chemoselective borylation of alkyl halides bearing alkene moieties has been developed. Although the reaction using Xantphos as a ligand gave the borylative cyclization products via borylcupration of carbon-carbon double bonds, the reaction using tricyclohexylphosphine (PCy₃) or 2-hydroxyphenyl phosphine ligand selectively gave the corresponding borylsubstitution products. This indicated that the ligand could control the chemoselectivity of the borylcopper(I)-mediated reactions between the borylcupration of terminal carbon-carbon double bonds and the borylsubstitution of alkyl halides.

1.1 Introduction

Organoboron compounds are versatile synthetic intermediates in organic chemistry because the carbon-boron bonds can be transformed to various functional groups.¹ Many examples of transition-metal catalyzed borylation reactions of carbon-carbon unsaturated bonds have been reported as a method with high functional group compatibility and high carbon-carbon bond selectivity.²⁻⁶ On the other hands, the recent development of transition-metal catalyzed borylsubstitution reactions carbon electrophiles have been going to able to apply to not only aryl electrophiles but also alkyl electrophiles (Fig. 1.1).⁷⁻¹⁶ These borylation reactions shows high functional group tolerance because those do not require the multi-step procedure including a preparation of the corresponding organometallic reagent. Marder and Liu's group and Ito's group first reported the copper(I)-catalyzed borylsubstitution of alkyl halides with diboron reagent and suggested that the reaction would proceed through a radical-mediated reaction.^{17,18}

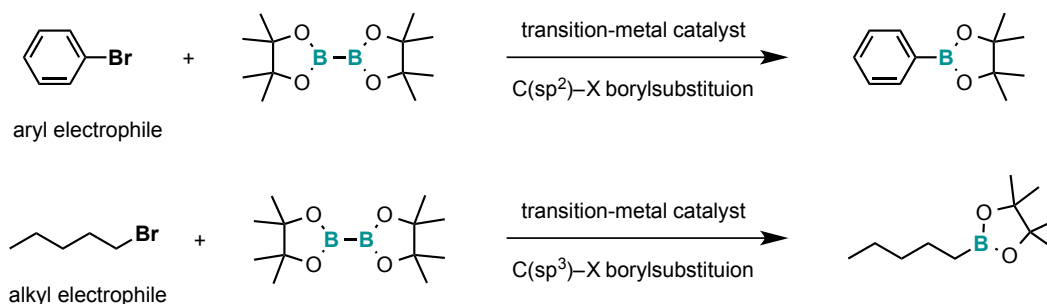


Fig. 1.1 Transition-metal catalyzed borylsubstitution of carbon electrophiles.

Copper(I)-catalyzed borylation with diboron reagent can also react with unactivated terminal alkenes through borylcupration.^{19,20} Furthermore, the borylation of alkyl halides bearing terminal alkene moieties by same method gave the borylative cyclization product through the borylcupration of an alkene followed by intramolecular cyclization of the alkylcopper(I) intermediate (Fig. 1.2).²¹ Therefore, it is possible that the reaction with borylcopper(I) species can proceed through different two reactivities: “addition-type reaction” of alkene moieties and “radical-type reaction” of alkyl halide moieties. However, the effective reaction conditions of borylation of alkyl halides bearing terminal alkene moieties providing the borylsubstitution products have not been found. In this chapter, the author describes the investigation of the factor what control the chemoselectivity between radical-type reactivity and substitution-type reactivity and develops the carbon–halogen bond selective borylation (Fig. 1.3).

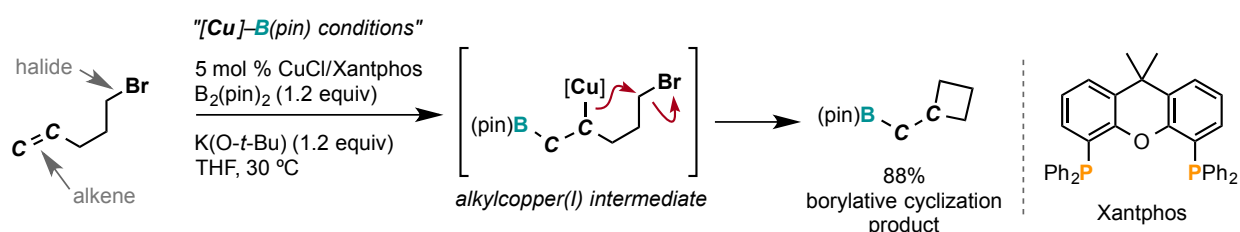


Fig. 1.2 Copper(I)-catalyzed borylative cyclization of terminal alkenes bearing alkyl halide moieties

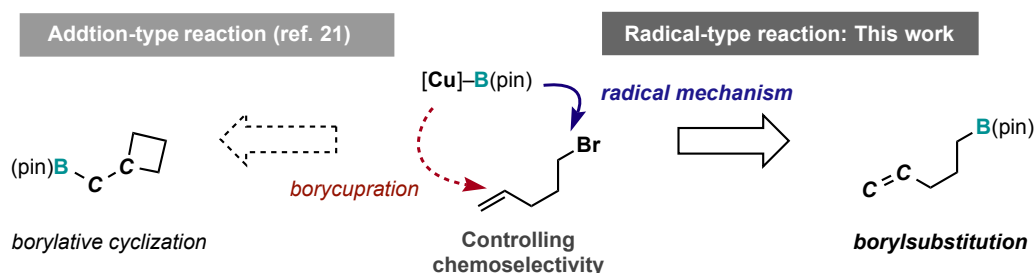


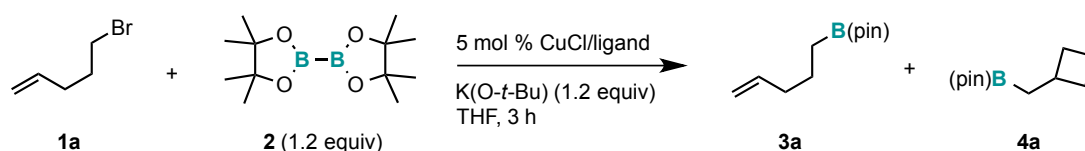
Fig. 1.3 Controlling chemoselectivity of borylation of alkyl halides bearing terminal alkene moieties with copper(I)-catalyst.

1.2 Result and Discussion

Based on the prior research on the borylative cyclization of alkyl halides bearing terminal alkene moieties, there was a possibility that the ligand would have an impact on the chemoselectivity.²¹ Thus, we carried out the detailed investigation of ligand (Table 1.1). The borylation reactions of alkyl halides a terminal alkene moiety **1a** were performed by a catalytic amount of copper(I) chloride and ligand and stoichiometric amount of bis(pinacolato)diboron (**2**) and base in THF at 30 °C. The reaction using Xantphos ligand showed high addition-type reactivity to give the borylative cyclization product **4a** (86%, **3a/4a** = <1:99; Table 1.1, entry 1). However, the use of dppp as a bisphosphine ligand exhibited the chemoselectivity (**3a/4a** = 58:42, entry 2). Whereas, the bisphosphine ligand, dppbz, bearing a small bite-angle resulted in the borylsubstitution selectivity (**3a/4a** = 93:7, entry 3). The reactions using

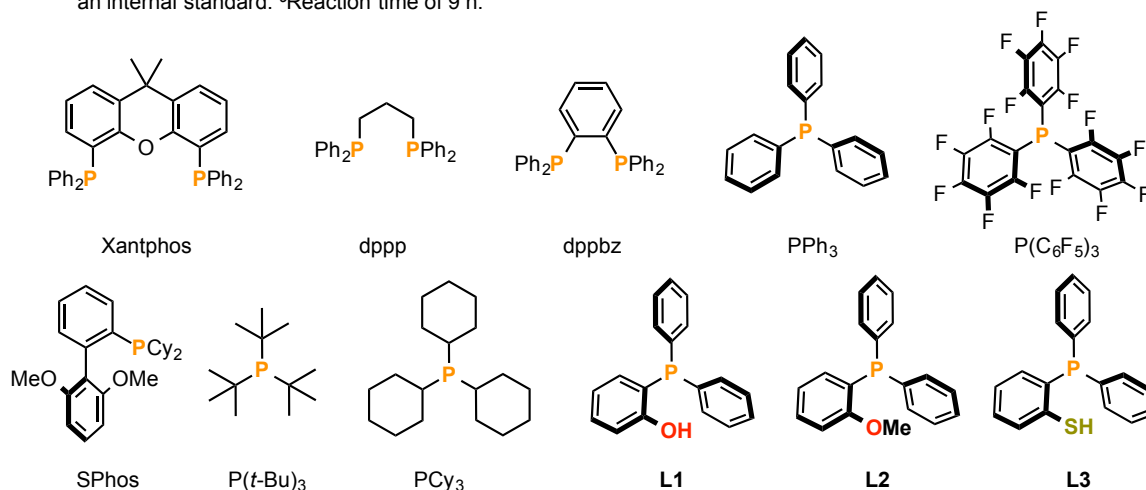
monophosphine ligands basically gave the borylsubstitution product **3a** with high selectivity (Entry 4–13). Although the moderate yields of **3a** were observed when the reaction employed PPh₃, an electron deficient monophosphine ligand P(C₆F₅)₃, a Buchwald-type ligand SPhos and an electron rich monophosphine P(*t*-Bu)₃ (53–62%, **3a/4a** = >98:2 entry 4–7), the reaction employing PCy₃ resulted in high yield (74%, entry 8). Interestingly, the monophosphine ligand bearing a hydroxy group **L1** also showed high yield of **3a** compared to PPh₃ (67%, entry 9). Furthermore, the lower reaction temperature raised the yield of **3a**, and the chemoselectivity was almost perfect. (PCy₃: 88%, **3a/4a** = >99:1 entry 10, **L1**: 80%, **3a/4a** = >99:1 entry 11). To investigate the effect of hydroxy group of **L1**, the methyl group protected ligand **L2** and the thiol ligand **L3** were tested. The use of **L2** exhibited lower reactivity than that of **L1**, but higher reactivity than that of PPh₃ (62%, entry 12). A trace amount of the product **3a** was obtained when the reaction using **L3** was carried out (1%, entry 13).

Table 1.1 Optimization of borylsubstitution selective reaction of **1a**.^a



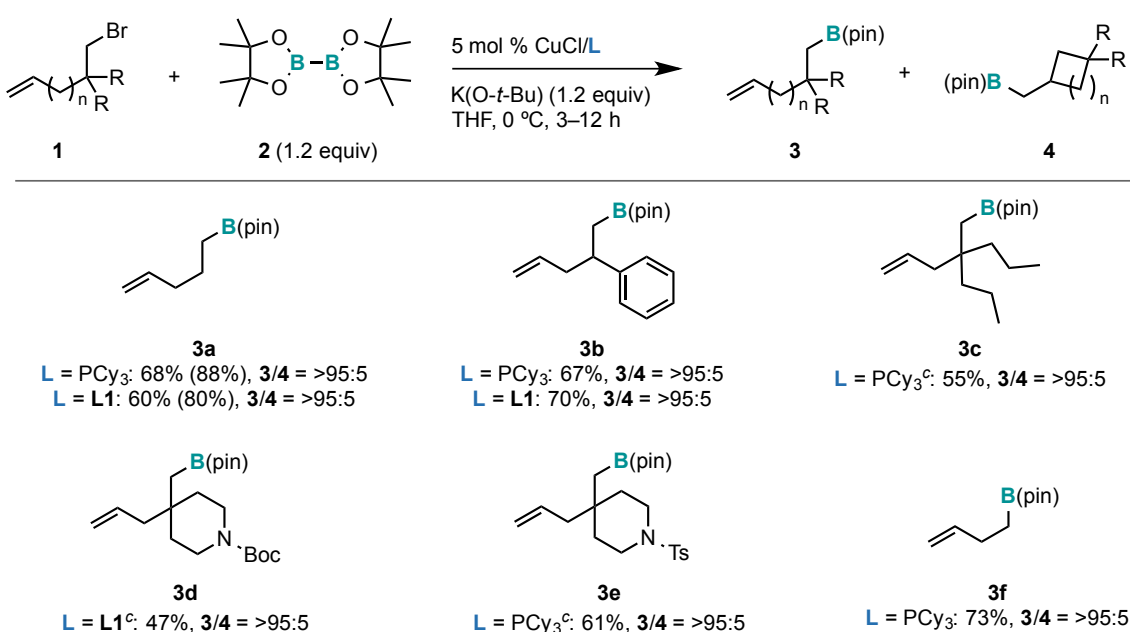
entry	ligand	temp. (°C)	yield of 3a (%) ^b	yield of 4a (%) ^b	3a/4a ^b
1	Xantphos	30	<1	86	<1:99
2	dppp	30	34	25	58:42
3	dppbz	30	55	4	93:7
4	PPh ₃	30	56	<1	99:1
5	P(C ₆ F ₅) ₃	30	53	1	98:2
6	SPhos	30	54	<1	>99:1
7	P(<i>t</i> -Bu) ₃	30	62	<1	>99:1
8	PCy ₃	30	74	<1	>99:1
9	L1	30	67	2	98:2
10	PCy ₃	0	88	<1	>99:1
11	L1	0	80	<1	>99:1
12	L2	0	45 (62) ^c	<1	>99:1
13	L3	0	1	<1	-

^aConditions: CuCl (0.025 mmol), ligand (0.025 mmol), **1a** (0.5 mmol), bis(pinacolato)diboron (**2**) (0.6 mmol), and K(O-*t*-Bu) (0.6 mmol) in THF (1.0 mL). ^bDetermined by GC analysis of the crude reaction mixture using an internal standard. ^cReaction time of 9 h.



With the borylsubstitution selective reaction conditions in hand, substrate screening was conducted (Table 1.2). The reactions of 5-bromo-1-pentene (**1a**) and a phenyl group substituted substrate **1b** proceeded to give the corresponding alkylboronates **3a** and **3b** in good yield respectively (**3a**: 68% and 60%, **3/4** = >95:5; **3b**: 67% and 70%, **3/4** = >95:5). The small decrease of yield for borylsubstitution product was observed even in 10 mol % catalyst loading when the substrates containing bulky substituents adjacent to the carbon–halogen bond **1c**, **1d** and **1e** were employed (**3c**: 55%, **3/4** = >95:5; **3d**: 47%, **3/4** = >95:5; **3e**: 61%, **3/4** = >95:5). Furthermore, the homoallylboronate **3f** was obtained in high yield with perfect chemoselectivity (73%, **3/4** = >95:5).

Table 1.2 Optimization of borylsubstitution selective reaction of **1a**.^a



^aConditions: CuCl (0.025 mmol), ligand (0.025 mmol), **1a** (0.5 mmol), bis(pinacolato)diboron (**2**) (0.6 mmol), and K(O-*t*-Bu) (0.6 mmol) in THF (1.0 mL) at 0 °C. ^bIsolated yield. GC yield was shown in the parenthesis. ^c10 mol % catalyst, **2** (1.5 equiv, 0.75 mmol) and K(O-*t*-Bu) (1.5 equiv, 0.75 mmol) were used instead of standard conditions.

Next, the borylation reaction of 6-bromo-1-hexene (**1g**) with PCy₃ as a borylsubstitution selective ligand gave the 6:94 mixture of substitution and substitution product (**3g/4g**). This reactivity should be assigned to the kinetically rapid 5-*exo-trig* radical cyclization because this copper(I)-catalyzed borylsubstitution of alkyl halides proceed through the alkyl radical intermediate (Fig. 1.4).^{17,18}

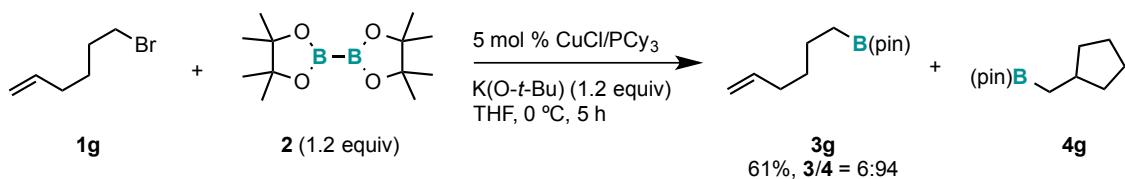


Fig. 1.4 Copper(I)-catalyzed borylation of 6-bromo-1-hexene (**1g**).

To demonstrate this ligand-controlled chemoselectivity of the borylation of alkyl halides bearing terminal alkene moieties, the borylations of alkyl halide substrate **1h** were performed (Fig. 1.5). The substrate **1h** was successfully converted to the borylative cyclization product **3h** and borylsubstitution product **4h** in good yield and perfect chemoselectivity by changing the ligand (**3h**: 64%, **3h/4h** = >95:5; **4h**: 91%, **3h/4h** = <5:95).

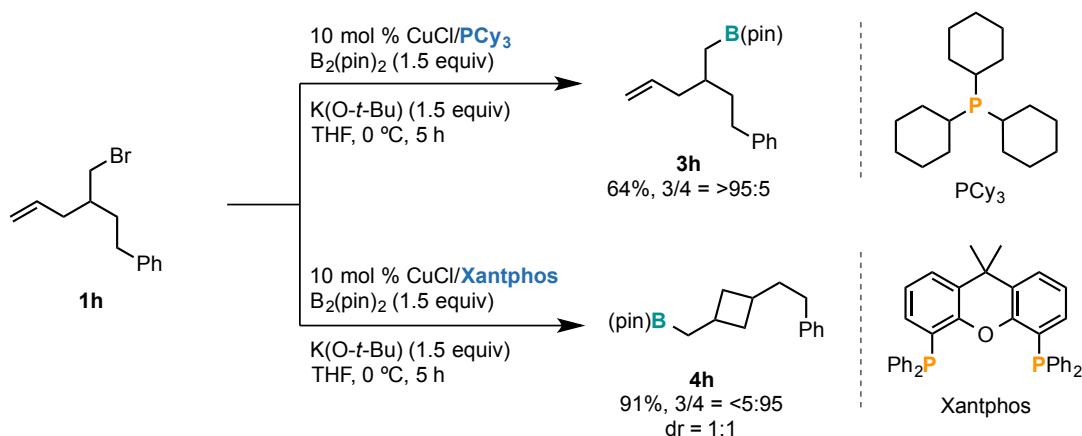


Fig. 1.5 Ligand-controlled borylation of alkyl halides bearing a terminal alkene **1h**.

Comparison experiments demonstrated the ligand-dependent reactivity of the copper(I)-catalyzed borylation reaction with diboron reagent (Fig. 1.6). The borylsubstitution selective ligands, **PCy₃** and **L1** in the borylation of a simple alkyl halide **6** showed high reactivity and completed the reaction within 1 hour (**PCy₃**: 99%, **L1**: 84%). On the other hand, the borylcupration selective ligand, **Xantphos**, which can react with alkyl halides at room temperature, resulted in extremely low reactivity at 0 °C (2%). The ligand-dependent reactivity to the alkenes with a simple alkene **8** and methanol as the alkylcopper(I) trapping reagent was also investigated. Although the reactions using **PCy₃** or **L1** gave a trace amount of product **9** (**PCy₃**: 99%, **L1**: 84%), the reaction using **Xantphos** exhibited high reactivity for the alkene **8** even in low temperature (93%). Furthermore, the calculation study of the borylcupration of a carbon–carbon double bond was carried out to compare the ligand effect for the reaction with alkene.²² This indicated that the borylsubstitution-selective ligands required higher activation energy for borylcupration of alkene compared to that of **Xantphos** (Fig. 1.7)

The proposed catalytic cycles for the borylative cyclization pathway and borylsubstitution pathway are shown in figure 1.8.²¹ At first, the copper(I) alkoxide **A** is generated from copper(I) chloride and alkoxide base. The reaction with the copper(I) alkoxide and diboron **2** gives the borylcopper(I) species **B**. The borylcopper(I) selectively reacts with alkyl halide bearing an alkene moiety to provide radical intermediate **C** and the copper(II) complex via the single electron involving mechanism when the monophosphine ligands **PCy₃** or **L1** were used. The borylation of the radical intermediate with the borylcopper(II) species and an alkoxide base finally afford the corresponding borylsubstitution product **3** and regenerates the copper(I) alkoxide **A**. In contrast, the borylcopper(I) complex bearing **Xantphos**

ligand selectively reacts with an alkene moiety of the substrate **1** to produce the alkylcopper(I) intermediate **D** via the borylcupration of the carbon–carbon double bond. The intramolecular cyclization reaction of the intermediate **D** with an alkoxide base occurs to provide the corresponding borylative cyclization product **4** and reproduces the copper(I) alkoxide **A**.

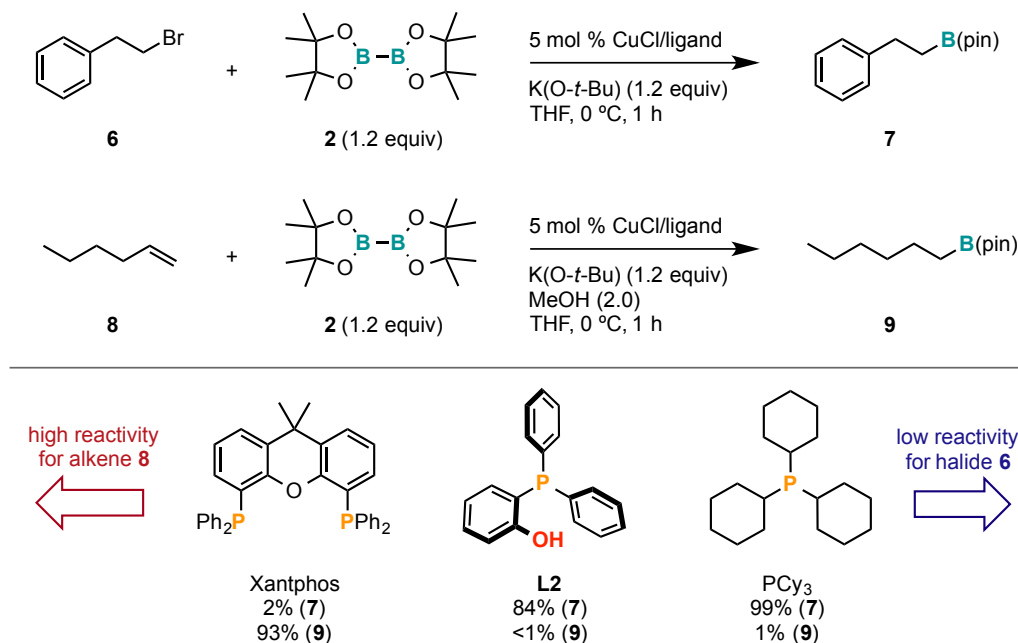


Fig. 1.6 Comparison experiments of ligand-dependent reactivity.

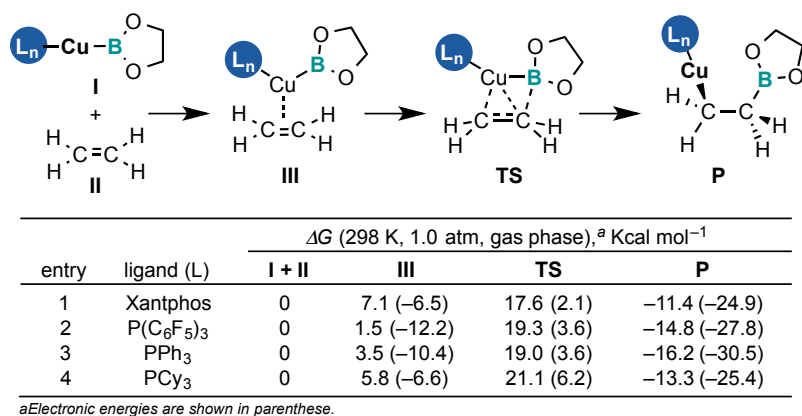


Fig. 1.7 DFT calculation of borylcupration of a carbon–carbon double bond with various phosphine ligands (B3PW91/cc-pVDZ in gas phase at 298 K).

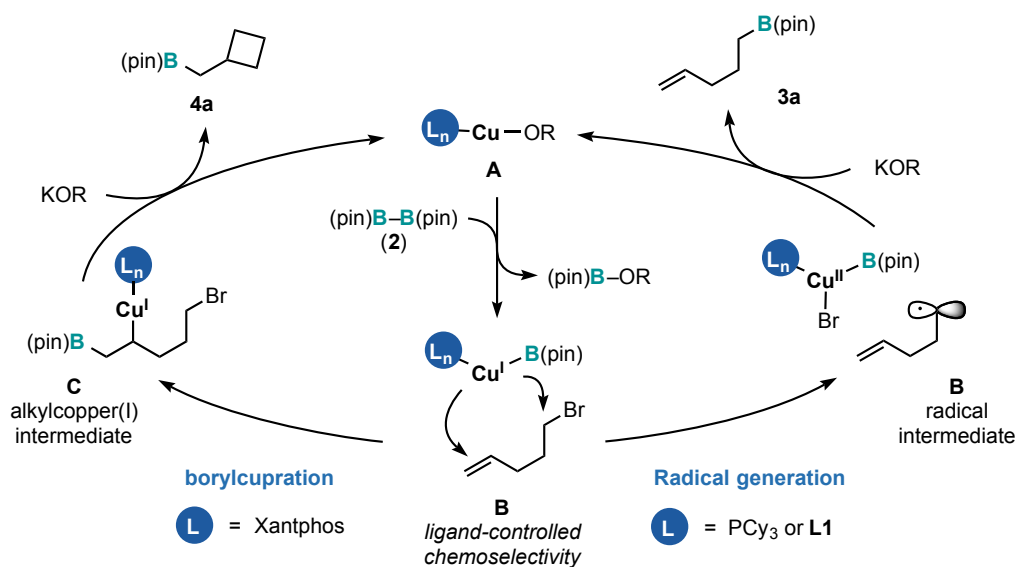


Fig. 1.8 Proposed catalytic cycles for borylsubstitution and borylative cyclization.

1.3 Conclusion

In summary of this chapter, the two different reactions, borylsubstitution and borylative cyclization, of the copper(I)-catalyzed borylation with a diboron reagent from the same substrate have been controlled by using the appropriate ligand. The mechanistic study revealed that the borylation using monophosphine ligands, PCy_3 or **L1** shows high chemoselectivity for the alkyl halides, whereas the reaction using bisphosphine bearing a large bite-angle, Xantphos, shows high chemoselectivity for the alkenes. Furthermore, this indicates the possibility for the ligand in the copper(I)-catalyzed borylation reaction can distinguish the two reactivities between the radical-type reactivity for alkyl halides and the addition-type reactivity for alkenes.

1.4 Experimental

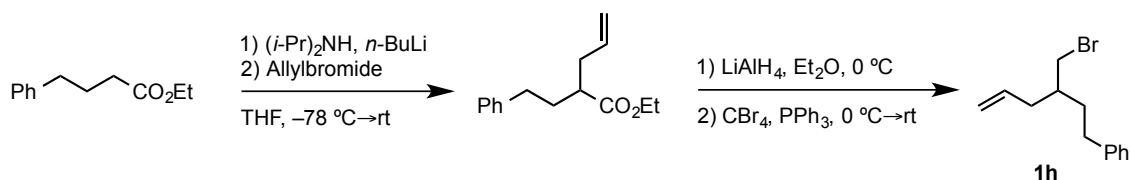
1.4.1 General

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4A). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^1H : 400 MHz and ^{13}C : 100 MHz). Tetramethylsilane (^1H) and CDCl_3 (^{13}C) were employed as the external standards, respectively. CuCl (ReagentPlus® grade, 224332-25G, $\geq 99\%$) and $\text{K}(\text{O}-t\text{-Bu})$ / THF (1.0 M, 328650-50ML) were purchased from Sigma-Aldrich Co. and used as received. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with a ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and a FID detector. High-resolution mass spectra were recorded at the Center for Instrumental Analysis, Hokkaido University.

1.4.2 General Experimental Procedure

Copper chloride (2.5 mg, 0.025 mmol) and bis(pinacolato)diboron (**2**) (152.4 mg, 0.60 mmol), *o*-diphenylphosphinophenol **L1** (7.0 mg, 0.025 mmol) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a teflon-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (0.4 mL) and $\text{K}(\text{O}-t\text{-Bu})/\text{THF}$ (1.0 M, 0.6 mL, 0.6 mmol) were added in the vial through the rubber septum using a syringe. After stirring for 30 min, **1a** (74.5 mg, 0.50 mmol) was added to the mixture at 0 °C. After the reaction was complete, the reaction mixture was passed through a silica gel column (radius: 10 mm, height of the column: 30 mm) eluting with Et_2O . The crude material was purified by flash column chromatography (SiO_2 , Et_2O /pentane, typically 0:100–2:98) to give the corresponding borylation product **3a** as colorless oil.

1.4.3 Substrate preparation



Compounds **1a–1g** were synthesized according to our previous publication.²¹ In an oven-dried 200 mL round bottomed flask, a hexane solution of $n\text{-BuLi}$ (1.55 M, 11.6 mL, 18.0 mmol) was added to a solution of $(i\text{-Pr})_2\text{NH}$ (3.05 mL, 21.8 mmol) in THF at 0 °C. The reaction mixture was stirred for 15 min and then cooled to $-78\text{ }^\circ\text{C}$. The ethyl ester (2.88 g, 15.0 mmol) was added dropwise to the reaction mixture and the reaction mixture was further stirred for 30 min. Allylbromide (1.95 mL, 22.5

mmol) was then added dropwise into the mixture. It was warmed to room temperature and stirred for 4 h. The reaction mixture was quenched by addition of saturated NH_4Cl aq. and extracted with Et_2O three time. The combined organic layer was then dried over MgSO_4 . After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain the corresponding ethyl ester (2.26 g, 9.8 mmol, 65%) as a colorless oil.

In an oven-dried round bottomed flask, a solution of the ethyl ester (2.09 g, 9.0 mmol) in Et_2O (10 mL) was added to a slurry of LiAlH_4 (512.3 mg, 13.5 mmol) in Et_2O (15 mL) at 0 °C. After stirred for 9 h, the reaction mixture was quenched by addition of water and stirred until a white solid was formed. The mixture was filtered and dried over MgSO_4 . The crude material was purified by flush column chromatography to obtain the corresponding alcohol (1.47 g, 7.7 mmol, 86%) as a colorless oil.

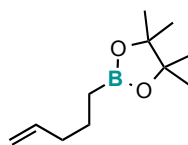
In a 100 mL round bottomed flask, CBr_4 (2.98 g, 9.0 mmol) and the alcohol (1.43 g, 7.5 mmol) were dissolved in dry THF (15 mL) and the mixture was cooled to 0 °C. PPh_3 (2.36 g, 9.0 mmol) was then added portionwise and the reaction mixture was stirred for 12 h. The reaction mixture was quenched by addition of water and extracted three times with Et_2O . The combined organic layer was dried over MgSO_4 . After filtration, the solvents were removed by evaporation. The crude product was purified by flush column chromatography to obtain **1h** (1.68 g, 6.6 mmol, 88%) as a colorless oil.

^1H NMR (392 MHz, CDCl_3 , δ): 1.67–1.79 (m, 3H), 2.19–2.23 (m, 2H), 2.57–2.71 (m, 2H), 3.45–3.52 (m, 2H), 5.06–5.15 (m, 2H), 5.67–5.78 (m, 1H), 7.18–7.21 (m, 3H), 7.26–7.31 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 32.8 (CH_2), 34.0 (CH_2), 36.6 (CH_2), 38.4 (CH_2), 38.6 (CH), 117.3 (CH_2), 125.8 (CH), 128.26 (CH), 128.35 (CH), 135.4 (CH), 141.8 (C). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{Br}$, 252.05136; found, 252.05091.

1.4.4 Borylation Product Characterization

The ^1H and ^{13}C NMR spectra of product **4g** were identical to those we previously reported.²¹

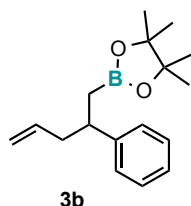
1.4.4.1 4,4,5,5-Tetramethyl-2-(pent-4-en-1-yl)-1,3,2-dioxaborolane (**3a**).²³



3a

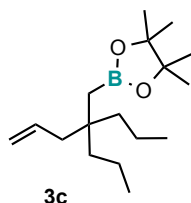
^1H NMR (392 MHz, CDCl_3 , δ): 0.79 (t, J = 7.9 Hz, 2H), 1.25 (s, 12H), 1.51 (quin, J = 7.6 Hz, 2H), 2.02–2.08 (m, 2H), 4.91–5.02 (m, 2H), 5.75–5.85 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 10.7 (br, s, B– CH_2), 23.3 (CH_2), 24.8 (CH_3), 36.3 (CH_2), 82.8 (C), 114.4 (CH_2), 138.9 (CH). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{11}\text{H}_{21}\text{BO}_2$, 196.16346; found, 196.16381.

1.4.4.2 4,4,5,5-Tetramethyl-2-(2-phenylpent-4-en-1-yl)-1,3,2-dioxaborolane (3b).



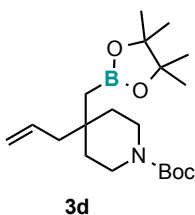
^1H NMR (392 MHz, CDCl_3 , δ): 1.07–1.14 (m, 13H), 1.21–1.26 (m, 1H), 2.28–2.41 (m, 2H), 2.94 (dt, $J = 7.1, 14.2$ Hz, 1H), 4.90–4.98 (m, 2H), 5.62–5.73 (m, 1H), 7.12–7.27 (m, 5H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 18.7 (br, s, B– CH_2), 24.60 (CH_3), 24.65 (CH_3), 41.3 (CH), 43.7 (CH_2), 82.9 (C), 116.0 (CH_2), 125.8 (CH), 127.4 (CH), 128.0 (CH), 137.1 (CH), 146.7 (C). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{17}\text{H}_{25}\text{BO}_2$, 272.19476; found, 272.19420.

1.4.4.3 2-(2,2-Dipropylpent-4-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3c).



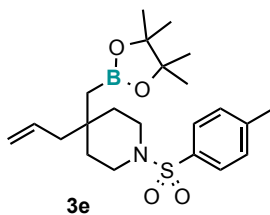
^1H NMR (392 MHz, CDCl_3 , δ): 0.75 (s, 2H), 0.83–0.88 (m, 6H), 1.23–1.25 (m, 20H), 2.06 (d, $J = 7.6$ Hz, 2H), 4.98–5.02 (m, 2H), 5.76–5.86 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 14.9 (CH_3), 16.7 (CH_2), 24.8 (CH_3), 37.7 (C), 41.6 (CH_2), 43.5 (CH_2), 82.5 (C), 116.4 (CH_2), 136.1 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (m/z): $[\text{M} - \text{Me}]^+$ calcd for $\text{C}_{16}\text{H}_{30}\text{BO}_2$, 265.23388; found, 265.23362.

1.4.4.4 *tert*-Butyl 4-allyl-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]piperidine-1-carboxylate (3d).



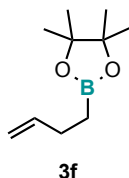
^1H NMR (392 MHz, CDCl_3 , δ): 0.87 (s, 2H), 1.23 (s, 12 H), 1.39–14.9 (m, 13H), 2.16 (d, $J = 7.5$ Hz, 2H), 3.28–3.34 (m, 2H), 3.42–3.46 (m, 2H), 5.01–5.06 (m, 2H), 5.77–5.87 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 19.7 (br, s, B– CH_2), 24.8 (CH_3), 28.4 (CH_3), 33.5 (C), 36.5 (CH_2), 39.7 (br, d, CH_2), 43.7 (CH_2), 79.0 (C), 82.8 (C), 117.5 (CH_2), 134.6 (CH), 155.0 (C). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{20}\text{H}_{36}\text{BNO}_4$, 365.27374; found, 365.27327.

1.4.4.6 4-Allyl-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-1-tosylpiperidine (3e).



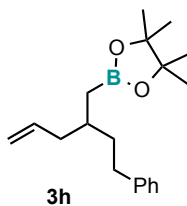
^1H NMR (392 MHz, CDCl_3 , δ): 0.72 (s, 2H), 1.21 (s, 12H), 1.57 (t, $J = 5.6$ Hz, 4H), 2.03 (d, $J = 7.7$ Hz, 2H), 2.44 (s, 3H), 2.85–2.91 (m, 2H), 3.10–3.15 (m, 2H), 4.94–5.04 (m, 2H), 5.65–5.79 (m, 1H), 7.32 (d, $J = 8.2$ Hz, 2H), 7.64 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 19.2 (br, s, B– CH_2), 21.5 (CH_3), 24.8 (CH_3), 32.8 (C), 36.0 (CH_2), 42.0 (CH_2), 43.7 (CH_2), 82.9 (C), 117.8 (CH_2), 127.6 (CH), 129.5 (CH), 133.4 (C), 134.1 (CH), 143.2 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{34}\text{BNO}_4\text{SNa}$, 442.21979; found, 442.22008.

1.4.4.7 2-(But-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3f).^{14,24}



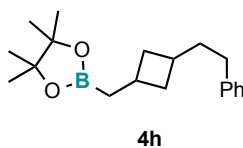
^1H NMR (392 MHz, CDCl_3 , δ): 0.89 (t, $J = 7.7$ Hz, 2H), 1.24 (s, 12H), 2.14–2.20 (m, 2H), 4.88–5.03 (m, 2H), 5.84–5.94 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 10.2 (br, s, B– CH_2), 24.8 (CH_3), 27.9 (CH_2), 83.0 (C), 113.1 (CH_2), 140.6 (CH). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{10}\text{H}_{19}\text{BO}_2$, 182.14781; found, 182.14816.

1.4.4.8 4,4,5,5-Tetramethyl-2-(2-phenethylpent-4-en-1-yl)-1,3,2-dioxaborolane (3h).



^1H NMR (392 MHz, CDCl_3 , δ): 0.85 (d, $J = 6.7$ Hz, 2H), 1.25 (s, 12H), 1.50–1.69 (m, 2H), 1.79 (septet, $J = 6.7$ Hz, 1H), 2.03–2.19 (m, 2H), 2.55–2.67 (m, 2H), 4.98–5.05 (m, 2H), 5.74–5.85 (m, 1H), 7.14–7.18 (m, 3H), 7.24–7.28 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 16.5 (br, s, B– CH_2), 24.8 (CH_3), 33.3 (CH_2), 33.9 (CH), 38.3 (CH_2), 40.8 (CH_2), 82.9 (C), 116.0 (CH_2), 125.5 (CH), 128.2 (CH), 128.3 (CH), 137.3 (CH), 143.1 (C). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{19}\text{H}_{29}\text{BO}_2$, 300.22606; found, 300.22607.

1.4.4.9 4,4,5,5-Tetramethyl-2-[(3-phenethylcyclobutyl)methyl]-1,3,2-dioxaborolane (4h).



The product **4h** was obtained as a diastereomeric mixture (1:1). The stereoselectivity was determined by ^1H NMR analysis of the crude reaction mixture.

^1H NMR (392 MHz, CDCl_3 , δ): 0.90 (d, $J = 6.7$ Hz, 2H), 1.00 (d, $J = 7.9$ Hz, 2H), 1.18–1.26 (m, 26H), 1.63 (dt, $J = 7.8$ Hz, 2H), 1.69–1.77 (m, 4H), 1.80–1.87 (m, 2H), 1.98–2.07 (m, 1H), 2.18–2.29 (m, 4H), 2.43–2.53 (m, 5H), 7.14–7.18 (m, 6H), 7.24–7.28 (m, 4H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 24.8 (CH_3), 27.9 (CH), 28.2 (CH), 30.7 (CH), 31.6 (CH), 33.6 (CH_2), 33.8 (CH_2), 35.0 (CH_2), 37.2 (CH_2), 38.3 (CH_2), 39.3 (CH_2), 82.8 (C), 125.5 (CH), 128.2 (CH), 128.3 (CH), 142.9 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{19}\text{H}_{29}\text{BO}_2$, 300.22606; found, 300.22631.

1.4.5 DFT Calculation Method

All calculations were performed with Gaussian 09W (revision C.01) program package.²² Geometry optimizations were carried out with B3PW91/cc-pVDZ in the gas-phase. Frequency calculations were conducted on the gas-phase optimized geometries to check the all the stationary points as either minima or transition states.

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Chapter 2

Ligand-Controlled Chemoselective Copper(I)-Catalyzed Borylative Radical Cyclization

Abstract The first stereoselective borylative radical cyclization of alkyl halides containing an alkene moiety with copper(I)/diboron catalyst system has been developed. The borylation products can be transformed to highly functionalized organic compounds through the derivatization of the newly formed C–B bond. This borylative radical cyclization offers a novel methodology for the stereoselective synthesis of various heterocyclic compounds.

2.1 Introduction

Radical cyclization reactions are recognized as useful methods for the construction of cyclic organic compounds.^{1–4} In classical radical cyclization reactions, radical species are first generated via a homolytic cleavage of C–X bond (X = halogen or heteroatom) and reacts with the C–C double bond to form the kinetically favorable cyclization intermediate.^{5,6} In particular, stereoselective cyclization of alkenyl halide substrates that were synthesized based on chiral allyl compounds has been recognized as the important method to access the chiral saturated heterocyclic compounds (for R² = OR, Ueno-Stork reaction).^{7,8} The use of various trapping reagents, the concomitant functionalization of the radical intermediate were also achieved (Fig. 2.1a).^{9–26} Alkylboronates are versatile building blocks for organic synthetic chemistry because they can be transformed to the compounds containing various functionalities in a stereospecific manner.²⁷ However, no practical method of stereoselective radical cyclization that can introduce C–B bond has been reported.^{28,29} Herein, we have reported the first stereoselective copper(I)-catalyzed borylative radical cyclization. This method can synthesize various highly functionalized cyclic organic compounds through transformation of the boryl group (Fig. 2.1b).

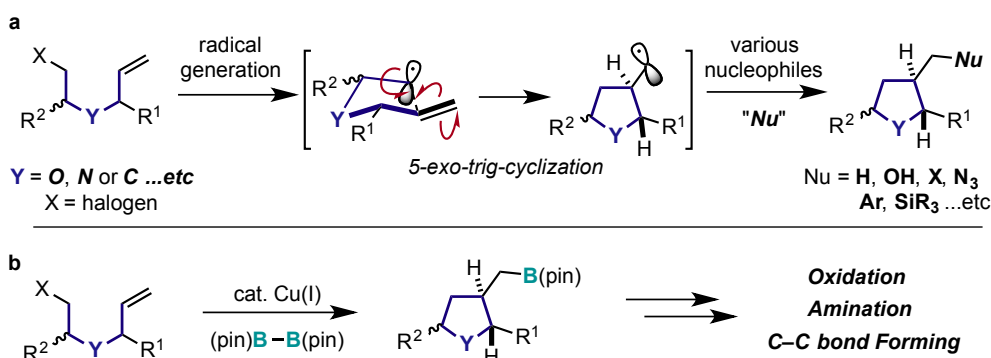


Fig. 2.1 a) Classical radical cyclization with concomitant functionalization. b) This work: borylative radical cyclization with copper(I)-catalyst.

Copper(I)-catalyzed borylation reaction with diboron compounds has recently been actively studied as efficient methods for the synthesis of organoboron compounds. For most of these reactions, addition of borylcopper(I) species generated in situ to carbon–carbon unsaturated bonds (borylcupration) has been considered as the key step.^{30–37} In 2012, our group and Marder’s group independently reported novel radical-related reactions of borylcopper(I) intermediate.^{28,38} The reaction of alkyl halides with copper(I)-catalyst and diboron reagent gave the corresponding alkylboronates. The mechanistic study of the boryl substitution reaction suggested the reaction proceeds through a radical pathway. Based on the study, we anticipated that the stereoselective borylative radical cyclization of alkyl halide **1** synthesized from the corresponding allyl alcohol could be developed. Although the various substrates are easily available, the attempted copper(I)-catalyzed reaction of this type of substrate arises fundamental chemoselectivity issues between borylcupration for allylic substitution or radical generation for stereoselective boryl cyclization.^{33–35} (Fig. 2.2).

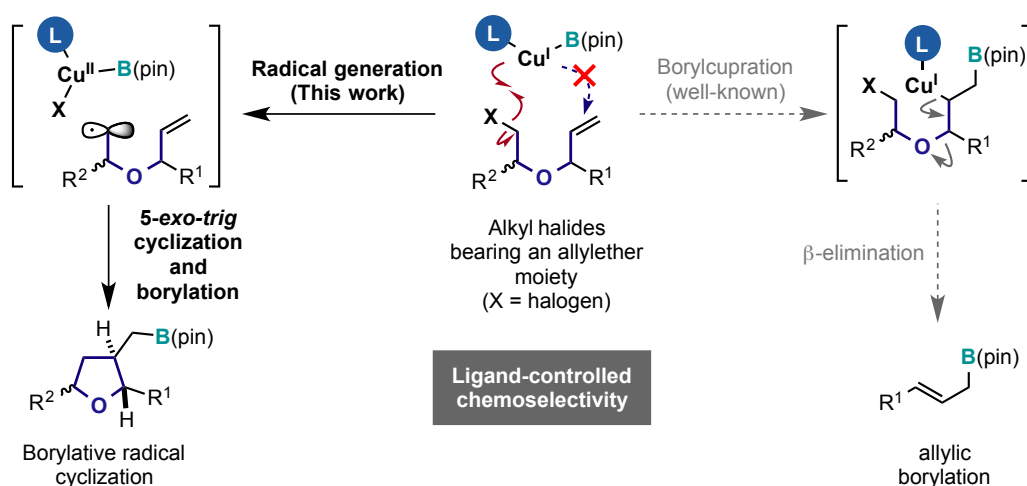


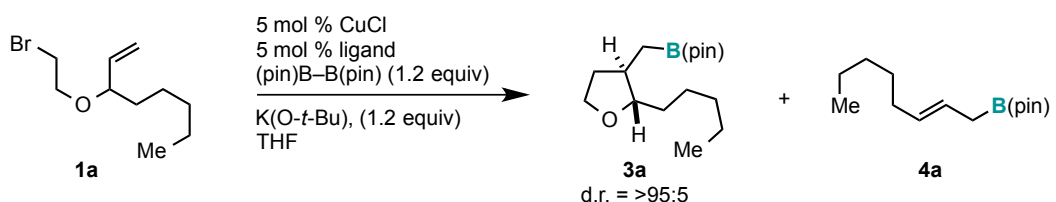
Fig. 2.2 Copper(I)-catalyzed borylative cyclization of terminal alkenes bearing alkyl halide moieties.

2.2 Result and Discussion

Thus, we first conducted the screening of ligands for the borylative radical cyclization over the allyl substitution (Table 2.1). Based on the previous ligand-controlled chemoselectivity of the borylation reaction, the reaction using PCy₃ resulted in high selectivity to give the desired cyclization product **3a** in high yield with excellent diastereoselectivity (entry 1: 86%, **3a/4a** = 96:4). Furthermore, the monophosphine ligand bearing a hydroxy group **L1** also exhibited high selectivity to provide **3a** in good yield (entry 2: 80%, **3a/4a** = 97:3). It should be noted that the reaction proceeded with excellent diastereoselectivity (dr = >95:5). This stereoselectivity corresponds with that of typical 5-*exo-trig* radical cyclization.^{5,6} The use of PPh₃, which showed high halide selectivity in our previous work, gave the mixture of cyclization product **3a** and allylic substitution product **4a** (entry 3: 45%, **3a/4a** = 66:34).²⁹ Whereas, the use of bisphosphine ligands such as Xantphos and dppbz showed allylic borylation selectivity to give the corresponding allylboronate product **4a** as a major product (entry 4:

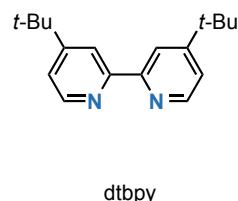
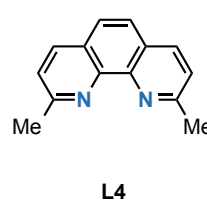
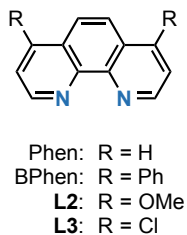
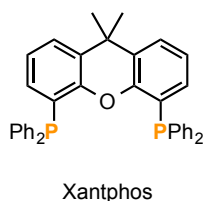
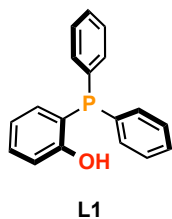
Xantphos, **3a/4a** = 13:87; entry 5: dppbz, **3a/4a** = 28:72). Subsequently, we found that phenanthroline is effective as a ligand for the cyclization to give **3a** in a high yield (entry 6: 73%, **3a/4a** = 91:9). And then, 4,7-diphenyl-phenanthroline (BPhen) showed higher reactivity than phenanthroline with keeping high selectivity (entry 7: 80%, **3a/4a** = 92:8). The various phenanthroline ligands were also tested. Although the cyclization reaction selectivity was high when the electron-rich ligand **L2** was used (entry 8: 75%, **3a/4a** = 89:11), the allylic borylation reaction occurred with moderate selectivity when the electron-deficient ligand **L3** was used (entry 9: 7%, **3a/4a** = 24:76). 2,9-Dimethyl phenanthroline ligand **L4** declined the cyclization selectivity and reactivity (entry 10: 48% **3a/4a** = 78:22). The reaction using the bipyridine ligand, dtbpy, resulted in low reactivity and selectivity (entry 11: **3a/4a** = 48:52). Subsequently, the reactions using the cyclization selective ligands, PCy₃ and BPhen, at room temperature gave the product in lower yield and selectivity compared to those of the reactions at 0 °C (entry 12: PCy₃, 70%, **3a/4a** = 92:8; entry 13: BPhen, 66%, **3a/4a** = 85:15). No selectivity was emerged in the reaction without ligand (entry 14: 7%, **3a/4a** = 38:62). The reaction conditions with PCy₃, **L1** and BPhen turned out to be effective for the stereoselective borylative radical cyclization of allyl ether substrate **1**.

Table 2.1 Optimization of borylsubstitution selective reaction of **1a**.^a



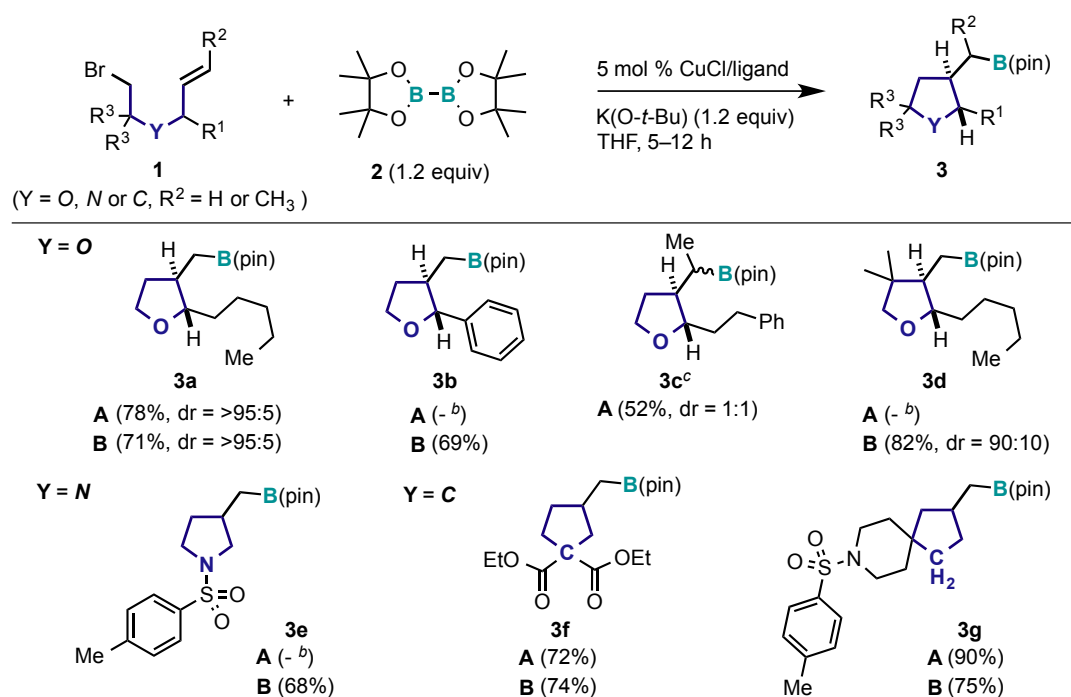
entry	ligand	temp (°C)	time (h)	yield (%) of 3a ^b	yield (%) of 4a ^b	3a/4a ^b
1	PCy ₃	0	6	86	4	96:4
2	L1	0	6	80	3	97:3
3	PPh ₃	0	24	45	23	66:34
4	Xantphos	0	24	1	9	13:87
5	dppbz	0	24	18	46	28:72
6	Phen	0	24	73	7	91:9
7	BPhen	0	6	80	7	92:8
8	L2	0	24	75	9	89:11
9	L3	0	24	7	22	24:76
10	L4	0	24	48	13	78:22
11	dtbpy	0	24	19	21	48:52
12	PCy ₃	30	6	70	6	92:8
13	BPhen	30	6	66	12	85:15
14	-	0	6	7	12	38:62

^aConditions: CuCl (0.025 mmol), ligand (0.025 mmol), **1a** (0.5 mmol), bis(pinacolato)diboron (**2**) (0.6 mmol), and K(O-t-Bu) (0.6 mmol) in THF (1.0 mL). ^bDetermined by GC analysis of the crude reaction mixture using an internal standard.



With optimized conditions in hand, we conducted the investigation of substrate scope with the three suitable reaction conditions (Table 2.2). The corresponding tetrahydrofuran derivative **3a** bearing a boryl group was obtained in a high yield with perfect diastereoselectivity (78%). Although the reaction conditions with PCy₃ was not effective for the substrate bearing allyl ether bearing phenyl group **1b**, the reaction using BPhen gave the desired product **3b** in a good yield (69%). The reaction of substrate containing linear internal alkene moiety (*E*)-**1c** also gave the corresponding secondary alkylboronate **3c** (52%). Furthermore, this borylative radical cyclization can react with the tertiary bromide substrate **1d** to provide the product containing highly functionalized tetrahydrofuran **3d** in high yield (82%). Subsequently, we tested the reaction of the nitrogen tethered substrate **1e**. The borylation product bearing tosyl-protected pyrrolidine moiety **3e** was obtained in a good yield (68%). The borylation of **1f** also gave the product containing cyclopentane ring **3f** in a high yield (74%). Furthermore, the spiro-cyclic product **3g** was obtained in a high yield (90%).

Table 2.2 Substrate scope for borylative radical cyclization of **1**.^a

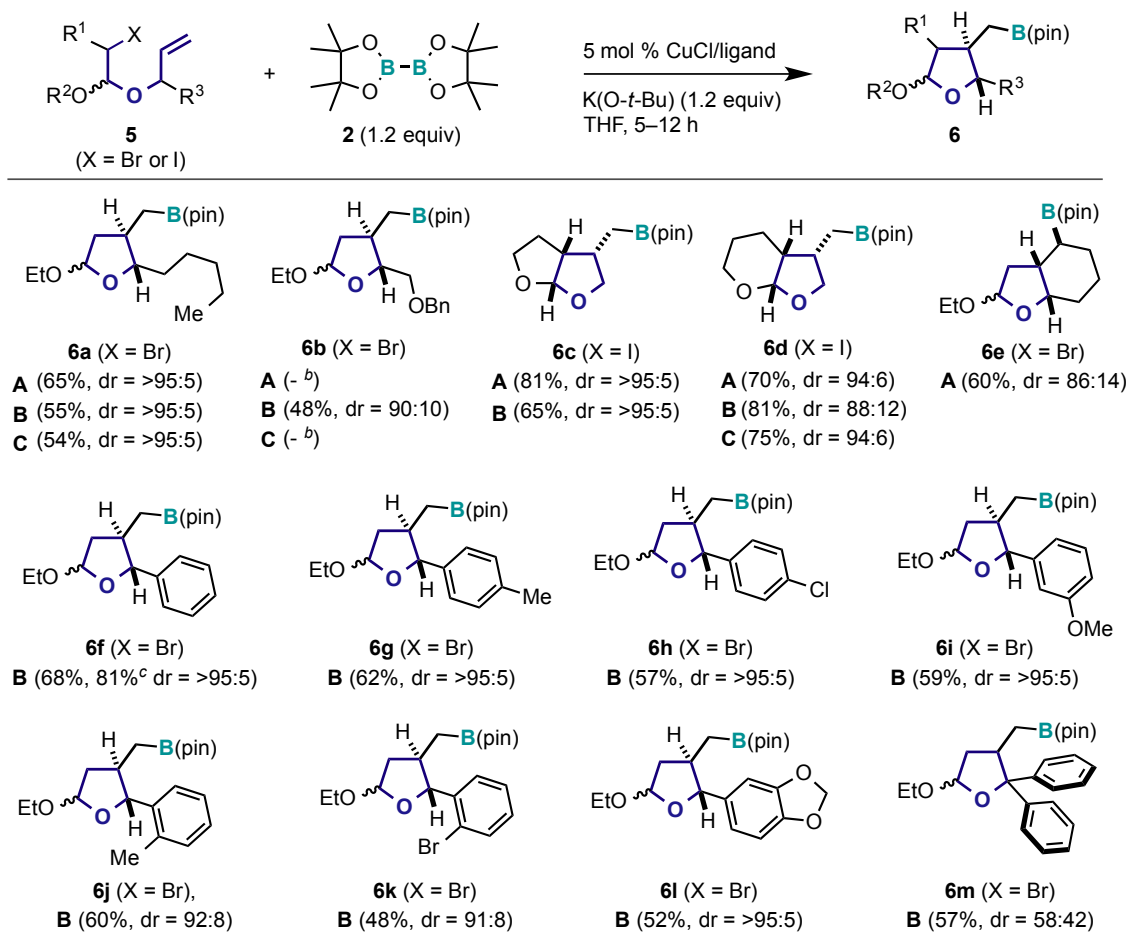


^aCommon conditions: CuCl (0.025 mmol), ligand (0.025 mmol), **1** (0.5 mmol), bis(pinacolato)diboron (**2**) (0.6 mmol), and K(O-*t*-Bu) (0.6 mmol) in THF (1.0 mL). Conditions A: PCy₃, 0 °C. Conditions B: BPhen, room temperature. Isolated yields. Diastereoselectivity was determined by GC and ¹H NMR analysis. ^bComplex mixture. ^cThe (*E*)-internal alkene substrate (R²=CH₃) was used.

To show the utility of this borylative radical cyclization, we applied this borylation reaction to Ueno-Stork radical cyclization for the synthesis of γ -lactol ethers containing boryl group (Table 2.3)^{3,7,8}. The substrate bearing alkyl chain **5a** was smoothly converted to the corresponding lactol ether **6a** in a good yield with high diastereoselectivity (65%). The reaction of benzyl protected alcohol substrate **5b** afforded the borylation product **6b** in a moderate yield (48%). The secondary iodide

substrates **5c** and **5d** could be applicable to this catalytic system and the corresponding borylation product **6c** and **6d** were obtained in high yields with good diastereoselectivity (**6c**: 81%, **6d**: 75%). The reaction of the substrate **5e** bearing cyclohexene moiety gave the secondary alkylboronate bearing acetal moiety **6e** in a moderate yield with moderate diastereoselectivity (60%). Subsequently, we conducted the reactions of aryl group substituted substrates. This reaction shows high functional group compatibility and gave the desired products bearing para-, meta-, and ortho-position substituted aryl group in good yields with stereoselectivity (**6f–6m**, 48–68%).

Table 2.3 Substrate scope for Ueno-Stoke-type borylative radical cyclization of **5**.^a



^aCommon conditions: CuCl (0.025 mmol), ligand (0.025 mmol) (0.5 mmol), bis(pinacolato)diboron (**2**) (0.6 mmol), and K(O-*t*-Bu) (0.6 mmol) in THF (1.0 mL). Conditions A: PCy₃, 0 °C. Conditions B: BPhen, room temperature. Conditions C: **L1**, 0 °C. Isolated yields. Diastereoselectivity was determined by GC and NMR analysis. ^bComplex mixture. ^cDetermined by GC analysis using crude material with an internal standard.

Next, we conducted the borylative radical cyclization of the optically active substrate synthesized from the corresponding optically active chiral allyl alcohol (*R*)-**7f** (Fig. 2.3a).³⁹ Optically active γ -lactone moieties were contained in various natural products and recognized as a useful synthetic intermediate (Fig. 2.3b).^{40,41} The oxidation of the boryl group of (*R,R*)-**6f**, silyl protection of hydroxyl group and oxidation of acetal moiety provided (*S,R*)-**8** in a good yield with perfect stereospecificity

(49% for 3 steps). Furthermore, the transformation of (*R,R*)-**6f** through homologation followed by oxidation of boryl group, benzyl protection and oxidation of acetal moiety gave the corresponding optically active lactone (*R,R*)-**9** in a high yield (56% yield for 4 steps). The acetal moiety of **9** could be converted to the allylation product **11** in high yield by the Lewis acid mediated reaction (90%). The amination of the boryl group of **3g** smoothly proceeded to give the spirocyclic amine **12** in good yield (Fig. 2.3c).

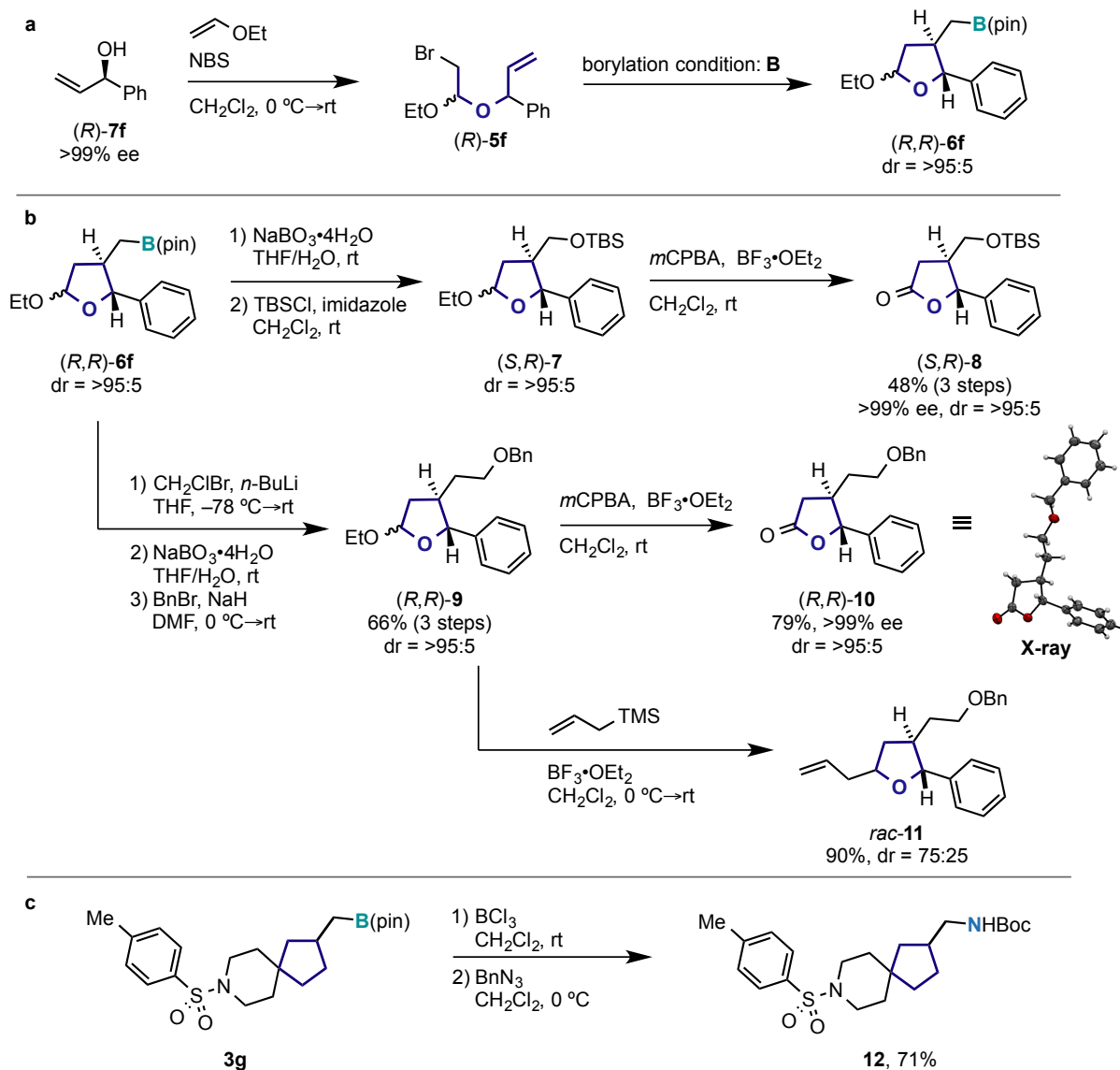


Fig. 2.3 a) Synthesis of optically active borylation product from chiral allyl alcohol. b) Synthetic application of borylative Ueno-Stoke radical cyclization products. c) Amination of borylation product.

To confirm the reaction mechanism, the borylation reaction of the substrate bearing cyclopropyl group (*E*)-**1h** was conducted (Fig. 2.4). The corresponding cyclopropyl-substituted borylation product was not detected, whereas the ring-opened product (*E*)-**3h** was obtained in a high yield (83%). This result suggested that this borylation reaction proceeds through radical intermediate.

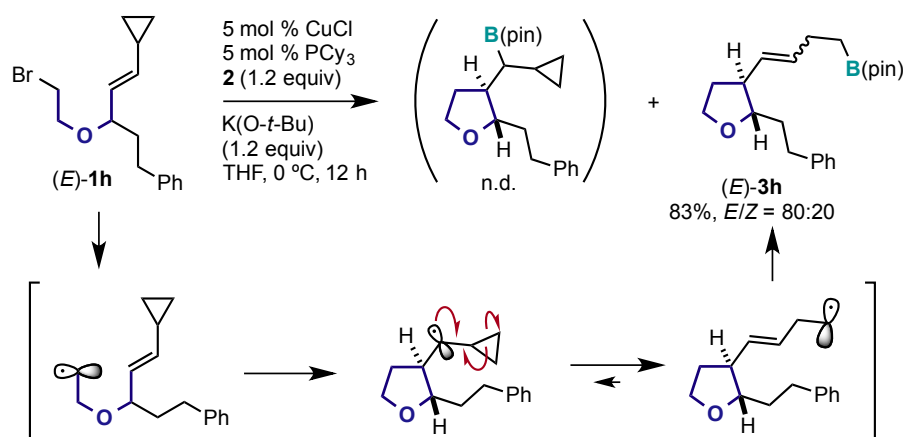
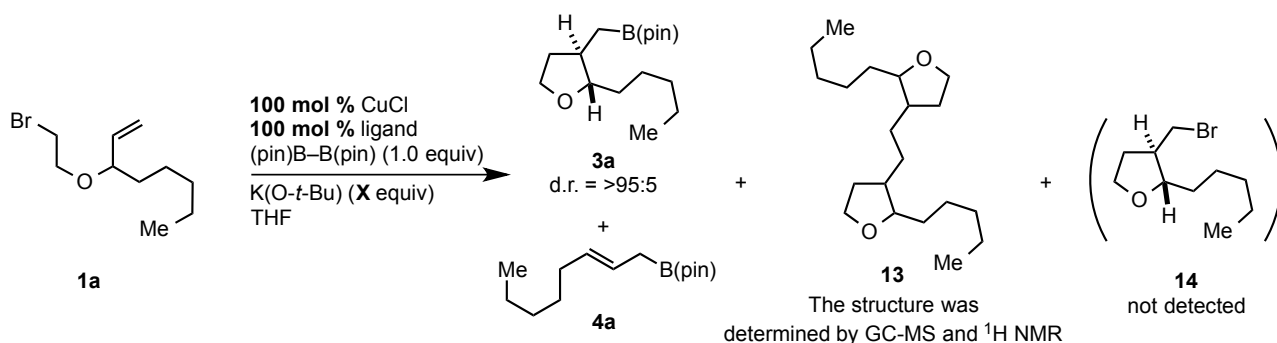


Fig. 2.4 Ligand-controlled borylation of alkyl halides bearing a terminal alkene **1h**.

To investigate the detailed mechanism of the copper(I)-catalyzed borylative radical cyclization, the stoichiometric experiments with **1a** were carried out. The reactions were performed with stoichiometric amounts of CuCl, ligand, K(O-*t*-Bu) and bis(pinacolato)diboron (**2**) in THF solvent (Table 2.4). The reactions with 1.0 equivalent of K(O-*t*-Bu) resulted in low yield of **3a** (entry 1: <1%; entry 3: 28%; entry 5: <1%), whereas the conversions of these reaction were moderate (entry 1: 42%; entry 3: 67%; entry 5: 16%). This suggests that the substrate **1a** would be decomposed due to the basic reaction conditions. Notably, the reactions with 2.0 equivalent of K(O-*t*-Bu) showed high reactivity to provide the cyclization product with almost same chemoselectivity, when BPhen or PCy₃ was used. The borylative radical cyclization product **3a** was obtained in moderate yield (entry 2: 46%; entry 4: 52%). The dimerization product **S3** was also detected by GC-MS and ¹H NMR analysis. The atom transfer cyclization product **S4** was not detected during a series of the reactions.

These experimental results indicate that the use of an excess amount of K(O-*t*-Bu) over CuCl and ligand is important for production of **3a**, and suggests that the cuprate, which is formed by the coordination of K(O-*t*-Bu) to copper(I) center, would be a key intermediate for the reaction. This hypothesis consists with the experimental results, where monophosphine ligand PCy₃ and bathophenanthroline (BPhen) ligand are appropriate for the borylative radical cyclization. The borylcopper(I) complexes bearing PCy₃ or BPhen would easily form the cuprate complex through the coordination of alkoxide base to the metal center because the bulkiness around the copper center of these borylcopper(I) complexes are smaller than those of the complex bearing bidentate bisphosphine ligand such as Xantphos and dppbz. Moreover, **L1** ligand can form the cuprate complex by intramolecular coordination of alkoxide moiety of **L1**.

Table 2.4 Stoichiometric reaction of **1a** for investigation of base effect.

entry	ligand	temp (°C)	X	time (h)	conv. of 1a (%) ^a	yield of 3a (%) ^a	yield of 4a (%) ^a	ratio of 3a/4a ^a	yield of 13 (%) ^b
1	BPhen	rt	1.0	6	42	<1	<1	-	<1
2	BPhen	rt	2.0	3	>99	46	2	96:4	35
3	PCy ₃	0	1.0	6	67	28	3	92:8	<1
4	PCy ₃	0	2.0	3	>99	52	5	91:9	22
5	L1	0	1.0	6	16	<1	<1	-	<1
6	L1	0	2.0	3	50	27	<1	>99:1	<1

^aDetermined by GC analysis. ^bDetermined by NMR analysis.

Based on the mechanistic study, we proposed a catalytic cycle of borylative radical cyclization (Fig. 2.5). The copper(I) alkoxide **A** would react with diboron reagent **2** to give the borylcopper(I) intermediate **B**. The cuprate **C** formed by coordination of a K(O-*t*-Bu) to copper(I) center of **B** should selectively react with alkyl halide moiety of the substrate **1** or **5** to generate radical intermediate **D** and copper(II) species **E** (radical reaction pathway). Kinetically favorable 5-*exo-trig* radical cyclization of **D** should form the intermediate **F**. In the case of high concentration of the intermediate **F**, the radical dimerization occurs to give the dimer bearing two cyclic structures **13**. Finally, the radical intermediate **F** should react with copper(II) species **E** to give the corresponding borylation product **3** or **6** and regenerate copper(I) alkoxide **A**. In contrast, the borylcopper(I) intermediate with a bisphosphine such as Xantphos forms the alkylcopper(I) intermediate **G** through the borylcupration of an alkene moiety of the substrate (borylcupration pathway). Following β-elimination from the intermediate **G** gives the corresponding allylboronate **4**.

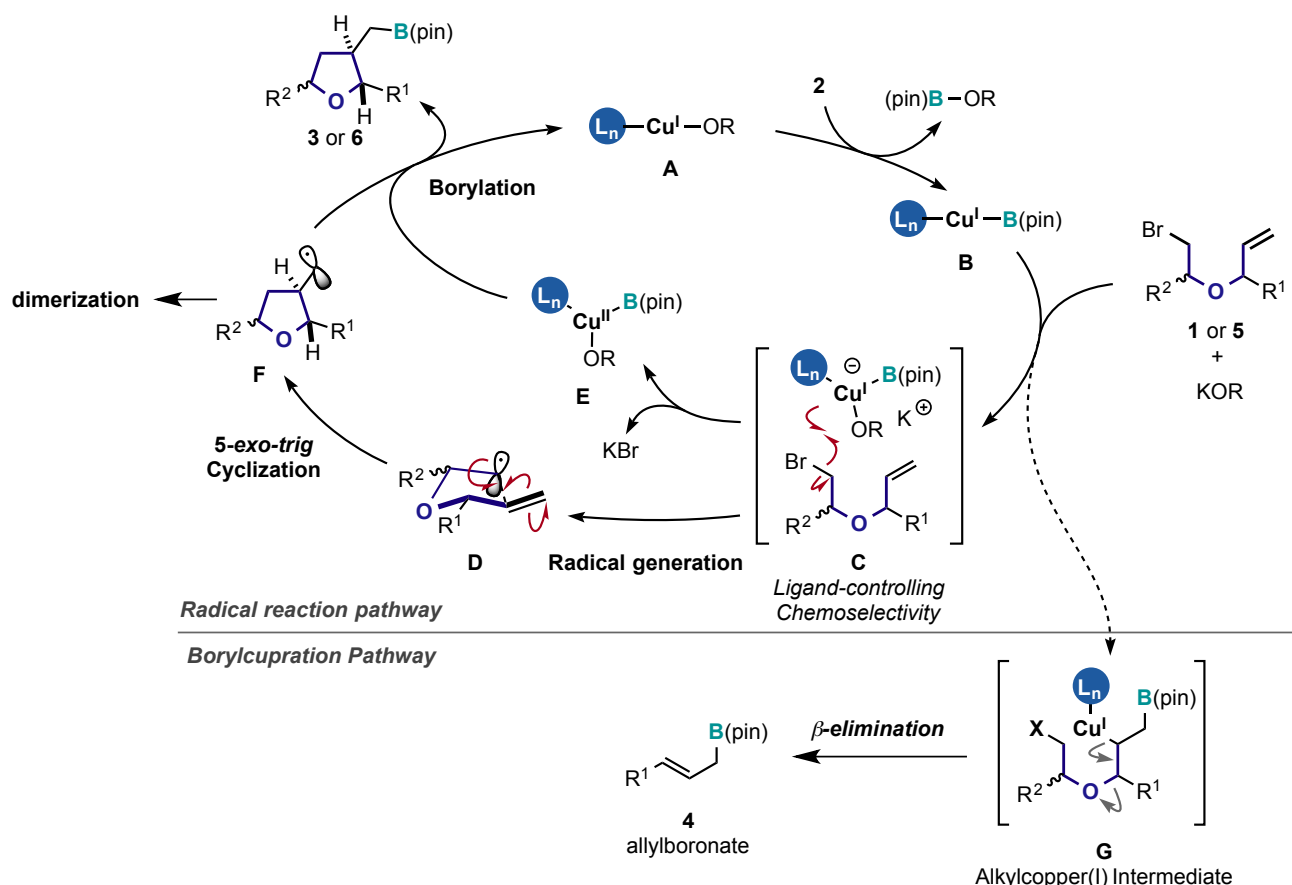


Fig. 2.5 Plausible reaction pathways for borylative radical cyclization and allylic borylation.

The borylation of the alkyl halides bearing an alkyne and alkene moiety (*E*)-**15a** was investigated (Fig. 2.6). The alkenylboronates (*Z,E*)-**16a** was obtained as a single isomer in high yield (80%), although the alkylboronate which is formed through the reaction with the alkene moiety was not observed. To understand this reaction selectivity, the borylation of the alkyne substrates bearing a bulky alkyl group **15b–15d** were carried out (Fig. 2.7). The stereoselectivity of alkenylboronates **16c–16d** depended on the bulkiness of substituents of alkynes. The substrates bearing a small substituent group such as a hydrogen atom and a methyl group provided the corresponding cyclization products with perfect selectivity ($R = H$, (*E*)-**16b**: 67%, $E/Z = >95:5$; $R = Me$, (*Z*)-**16c**: 74%, $E/Z = <5:95$). In contrast, the stereoselectivity of the alkenylboronate was decreased when the substrate bearing a bulky alkyl moiety such as *iso*-propyl group was used ($R = i\text{-Pr}$, (*Z*)-**16d**: 66%, $E/Z = 16:84$). Moreover, the borylative cyclization of the substrate containing a *tert*-butyl group proceeded to afford the product as a mixture of stereoisomers ($R = t\text{-Bu}$, (*Z*)-**16e**: $E/Z = 1:1$). Notably, this stereoselectivity of alkenylboronates also depended on a leaving group when the bulky alkyl group-substituted alkyne substrate was used (Fig. 2.8). The substrate bearing an mesylate as a leaving group **15f** improved the stereoselectivity compared that of the substrate bearing a bromide moiety **15d**.

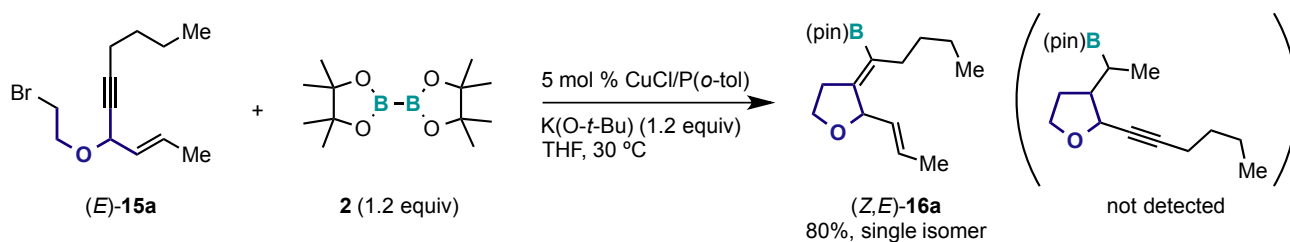


Fig. 2.6 Borylation of alkyl halide bearing alkene and alkyne moieties.

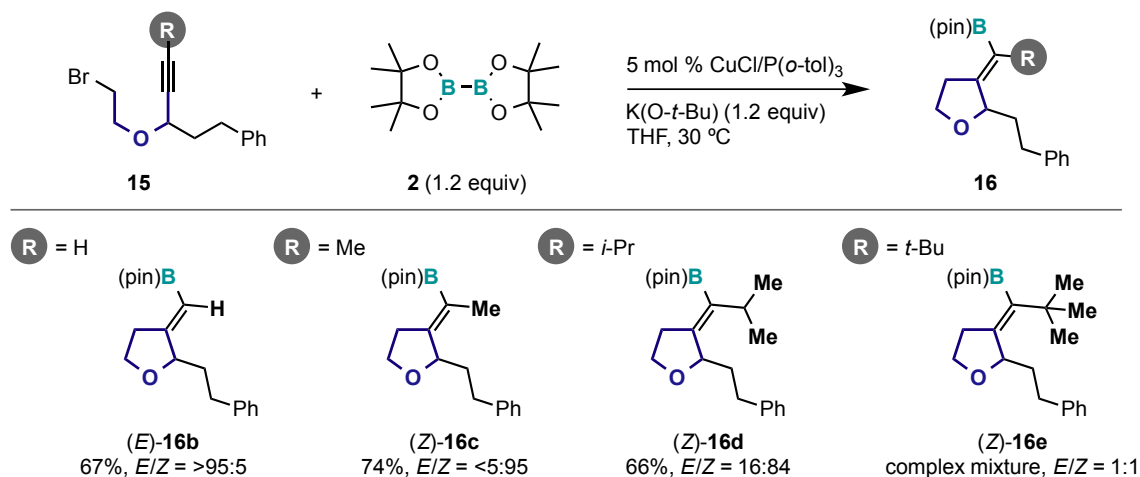


Fig. 2.7 Borylation of alkyl halide bearing alkene and alkyne moieties.

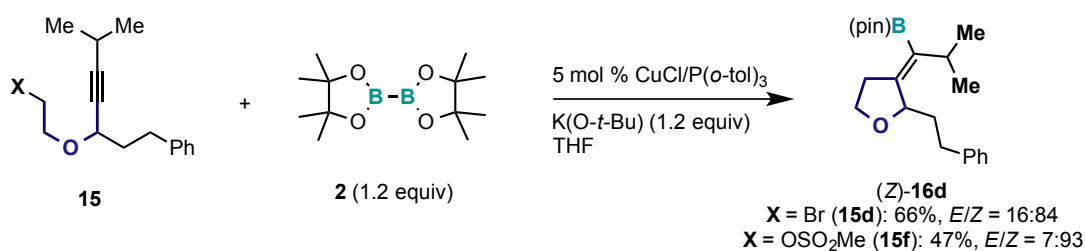


Fig. 2.8 Leaving group effect for stereoselectivity of borylative cyclization.

To confirm the reaction mechanism of the borylation of the alkyl halides bearing an alkyne moiety, the borylation of the mixture sample including an alkyl halide bearing an alkyne moiety **15g** and a simple alkyl halide **17** was conducted as a control experiment (Fig. 2.9). Only the borylative cyclization product (*E*)-**16f** was obtained in high yield although the borylsubstitution product **18** was not observed. As a summary of these mechanistic study, they suggested that the carbon–carbon triple bond strongly coordinates to the copper(I)-center to suppress the cuprate(I) which is active species for the radical reaction when the substrates bearing an alkyne moiety were used. The borylcupration from this π -complex would proceed toward non-radical mediated borylative cyclization in the case of the

alkyne substituent R^1 was small.^{42,43} However, the borylcopper(I) would form the cuprate to react with alkyl halide moiety when dissociation of the copper(I)-alkyne complex occurs due to the steric repulsion of the alkyne substituent (R^1). After generation of the radical species by the cuprate(I), 5-*exo-dig* cyclization would proceed to give the alkenyl radical intermediate. The resulting alkenyl radical intermediate would give the stereoisomer of **16** (Fig. 2.10).

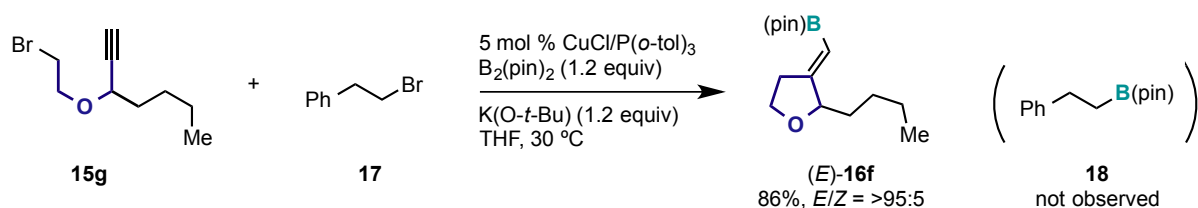


Fig. 2.9 Control experiment for investigation of chemoselectivity.

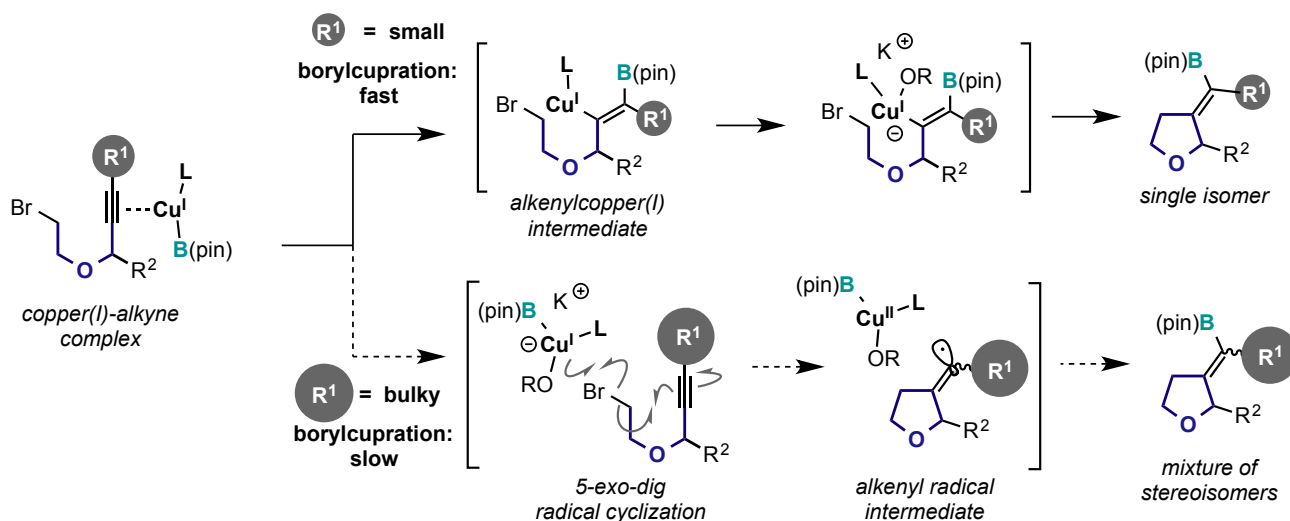


Fig. 2.10 Reaction mechanisms for non-radical and radical borylative cyclization.

2.3 Conclusion

In conclusion, we developed a copper(I)-catalyzed borylative radical cyclization of alkyl halides bearing alkene moieties. The optimized copper(I)-catalyst system achieved high chemoselectivity and gave the borylation products containing various functional groups with high stereoselectivity. Furthermore, the product could be transformed to the functionalized γ -lactones with high stereoselectivity. This borylative radical cyclization reaction can be recognized as a novel method for radical cyclization chemistry. This radical reactivity in the borylation of alkyl halides with the copper(I)-catalyst also depends on the substrate. The reaction of substrates bearing alkyne moieties proceeds through the borylcupration of carbon–carbon triple bonds prior to the radical reaction with

alkyl halide moieties. Whereas, the reaction selectivity between the borylcupration-mediated borylative cyclization and radical-mediated cyclization would be influenced by bulkiness of the substituent of the alkynes. Further development of the borylative radical cyclization including expansion of substrate scope and application of borylation product as well as the detailed investigation of the reaction mechanism is now in progress.

2.4 Experimental

2.4.1 General

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4A). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^1H : 400 MHz, ^{13}C : 100 MHz). Tetramethylsilane (^1H) and CDCl_3 (^{13}C) were employed as the external standards, respectively. CuCl (ReagentPlus® grade, 224332-25G, $\geq 99\%$) and $\text{K}(\text{O}-t\text{-Bu})/\text{THF}$ (1.0 M, 328650-50ML) were purchased from Sigma-Aldrich Co. and used as received. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with a ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and a FID detector. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University.

2.4.2 General Experimental Procedure

2.4.2.1 General procedure for borylative radical cyclization of alkene substrates.

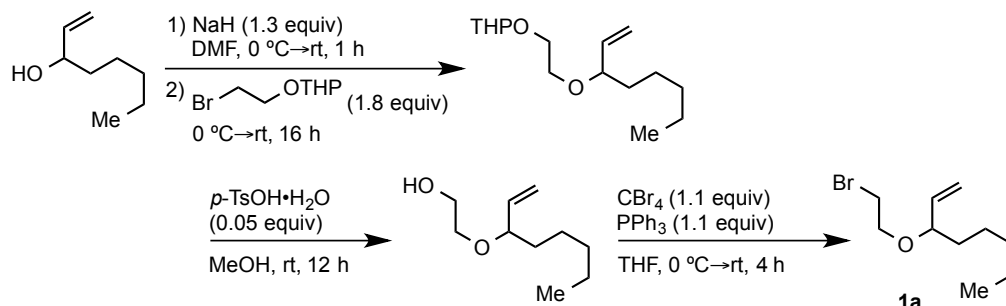
Copper chloride (2.50 mg, 0.0250 mmol) and bis(pinacolato)diboron (**2**) (152 mg, 0.600 mmol), PCy_3 (7.00 mg, 0.0250 mmol) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a Teflon-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (0.400 mL) and $\text{K}(\text{O}-t\text{-Bu})/\text{THF}$ (1.00 M, 0.600 mL, 0.600 mmol) were added in the vial through the rubber septum using a syringe. After stirring for 30 min at 0 °C, **1a** (118 mg, 0.500 mmol) was added to the mixture at 0 °C. After the reaction was complete, the reaction mixture was passed through a short silica gel (Φ : 10 mm, height of the silica-gel column: 30 mm) eluting with Et_2O . The crude material was purified by flash column chromatography (SiO_2 , Et_2O /hexane, typically 0:100–10:90) to give the corresponding borylation product **3a** as a colorless oil.

2.4.2.2 General procedure for borylative cyclization of alkyne substrates.

Copper chloride (2.5 mg, 0.025 mmol) and bis(pinacolato)diboron (**2**) (152.4 mg, 0.60 mmol), tri(*o*-tolyl)phosphine (7.6 mg, 0.025 mmol) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a teflon-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (0.4 mL) and $\text{K}(\text{O}-t\text{-Bu})/\text{THF}$ (1.0 M, 0.6 mL, 0.6 mmol) were added in the vial through the rubber septum using a syringe. After stirring for 30 min, **1a** (117.0 mg, 0.50 mmol) was added to the mixture at 30 °C. After the reaction was complete, the reaction mixture was passed through a short silica gel (Φ : 10 mm, height of the silica-gel column: ca. 30 mm) eluting with Et_2O . The crude material was purified by flash column chromatography (SiO_2 , Et_2O /hexane, typically 0:100–14:86) to give the corresponding borylation product (*E*)-**3a** as a colorless oil.

2.4.3 Substrate preparation

2.4.3.1 Preparation of 3-(2-bromoethoxy)oct-1-ene (**1a**).



In a vacuum dried 200 mL round bottomed flask, 1-octen-3-ol (898 mg, 7.00 mmol) was added to the suspension of NaH (60.0 wt%, 420 mg, 10.5 mmol) in dry DMF (14.0 mL) at 0 °C under nitrogen atmosphere. After stirred for 1 hour at room temperature, THP protected bromoethanol (2.93 g, 14.0 mmol) was added dropwise at 0 °C. Then, it was warmed to room temperature and stirred for 17 hours. The reaction mixture was quenched by H₂O at 0 °C and extracted with Et₂O three times. The combined organic layer was then dried over MgSO₄. After filtration, the solvents were removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, Et₂O/Hexane, 0:100–15:85) to obtain mixture of the corresponding THP protected allyl ether and a small amount of THP protected bromoethanol. This obtained mixture was submitted to the next reaction without further purification.

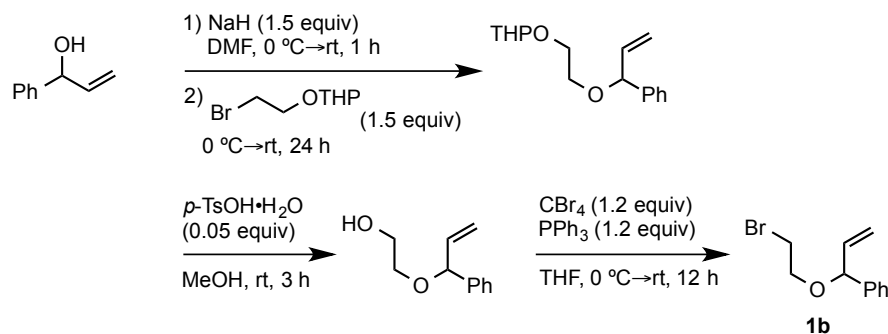
In a 100 mL round bottomed flask, *p*-TsOH·H₂O (5 mol %, 55.6 mg, 0.290 mmol) was added to the solution of THP protected allyl ether and MeOH (10.0 mL) at room temperature. After stirred for 12 hours, the reaction mixture was quenched by saturated aqueous NaHCO₃ solution and extracted with Et₂O three times. The combined organic layer was then dried over MgSO₄. After filtration, the solvents were removed by evaporation under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, EtOAc/Hexane, 0:100–25:75) to give the corresponding deprotected product (548 mg, 3.20 mmol, 45% for 2 steps) as a colorless oil.

In a vacuum dried 50 mL round bottom flask, CBr₄ (1.26 g, 3.80 mmol) and the alcohol (548 mg, 3.20 mmol) were dissolved in dry THF (7.00 mL) and mixture was cooled to 0 °C. PPh₃ (1.00 g, 3.80 mmol) was then added portionwise and the reaction mixture was stirred for 3 hours. The reaction mixture was quenched by addition of water and extracted three times with CH₂Cl₂. After evaporation of solvent, the residue was washed by hexane followed by filtration. The solvent was removed by evaporation under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, Et₂O/Hexane, 0:100–2:98) to give the corresponding bromide **1a** (614 mg, 2.60 mmol, 82%) as a colorless oil.

¹H NMR (392 MHz, CDCl₃, δ): 0.89 (t, *J* = 6.7 Hz, 3H), 1.23–1.51 (m, 6H), 1.57–1.66 (m, 2H), 3.45 (t, *J* = 6.5 Hz, 2H), 3.57–3.70 (m, 2H), 3.81 (dt, *J* = 6.3, 10.8 Hz, 1H), 5.17–5.21 (m, 2H), 5.63–5.73 (m, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 13.9 (CH₃), 22.5 (CH₂), 24.9 (CH₂), 30.6 (CH₂), 31.6 (CH₂), 35.3 (CH₂), 68.2 (CH₂), 81.9 (CH), 116.9 (CH₂), 138.8 (CH). HRMS–ESI (*m/z*): [M]⁺ calcd

for C₁₀H₁₉BrO, 234.0619; found, 234.0617.

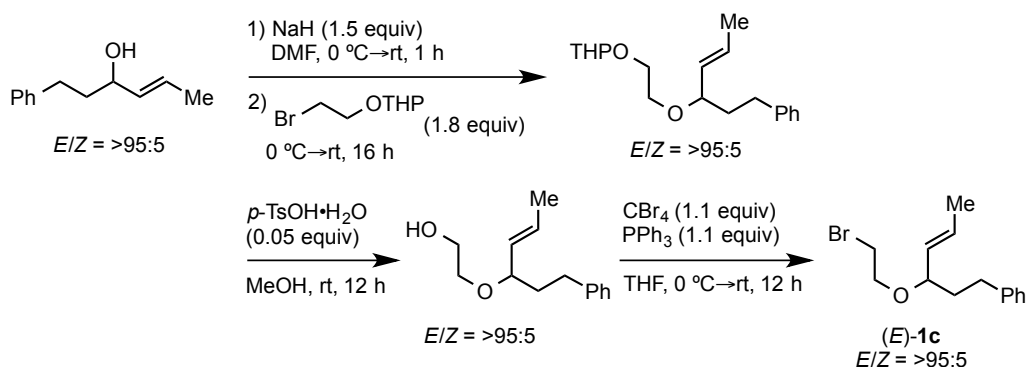
2.4.3.2 [1-(2-Bromoethoxy)allyl]benzene (**1b**).



1b was prepared from the corresponding allyl alcohol according to the procedure described above. **1b** was prepared from the corresponding allyl alcohol (3.32 g, 25.0 mmol) according to the procedure described above. The etherification product was obtained in 44% yield (2.85 g, 10.9 mmol). The deprotection of THP proceeded in 82% yield (1.58 g, 8.86 mmol). **1b** was obtained in 87% yield (1.86 g, 7.72 mmol) as a colorless oil.

¹H NMR (401 MHz, CDCl₃, δ): 3.48 (t, *J* = 6.2 Hz, 2H), 3.67–3.81 (m, 2H), 4.80 (d, *J* = 6.8 Hz, 1H), 5.22 (d, *J* = 10.4 Hz, 1H), 5.30 (d, *J* = 17.1 Hz, 1H), 5.95 (ddd, *J* = 6.8, 10.2, 17.0 Hz, 1H), 7.26–7.36 (m, 5H). ¹³C NMR (99 MHz, CDCl₃, δ): 30.5 (CH₂), 68.3 (CH₂), 83.2 (CH), 116.6 (CH₂), 126.7 (CH), 127.7 (CH), 128.4 (CH), 138.3 (CH), 140.1 (C). HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₁₁H₁₃OBrNa, 263.0042; found, 263.0043.

2.4.3.3 (*E*)-[3-(2-Bromoethoxy)hex-4-en-1-yl]benzene [(*E*)-**1c**].

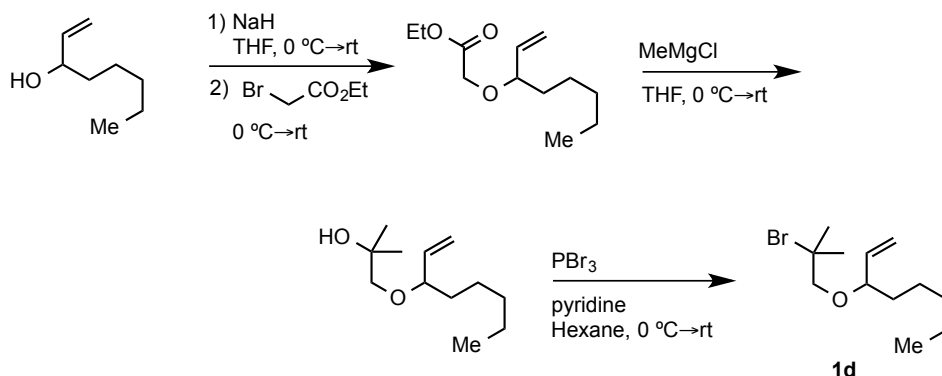


(*E*)-**1c** was prepared from the corresponding allyl alcohol (1.23 g, 7.00 mmol) according to the procedure described above. The etherification product was obtained in 43% (913 mg, 3.00 mmol). The deprotection of THP proceeded in 97% yield (643 mg, 2.92 mmol). (*E*)-**1c** was obtained in 71% yield (821 mg, 2.06 mmol) as a colorless oil.

¹H NMR (392 MHz, CDCl₃, δ): 1.71–1.80 (m, 4H), 1.89–1.99 (m, 1H), 2.63–2.76 (m, 2H), 3.45 (t, *J* = 6.3 Hz, 2H), 3.52–3.65 (m, 2H), 3.79 (dt, *J* = 6.1, 10.8 Hz, 1H), 5.31–5.38 (m, 1H), 5.65 (dq, *J* = 6.4, 15.3 Hz, 1H), 7.16–7.20 (m, 3H), 7.26–7.30 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 17.6 (CH₃), 30.8 (CH₂), 31.5 (CH₂), 37.1 (CH₂), 67.8 (CH₂), 80.3 (CH), 125.6 (CH), 128.2 (CH), 128.4 (CH),

129.0 (CH), 131.5 (CH), 141.9 (C). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{19}BrONa$, 305.0512; found, 305.0509.

2.4.3.4 Preparation of 3-(2-bromo-2-methylpropoxy)oct-1-ene (1d).



In a vacuum dried 200 mL round bottomed flask, 1-octen-3-ol (3.80 mL, 25.0 mmol) was added to the suspension of NaH (60.0 wt%, 1.10 g, 27.5 mmol) and dry THF (25.0 mL) at 0 °C under nitrogen atmosphere. After stirred for 1 hour at room temperature, ethyl bromoacetate (3.30 mL, 30.0 mmol) was added dropwise at 0 °C. Then, it was warmed to room temperature and stirred for 20 hours. The reaction mixture was quenched by H_2O at 0 °C and extracted with Et_2O three times. The combined organic layer was then dried over $MgSO_4$. After filtration, the solvents were removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , Et_2O /Hexane, 0:100–15:85). The obtained ester was submitted to the subsequent reaction without further purification.

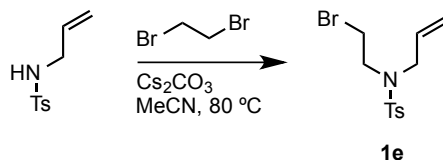
In a 200 mL round bottomed flask, a solution of $MeMgCl$ in THF (3.00 M, 16.0 mL, 48.0 mmol) was added dropwise to the solution of the ester in THF (60.0 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 hours. The resulting mixture was quenched by saturated aqueous NH_4Cl solution at 0 °C and extracted with Et_2O three times. The combined organic layer was washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed by evaporation under reduced pressure. The crude material was purified by column chromatography (SiO_2 , Et_2O /Hexane, 0:100–12:88) to obtain the corresponding tertiary alcohol (1.59 g, 32% for 2 steps) as a colorless oil.

PBr_3 (893 mg, 3.30 mmol) was added to a solution of the tertiary alcohol (1.59 g, 7.90 mmol) in hexane (16.0 mL) at 0 °C. After stirred for 2 hours at 0 °C, the reaction mixture was warmed to room temperature and stirred for 3 hours. The mixture was diluted with Et_2O and extracted with saturated aqueous $NaHCO_3$ solution. The combined organic layer was washed with brine and dried by $MgSO_4$. After filtration, the solvents were removed by evaporation under reduced pressure. The obtained crude mixture was purified by column chromatography (SiO_2 , Et_2O /Hexane, 0:100–3:97) to obtain the corresponding tertiary bromide **1d** (546 mg, 26%) as a colorless oil.

1H NMR (392 MHz, $CDCl_3$, δ): 0.88 (t, J = 6.7 Hz, 3H), 1.23–1.51 (m, 7H), 1.58–1.66 (m, 1H), 1.74 (s, 3H), 1.75 (s, 3H), 3.38 (d, J = 9.9 Hz, 1H), 3.61 (d, J = 9.9 Hz, 1H), 3.69 (q, J = 7.0 Hz, 1H),

5.15–5.20 (m, 2H), 5.69 (ddd, $J = 7.3, 10.2, 17.4$ Hz, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 14.0 (CH_3), 22.6 (CH_2), 25.0 (CH_2), 31.0 (CH_3), 31.7 (CH_2), 35.4 (CH_2), 64.1 (C), 78.4 (CH_2), 82.1 (CH), 116.5 (CH_2), 139.1 (CH). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{23}\text{BrONa}$, 285.0830; found, 285.0824.

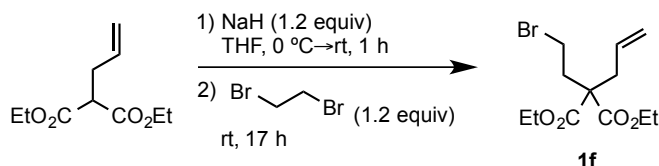
2.4.3.5 Preparation of *N*-allyl-*N*-(2-bromoethyl)-4-methylbenzenesulfonamide (**1e**).⁴⁴



To the suspension of Ts-protected allyl amine (1.06 g, 5.00 mmol) and Cs_2CO_3 (2.44 g, 7.50 mmol) in CH_3CN (20.0 mL) was added 1,2-dibromoethane (4.27 mL, 50.0 mmol) at room temperature. The reaction mixture was stirred for 17 hours at 80 °C. After filtration, the solvents were removed by evaporation under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2 , EtOAc/Hexane, 0:100–25:75) to give the corresponding bromide **1e** (1.04 g, 65%) as a colorless oil.

^1H NMR (392 MHz, CDCl_3 , δ): 2.44 (s, 3H), 3.39–3.48 (m, 4H), 3.82 (d, $J = 6.7$ Hz, 2H), 5.18–5.23 (m, 2H), 5.69 (ddt, $J = 6.4, 9.8, 17.5$ Hz, 1H), 7.33 (d, $J = 8.2$ Hz, 2H), 7.71 (dt, $J = 1.8, 8.7$ Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 21.4 (CH_3), 29.2 (CH_2), 48.7 (CH_2), 51.8 (CH_2), 119.5 (CH_2), 127.0 (CH), 129.7 (CH), 132.7 (CH), 136.0 (C), 143.6 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{16}\text{O}_2\text{NBrNaS}$, 339.9977; found, 339.9975.

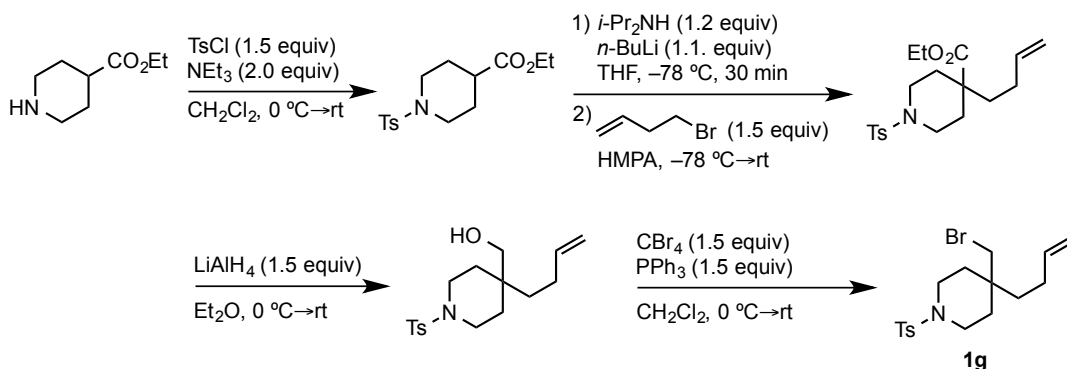
2.4.3.6 Preparation of diethyl 2-allyl-2-(2-bromoethyl)malonate (**1f**).⁴⁵



In a vacuum dried 200 mL round bottomed flask, diethyl allyl malonate (2.00 g, 10.0 mmol) was added to the suspension of NaH (60.0 wt%, 480 mg 12.0 mmol) and dry THF (12.0 mL) at 0 °C under nitrogen atmosphere. After stirred for 1 hour at room temperature, 1,2-dibromoethane (1.03 mL, 12.0 mmol) was added dropwise at room temperature. After stirred for 17 hours. The reaction mixture was quenched by H_2O at 0 °C and extracted with Et_2O three times. The combined organic layer was then dried over MgSO_4 . After filtration, the solvents were removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , Et_2O /Hexane, 0:100–9:91) to give the corresponding bromide **1f** (906 mg, 2.90 mmol, 29%) as a colorless oil.

^1H NMR (392 MHz, CDCl_3 , δ): 1.27 (t, $J = 7.0$ Hz, 6H), 2.42–2.47 (m, 2H), 2.66 (d, $J = 7.3$ Hz, 2H), 3.34–3.38 (m, 2H), 4.15–4.26 (m, 4H), 5.12–5.17 (m, 2H), 5.60–5.70 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 13.8 (CH_3), 26.8 (CH_2), 36.0 (CH_2), 37.5 (CH_2), 57.2 (C), 61.3 (CH_2), 119.4 (CH_2), 131.6 (CH), 169.9 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{12}\text{H}_{19}\text{O}_4\text{BrNa}$, 329.0359; found,

2.4.3.7 Preparation of 4-allyl-4-(2-bromoethyl)-1-tosylpiperidine (1g).



In a vacuum dried 100 mL round bottom flask, TsCl (2.86 g, 15.0 mmol) was added to the solution of amine (1.54 mL, 10.0 mmol) and NEt₃ (2.79 mL, 20.0 mmol) in CH₂Cl₂ (15.0 mL) at 0 °C. After stirred for 12 hours at room temperature, the reaction mixture was quenched by water and extracted with CH₂Cl₂ three times. The combined organic layer was dried over MgSO₄. After filtration, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, EtOAc/Hexane, 0:100–30:70) to give the Ts-protected product (2.73 g, 8.80 mmol, 88%) as a white solid.

A hexane solution of *n*-BuLi (1.55 M, 5.00 mL, 7.70 mmol) was added dropwise to a solution of *i*-Pr₂NH (1.18 mL, 8.40 mmol) in THF (5.00 mL) at 0 °C. The reaction mixture was stirred for 20 min and then cooled to –78 °C. A solution of the ester (2.32 g, 7.00 mmol) in THF (5.00 mL) was added and the reaction mixture was stirred for 30 min at –78 °C. The solution of 4-bromo-1-butene (1.07 mL, 10.5 mmol) in HMPA (1.00 mL) was then added dropwise into the reaction mixture. It was warm to room temperature and stirred for 6 hours. The reaction mixture was quenched by addition of saturated aqueous NH₄Cl solution and extracted with Et₂O three times. The combined organic layer was then dried over MgSO₄. After filtration, the solvents were removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, Et₂O/Hexane, 0:100–20:80) to obtain the corresponding alkylated ester (2.27 g, 6.20 mmol, 89%) as a white solid.

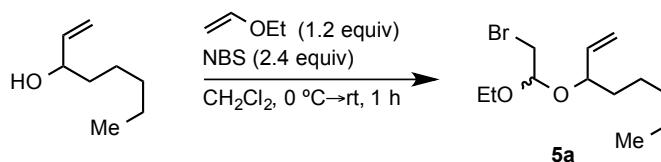
In a 200 mL round bottom flask, a solution of the alkylated ester (2.27 g, 6.20 mmol) in Et₂O (15.0 mL) was added to a slurry of LiAlH₄ (353 mg, 9.30 mmol) in Et₂O (30.0 mL) dropwise at 0 °C. After stirred for 12 hours, the reaction mixture was quenched by addition of water and stirred until a white solid was formed. The mixture was filtered to remove the white precipitation, and dried over MgSO₄. After filtration, the solvents were removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, EtOAc/Hexane, 0:100–30:70) to obtain the corresponding alcohol (1.66 g, 5.10 mmol, 83%) as a white solid.

In a vacuum dried 50 mL round bottom flask, CBr₄ (2.54 g, 7.70 mmol) and the alcohol (1.66 g, 5.10 mmol) were dissolved in dry CH₂Cl₂ (25.0 mL) and the mixture was cooled to 0 °C. PPh₃ (2.01 g, 7.70 mmol) was then added portionwise. The reaction mixture was stirred for 24 hours. The reaction

mixture was quenched by addition of water and extracted three times with CH₂Cl₂. After evaporation of solvent under reduced pressure, the residue was washed with hexane followed by filtration to remove the phosphine oxide. The solvent was removed by evaporation under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, EtOAc/Hexane, 0:100–25:75) to give the corresponding bromide **1g** (655 mg, 1.69 mmol, 33%) as a white solid.

¹H NMR (392 MHz, CDCl₃, δ): 1.39–1.43 (m, 2H), 1.65 (t, *J* = 5.8 Hz, 4H), 1.89–1.95 (m, 2H), 2.45 (s, 3H), 2.90–2.97 (m, 2H), 3.03–3.09 (m, 2H), 3.25 (s, 2H), 4.93–5.03 (m, 2H), 5.75 (ddt, *J* = 6.5, 10.2, 16.6 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 21.5 (CH₃), 26.8 (CH₂), 33.0 (CH₂), 34.5 (C), 34.6 (CH₂), 40.7 (CH₂), 41.8 (CH₂), 114.9 (CH₂), 127.6 (CH), 129.7 (CH), 133.1 (C), 137.9 (CH), 143.6 (C). HRMS–EI (*m/z*): [M+Na]⁺ calcd for C₁₇H₂₄O₂NBrNaS, 408.0603; found, 408.0604.

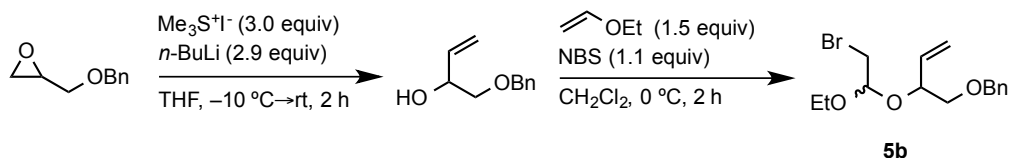
2.4.3.8 Preparation of 3-(2-bromo-1-ethoxyethoxy)oct-1-ene (**5a**).⁴⁶



Ethyl vinyl ether (2.30 mL, 24.0 mmol) was added dropwise to a solution of allyl alcohol (1.28 g, 10.0 mmol) and NBS (2.14 g, 12.0 mmol) in CH₂Cl₂ (71.0 mL) at 0 °C. After stirred for 1 hour at room temperature, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, Et₂O/Hexane, 0:100–10:90) to give the corresponding acetal product **5a** (1.63 g, 5.80 mmol, 58%) as a colorless oil. The product **5a** was obtained as a diastereomixture in term of the acetal group.

¹H NMR (392 MHz, CDCl₃, δ): 0.88 (t, *J* = 6.7 Hz, 3H), 1.18–1.67 (m, 11H), 3.31–3.74 (m, 4H), 3.89 (q, *J* = 6.9 Hz, 0.5H), 4.00 (q, *J* = 7.0 Hz, 0.5H), 4.67 (t, *J* = 6.3 Hz, 0.5H), 4.70 (t, *J* = 6.3 Hz, 0.5H), 5.15–5.23 (m, 2H), 5.62–5.83 (m, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 13.9 (CH₃), 14.9 (CH₃), 15.2 (CH₃), 22.5 (CH₂), 24.7 (CH₂), 24.8 (CH₂), 31.60 (CH₂), 31.63 (CH₂), 32.1 (CH₂), 32.4 (CH₂), 35.2 (CH₂), 35.3 (CH₂), 61.1 (CH₂), 62.4 (CH₂), 78.6 (CH), 79.5 (CH), 98.8 (CH), 100.4 (CH), 116.4 (CH₂), 117.6 (CH₂), 138.4 (CH), 139.2 (CH). HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₁₂H₂₃O₂BrNa, 301.0774; found, 301.0775.

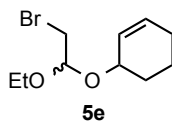
2.4.3.9 Preparation of [(2-(2-bromo-1-ethoxyethoxy)but-3-en-1-yl)oxy]methyl}benzene (**5b**).⁴⁷



In a vacuum dried 200 mL round bottom flask, a hexane solution of *n*-BuLi (1.55 M, 18.7 mL, 29.0 mmol) was added to a solution of Me₃SI (6.12 g, 30.0 mmol) in THF dropwise at $-10\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for 20 min and then cooled to $-78\text{ }^{\circ}\text{C}$. The epoxide (1.64 g, 10.0 mmol) was added and the reaction mixture was stirred for 2 hours at $-10\text{ }^{\circ}\text{C}$. The reaction mixture was quenched by addition of saturated aqueous NH₄Cl solution and extracted with Et₂O three times. The combined organic layer was then dried over MgSO₄. After filtration, the solvents were removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, Et₂O/Hexane, 0:100–28:72) to obtain the corresponding allyl alcohol (1.76 g, 9.90 mmol, 99%) as a colorless oil. **5b** was then synthesized with NBS/ethyl vinyl ether reagents according to the same procedure described for **5a** (1.52 g, 4.62 mmol, 66%, colorless oil). The product **5b** was obtained as a diastereomixture in term of the acetal group.

¹H NMR (392 MHz, CDCl₃, δ): 1.18–1.23 (m, 3H), 3.34–3.76 (m, 6H), 4.23–4.32 (m, 1H), 4.55–4.58 (m, 2H), 4.76 (t, $J = 5.6\text{ Hz}$, 0.5H), 4.83 (dd, $J = 4.0, 6.3\text{ Hz}$, 0.5H), 5.21–5.38 (m, 2H), 5.73–5.89 (m, 1H), 7.26–7.37 (m, 5H). ¹³C NMR (99 MHz, CDCl₃, δ): 14.9 (CH₃), 15.1 (CH₃), 31.9 (CH₂), 32.3 (CH₂), 61.1 (CH₂), 62.4 (CH₂), 72.7 (CH₂), 73.2 (CH₂), 73.3 (CH₂), 77.0 (CH), 77.6 (CH), 99.3 (CH), 101.5 (CH), 117.5 (CH), 118.8 (CH₂), 127.49 (CH), 127.52 (CH), 128.2 (CH), 128.3 (CH), 135.1 (CH), 135.7 (CH), 137.9 (C), 138.0 (C). HRMS–ESI (m/z): [M+Na]⁺ calcd for C₁₅H₂₁O₃BrNa, 351.0566; found, 351.0564.

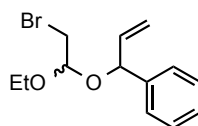
2.4.3.10 Preparation of 3-(2-bromo-1-ethoxyethoxy)cyclohex-1-ene (**5e**).⁴⁶



5e was prepared from the corresponding allyl alcohol (883 mg, 9.00 mmol) according to the procedure described above. The product **5e** was obtained in 67% yield (1.50 g, 6.03 mmol, colorless oil) as a diastereomixture in term of the acetal group.

¹H NMR (392 MHz, CDCl₃, δ): 1.24 (t, $J = 7.2\text{ Hz}$, 3H), 1.55–1.63 (m, 1H), 1.70–1.90 (m, 3H), 1.94–2.09 (m, 2H), 3.34–3.43 (m, 2H), 3.55–3.75 (m, 2H), 4.16 (br, 1H), 4.80 (t, $J = 5.6\text{ Hz}$, 1H), 5.73–5.77 (m, 1H), 5.87–5.92 (m, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 15.1 (CH₃), 18.7 (CH₂), 19.0 (CH₂), 24.9 (CH₃), 28.5 (CH₂), 29.6 (CH₂), 32.2 (CH₂), 32.3 (CH₂), 61.0 (CH₂), 61.4 (CH₂), 70.4 (CH), 70.8 (CH), 100.0 (CH), 100.6 (CH), 127.0 (CH), 127.4 (CH), 131.2 (CH), 131.4 (CH). HRMS–ESI (m/z): [M+Na]⁺ calcd for C₁₀H₁₇BrO₂Na, 271.0304; found, 271.0303.

2.4.3.11 [1-(2-Bromo-1-ethoxyethoxy)-prop-2-enyl]benzene (**5f**).¹⁷

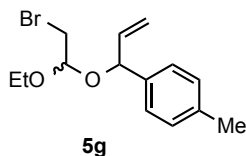


5f

5f was prepared from the corresponding allyl alcohol according to the procedure described above. The product **5f** was obtained in 64% yield (1.62 g, 8.58 mmol, colorless oil) as a diastereomixture in term of the acetal group.

¹H NMR (392 MHz, CDCl₃, δ): 1.16 (t, J = 7.3 Hz, 1.5H), 1.23 (t, J = 7.1 Hz, 1.5H), 3.33–3.41 (m, 2H), 3.46–3.64 (m, 2H), 4.65 (t, J = 5.5 Hz, 0.5H), 4.88 (t, J = 5.7 Hz, 0.5H), 5.09–5.38 (m, 3H), 5.92 (ddd, J = 7.2, 10.1, 17.2 Hz, 0.5H), 6.02 (ddd, J = 6.4, 10.5, 17.0 Hz, 0.5H), 7.28–7.34 (m, 5H). ¹³C NMR (99 MHz, CDCl₃, δ): 15.0 (CH₃), 15.1 (CH₃), 31.9 (CH₂), 32.0 (CH₂), 61.4 (CH₂), 61.7 (CH₂), 79.2 (CH₂), 79.4 (CH₂), 99.1 (CH₂), 99.3 (CH₂), 115.8 (CH₂), 117.3 (CH₂), 126.6 (CH), 127.1 (CH), 127.6 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 137.8 (CH), 138.6 (CH), 139.8 (C), 140.6 (C). HRMS–ESI (m/z): [M+Na]⁺ calcd for C₁₃H₁₇O₂BrNa, 307.0304; found, 307.0306.

2.4.3.12 1-[1-(2-Bromo-1-ethoxyethoxy)-prop-2-enyl]-4-methylbenzene (**5g**).

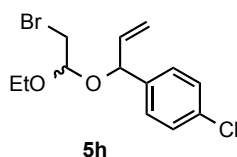


5g

5g was prepared from the corresponding allyl alcohol (2.22 g, 15.0 mmol) according to the procedure described above. The product **5g** was obtained in 52% yield (1.55 g, 7.80 mmol, colorless oil) as a diastereomixture in term of the acetal group.

¹H NMR (392 MHz, CDCl₃, δ): 1.16 (t, J = 7.0 Hz, 1.5H), 1.23 (t, J = 7.0 Hz, 1.5H), 2.34 (s, 1.5H), 2.35 (s, 1.5H), 3.31–3.40 (m, 2H), 3.43–3.66 (m, 2H), 4.63 (t, J = 5.4 Hz, 0.5H), 4.86 (t, J = 5.4 Hz, 0.5H), 5.05–5.35 (m, 3H), 5.91 (ddd, J = 7.2, 10.1, 17.3 Hz, 0.5H), 6.01 (ddd, J = 6.4, 10.4, 16.9 Hz, 0.5H), 7.15–7.18 (m, 2H), 7.22–7.27 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 15.05 (CH₃), 15.15 (CH₃), 21.06 (CH₃), 21.08 (CH₃), 31.97 (CH₂), 32.05 (CH₂), 61.4 (CH₂), 61.7 (CH₂), 79.1 (CH), 79.3 (CH), 99.1 (CH), 99.3 (CH), 115.6 (CH₂), 117.0 (CH₂), 126.6 (CH), 127.1 (CH), 129.0 (CH), 129.2 (CH), 136.8 (C), 137.4 (C), 137.6 (C), 138.0 (CH), 138.7 (CH). HRMS–ESI (m/z): [M+Na]⁺ calcd for C₁₄H₁₉O₂BrNa, 321.0461; found, 321.0460.

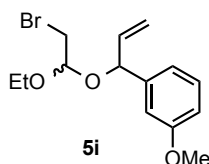
2.4.3.13 1-[1-(2-Bromo-1-ethoxyethoxy)-prop-2-enyl]-4-chlorobenzene (**5h**).



5h was prepared from the corresponding allyl alcohol (1.18 g, 7.00 mmol) according to the procedure described above. The product **5h** was obtained in 51% yield (761 mg, 3.57 mmol, colorless oil) as a diastereomixture in term of the acetal group.

^1H NMR (401 MHz, CDCl_3 , δ): 1.17 (t, $J = 7.0$ Hz, 1.5H), 1.22 (t, $J = 7.2$ Hz, 1.5H), 3.33–3.41 (m, 2H), 3.47–3.64 (m, 2H), 4.63 (t, $J = 5.2$ Hz, 0.5H), 4.87 (t, $J = 5.4$ Hz, 0.5H), 5.07–5.11 (m, 1H), 5.18–5.37 (m, 2H), 5.86 (ddd, $J = 7.2, 10.2, 17.2$ Hz, 0.5H), 5.97 (ddd, $J = 6.4, 10.4, 16.8$ Hz, 0.5H), 7.29–7.35 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3 , δ): 15.08 (CH_3), 15.11 (CH_3), 31.8 (CH_2), 31.9 (CH_2), 61.6 (CH_2), 61.7 (CH_2), 78.4 (CH), 78.6 (CH), 99.2 (CH), 99.4 (CH), 116.2 (CH_2), 117.9 (CH_2), 128.0 (CH), 128.47 (CH), 128.52 (CH), 128.6 (CH), 133.3 (C), 133.6 (C), 137.4 (CH), 138.2 (CH), 138.4 (C), 139.2 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{BrClNa}$, 340.9914; found, 340.9917.

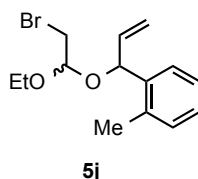
2.4.3.14 1-[1-(2-Bromo-1-ethoxyethoxy)-prop-2-enyl]-3-methoxybenzene (**5i**).



5i was prepared from the corresponding allyl alcohol (2.45 g, 15.0 mmol) according to the procedure described above. The product **5i** was obtained in 48% yield (1.52 g, 7.20 mmol, colorless oil) as a diastereomixture in term of the acetal group.

^1H NMR (392 MHz, CDCl_3 , δ): 1.17 (t, $J = 7.0$ Hz, 1.5H), 1.23 (t, $J = 7.2$ Hz, 1.5H), 3.33–3.41 (m, 2H), 3.45–3.66 (m, 2H), 3.81 (s, 1.5H), 3.82 (s, 1.5H), 4.66 (t, $J = 5.4$ Hz, 0.5H), 4.88 (t, $J = 5.4$ Hz, 0.5H), 5.08 (dd, $J = 6.5, 12.3$, 1H), 5.16–5.38 (m, 2H), 5.91 (ddd, $J = 7.2, 10.1, 17.3$ Hz, 0.5H), 6.00 (ddd, $J = 6.3, 10.6, 17.1$ Hz, 0.5H), 6.81–6.86 (m, 1H), 6.91–6.96 (m, 2H), 7.24–7.29 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 15.1 (CH_3), 15.2 (CH_3), 32.0 (CH_2), 32.1 (CH_2), 55.18 (CH_3), 55.21 (CH_3), 61.5 (CH_2), 61.9 (CH_2), 79.1 (CH), 79.3 (CH), 99.3 (CH), 99.4 (CH), 112.2 (CH_2), 112.4 (CH_2), 113.1 (CH), 113.6 (CH), 116.0 (CH_2), 117.4 (CH_2), 119.0 (CH), 119.5 (CH), 129.4 (CH), 129.5 (CH), 137.8 (CH), 138.5 (CH), 141.5 (C), 142.3 (C), 159.6 (C), 159.8 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{O}_3\text{BrNa}$, 337.0410; found, 337.0411.

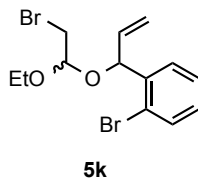
2.4.3.15 1-[1-(2-Bromo-1-ethoxyethoxy)-prop-2-enyl]-2-methylbenzene (**5j**).



5j was prepared from the corresponding allyl alcohol (2.25 g, 15.0 mmol) according to the procedure described above. The product **5j** was obtained in 75% yield (2.24 g, 11.3 mmol, colorless oil) as a diastereomixture in term of the acetal group.

^1H NMR (401 MHz, CDCl_3 , δ): 1.15 (t, $J = 7.0$ Hz, 1.5H), 1.23 (t, $J = 7.2$ Hz, 1.5H), 2.34 (s, 1.5H), 2.35 (s, 1.5H), 3.34–3.43 (m, 2H), 3.453.63 (m, 2H), 4.62 (t, $J = 5.6$ Hz, 0.5H), 4.89 (t, $J = 5.6$ Hz, 0.5H), 5.14–5.37 (m, 3H), 5.88 (ddd, $J = 6.9, 10.5, 17.3$ Hz, 0.5H), 5.99 (ddd, $J = 6.1, 10.5, 16.7$ Hz, 0.5H), 7.12–7.23 (m, 3H), 7.41–7.47 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 15.0 (CH_3), 15.2 (CH_3), 19.1 (CH_3), 19.2 (CH_3), 31.8 (CH_2), 32.1 (CH_2), 61.4 (CH_2), 61.6 (CH_2), 75.9 (CH), 76.1 (CH), 99.0 (CH), 99.4 (CH), 115.8 (CH_2), 117.0 (CH_2), 126.1 (CH), 126.2 (CH), 126.7 (CH), 127.1 (CH), 127.5 (CH), 127.6 (CH), 130.3 (CH), 130.4 (CH), 134.8 (C), 135.6 (C), 137.1 (CH), 137.6 (C), 137.7 (C), 138.6 (CH). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{19}\text{O}_2\text{BrNa}$, 321.0461; found, 321.0462.

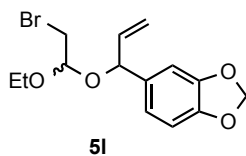
2.4.3.16 1-Bromo-2-[1-(2-bromo-1-ethoxyethoxy)-prop-2-enyl]benzene (**5k**).



5k was prepared from the corresponding allyl alcohol (3.11 g, 15.0 mmol) according to the procedure described above. The product **5k** was obtained in 51% yield (1.88 g, 5.2 mmol, colorless oil) as a diastereomixture in term of the acetal group.

^1H NMR (392 MHz, CDCl_3 , δ): 1.14 (t, $J = 7.0$ Hz, 1.5H), 1.24 (t, $J = 7.2$ Hz, 1.5H), 3.38 (t, $J = 5.4$ Hz, 2H), 3.45–3.68 (m, 2H), 4.61 (t, $J = 5.4$ Hz, 0.5H), 4.89 (t, $J = 5.4$ Hz, 0.5H), 5.17–5.44 (m, 2H), 5.54 (d, $J = 6.7$ Hz, 0.5H), 5.63 (d, $J = 5.4$ Hz, 0.5H), 5.85 (ddd, $J = 6.7, 10.3, 17.3$ Hz, 0.5H), 5.95 (ddd, $J = 5.8, 10.3, 17.1$ Hz, 0.5H), 7.12–7.18 (m, 1H), 7.32–7.37 (m, 1H), 7.51–7.57 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 15.0 (CH_3), 15.1 (CH_3), 31.9 (CH_2), 32.0 (CH_2), 62.1 (CH_2), 62.8 (CH_2), 76.8 (CH), 77.3 (CH), 99.7 (CH), 99.9 (CH), 116.2 (CH_2), 117.2 (CH_2), 122.0 (C), 122.9 (C), 127.7 (CH), 127.8 (CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 129.2 (CH), 132.4 (CH), 132.5 (CH), 136.4 (CH), 136.8 (CH), 139.1 (C), 140.0 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{Br}_2\text{Na}$, 384.9409; found, 384.9413.

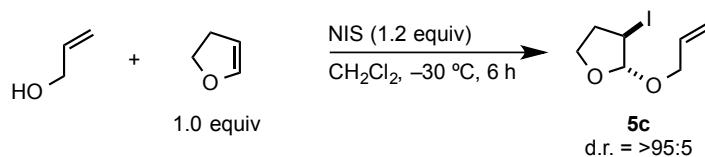
2.4.3.17 5-[1-(2-Bromo-1-ethoxyethoxy)-prop-2-enyl]benzo[d][1,3]dioxole (**5l**).



5l was prepared from the corresponding allyl alcohol (2.68 g, 15.0 mmol) according to the procedure described above. The product **5l** was obtained in 24% yield (793 mg, 3.6 mmol, colorless oil) as a diastereomixture in term of the acetal group.

^1H NMR (392 MHz, CDCl_3 , δ): 1.18 (t, $J = 7.0$ Hz, 1.5H), 1.23 (t, $J = 7.2$ Hz, 1.5H), 3.33–3.40 (m, 2H), 3.45–3.65 (m, 2H), 4.64 (t, $J = 5.6$ Hz, 0.5H), 4.85 (t, $J = 5.4$ Hz, 0.5H), 5.02 (dd, $J = 6.5$, 11.4, 1H), 5.15–5.35 (m, 2H), 5.84–6.02 (m, 3H), 6.76–6.88 (m, 3H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 14.9 (CH_3), 15.0 (CH_3), 31.8 (CH_2), 31.9 (CH_2), 61.3 (CH_2), 61.4 (CH_2), 78.7 (CH), 78.9 (CH), 98.7 (CH), 99.2 (CH), 100.8 (CH_2), 100.9 (CH_2), 107.1 (CH), 107.3 (CH), 107.8 (CH), 115.4 (CH_2), 116.9 (CH_2), 120.0 (CH), 120.7 (CH), 133.6 (C), 134.5 (C), 137.7 (CH), 138.5 (CH), 146.9 (C), 147.1 (C), 147.5 (C), 147.7 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{14}\text{H}_{17}\text{O}_4\text{BrNa}$, 351.0202; found, 351.0204.

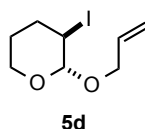
2.4.3.18 Preparation of 2-allyloxy-3-iodotetrahydrofuran (**5c**).¹⁷



To a solution of allyl alcohol (544 mg, 8.00 mmol) and enol ether (605 mg, 8.00 mmol) in CH_2Cl_2 (8.00 mL) was added NIS (2.16 g, 9.60 mmol) portionwise at $-30\text{ }^\circ\text{C}$. After stirred for 6 hours, the reaction mixture was quenched by saturated aqueous NaHCO_3 solution and extracted with CH_2Cl_2 three times and the combined organic layer was washed with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution and brine. The organic layer was dried over MgSO_4 . After filtration, the solvent was removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , EtOAc/Hexane , 0:100–5:95) to give the corresponding acetal product **5c** (445 mg, 1.75 mmol, 22%) as a colorless oil. The product **5c** was obtained as a single isomer (>95:5).

^1H NMR (392 MHz, CDCl_3 , δ): 2.17–2.24 (m, 1H), 2.59–2.69 (m, 1H), 3.95–4.20 (m, 5H), 5.16–5.31 (m, 2H), 5.39 (s, 1H), 5.84–5.93 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 24.6 (CH), 35.5 (CH_2), 66.9 (CH_2), 67.9 (CH_2), 109.6 (CH), 117.2 (CH_2), 134.0 (CH). HRMS–APCI (m/z): $[\text{M}-\text{OC}_3\text{H}_5(\text{allyl})]^+$ calcd for $\text{C}_4\text{H}_6\text{OI}$, 196.9458; found, 196.9461.

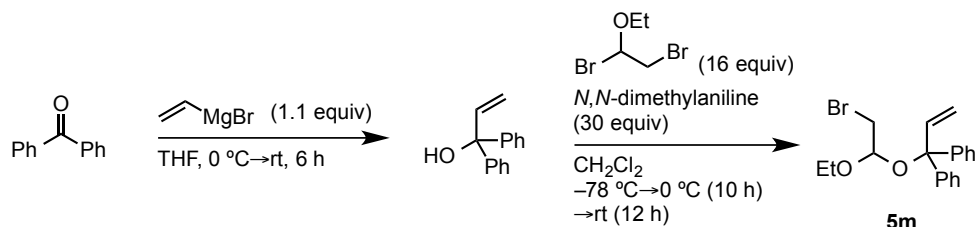
2.4.3.19 2-Allyloxy3-iodotetrahydro-2H-pyran (**5d**).¹²



5d was prepared from the corresponding allyl alcohol (581 mg, 10.0 mmol) and enol ether (1.01 g, 12.0 mmol) according to the procedure described above. The product **5d** was obtained in 82% yield (2.20 g, 8.20 mmol, colorless oil) as a single isomer (>95:5).

¹H NMR (392 MHz, CDCl₃, δ): 1.54–1.63 (m, 1H), 1.73–1.82 (m, 1H), 1.99–2.07 (m, 1H), 2.34–2.43 (m, 1H), 3.59 (ddd, *J* = 3.6, 7.4, 11.2 Hz, 1H), 3.97–4.14 (m, 3H), 4.24–4.29 (m, 1H), 4.69 (d, *J* = 5.4 Hz, 1H) 5.20–5.36 (m, 2H), 5.89–5.99 (m, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 25.3 (CH₂), 29.1 (CH), 32.5 (CH₂), 63.3 (CH₂), 68.7 (CH₂), 101.3 (CH₂), 117.3 (CH), 133.7 (CH₂). HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₈H₁₃O₂INa, 290.9852; found, 290.9854.

2.4.3.20 Preparation of [1-(2-bromo-1-ethoxyethoxy)prop-2-ene-1,1-diyl]dibenzene (**5m**).⁴⁸



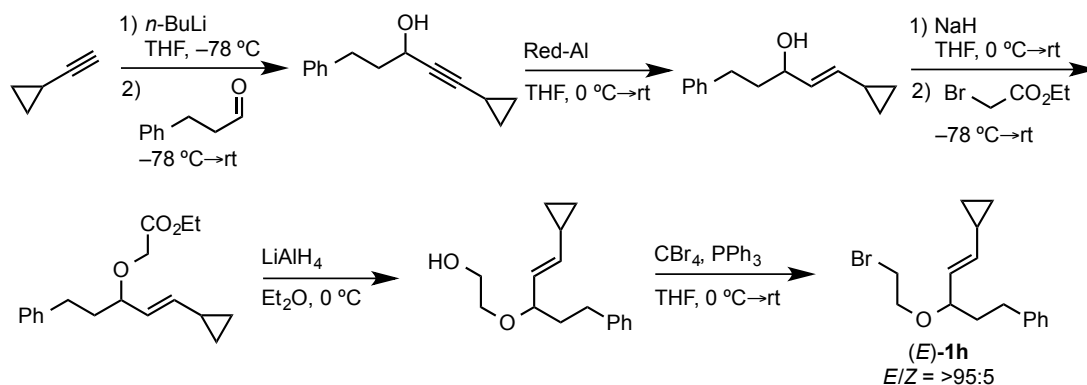
In the 200 mL round bottom flask, vinyl magnesium bromide (1.00 M, 11.0 mL, 11.0 mmol) was added to the solution of benzophenone (1.82 g, 10.0 mmol) in THF (50.0 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 6 hours. The reaction mixture was quenched by saturated aqueous NH₄Cl solution and extracted with EtOAc three times. The combined organic layer was dried over MgSO₄. After filtration, solvents were removed by evaporation under reduced pressure. The crude material was purified by flash chromatography (SiO₂, Et₂O/Hexane, 0:100–20:80) to give the corresponding alcohol (2.00 g, 9.50 mmol, 95%) as a colorless oil.

In a round bottom flask, Br₂ (3.84 mL, 75.0 mmol) was dissolved in dry CH₂Cl₂ (33.3 mL) at –78 °C. Ethyl vinyl ether (7.70 mL, 80.0 mmol) was slowly added to the resulting solution over a 30 min period, and the mixture was stirred for 15 min at –78 °C then for 10 min at room temperature. The reaction mixture was cooled to –78 °C and transferred via cannula to another round bottom flask where the solution of allyl alcohol (1.00 g, 5.00 mmol) and *N,N*-dimethyl aniline (19.0 mL) in dry CH₂Cl₂ (67.0 mL) had been prepared. The resulting mixture was warmed to 0 °C and stirred for 10 hours. Then, the mixture was warmed to room temperature and further stirred for 12 hours. The reaction mixture was quenched by 1.0 M aqueous HCl solution and extracted with 1 M aqueous HCl solution 6 times, water and brine. The organic layer was dried over MgSO₄. After filtration, solvents were removed by evaporation under reduced pressure. The crude product was purified flash column chromatography (SiO₂, Et₂O/Hexane, 0:100–15:85) to give the product **5m** (1.31 g, 3.62 mmol, 72%) as a colorless oil.

¹H NMR (392 MHz, CDCl₃, δ): 1.06 (t, *J* = 7.0 Hz, 3H), 3.30–3.37 (m, 2H), 3.42–3.50 (m, 2H),

4.80 (dd, $J = 4.3, 6.5$ Hz, 1H), 4.92 (dd, $J = 1.4, 17.0$ Hz, 1H), 5.40 (dd, $J = 1.4, 10.8$ Hz, 1H), 6.67 (dd, $J = 10.8, 17.0$ Hz, 1H), 7.22–7.39 (m, 10H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 14.8 (CH_3), 32.4 (CH_2), 59.7 (CH_2), 85.2 (C), 96.5 (CH), 118.5 (CH_2), 127.2 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 140.7 (CH), 143.1 (C), 143.8 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{21}\text{O}_2\text{BrNa}$, 383.0617; found, 383.0619.

2.4.3.21 Preparation of 3-(2-bromo-1-ethoxyethoxy)cyclohex-1-ene [(*E*)-1h].



In a vacuum dried 200 mL round bottomed flask, cyclopropyl alkyne (2.54 mL, 30.0 mmol) was dissolved in dry THF (60.0 mL), and was cooled to -78 °C under nitrogen atmosphere. A hexane solution of *n*-BuLi (1.55 M, 19.4 mL, 30.0 mmol) was then added dropwise slowly. After stirred for 1 hour, aldehyde (3.05 mL, 20.0 mmol) was added dropwise at -78 °C. Then, it was warmed to room temperature and stirred for 20 hours. The reaction mixture was quenched by H_2O at 0 °C and extracted with Et_2O three times. The combined organic layer was then dried over MgSO_4 . After filtration, the solvents were removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , EtOAc/Hexane , 0:100–25:75) to obtain the corresponding propargyl alcohol (3.72 g, 22.2 mmol) as a colorless oil.

The propargyl alcohol (1.68 g, 8.70 mmol) was dissolved in dry THF (50.0 mL), and was cooled to 0 °C under nitrogen atmosphere. A toluene solution of Red-Al (1.00 M, 4.70 mL) was added dropwise, and then the reaction mixture was warmed to room temperature. After stirred for 3 hours, the reaction mixture was quenched by saturated aqueous Rochelle salt solution and extracted with Et_2O three times. The combined organic layer was then dried over MgSO_4 . After filtration, the solvents were removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , $\text{Et}_2\text{O/Hexane}$, 0:100–25:75) to give the corresponding allyl alcohol (1.40 g, 6.90 mmol, 83%) as a colorless oil.

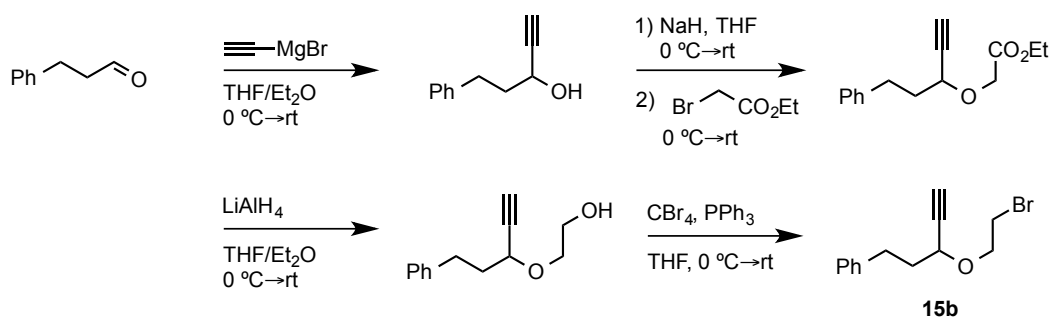
In a vacuum dried 200 mL round bottomed flask, the allyl alcohol (2.12 g, 10.5 mmol) was added to the suspension of NaH (60 wt%, 462 mg, 11.6 mmol) and dry THF (7.00 mL) at 0 °C under nitrogen atmosphere. After stirred for 1 hour at room temperature, ethyl bromoacetate (1.40 mL, 12.6 mmol) was added dropwise at 0 °C. Then, it was warmed to room temperature and stirred for 20 hours. The reaction mixture was quenched by H_2O at 0 °C and extracted with Et_2O three times. The combined

organic layer was then dried over MgSO_4 . After filtration, the solvents were removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , Et_2O /Hexane, 0:100–12:88) to obtain the corresponding ester (1.34 g, 4.60 mmol, 44%) as a colorless oil.

To a slurry of LiAlH_4 (262 mg, 6.90 mmol) in Et_2O (20.0 mL) was added a solution of the ester (1.34 g, 4.60 mmol) in Et_2O (10.0 mL) dropwise at 0 °C. After stirred for 2 hours, the reaction mixture was quenched by addition of water and stirred until a white solid was formed. The mixture was filtered and dried over MgSO_4 . After filtration, the solvents were removed by evaporation under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , EtOAc /Hexane, 0:100–25:75) to obtain the corresponding alcohol (639 mg, 2.59 mmol, 56%) as a colorless oil. (*E*)-**1h** was then synthesized by bromination with $\text{CBr}_4/\text{PPh}_3$ reagents according to the same procedure described for **1a** (704 mg, 2.30 mmol, 87%, colorless oil).

^1H NMR (392 MHz, CDCl_3 , δ): 0.36–0.39 (m, 2H), 0.71–0.75 (m, 2H), 1.35–1.44 (m, 1H), 1.72–1.81 (m, 1H), 1.90–1.99 (m, 1H), 2.64–2.77 (m, 2H), 3.45 (t, $J = 6.1$ Hz, 2H), 3.52–3.63 (m, 2H), 3.81 (dt, $J = 6.1, 10.8$ Hz, 1H), 5.14 (dd, $J = 9.0, 15.2$ Hz, 1H), 5.39 (dd, $J = 8.1, 15.3$ Hz, 1H), 7.16–7.20 (m, 3H), 7.25–7.29 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 6.8 (CH_2), 6.9 (CH_2), 13.3 (CH), 30.9 (CH_2), 31.5 (CH_2), 37.2 (CH_2), 67.8 (CH_2), 80.2 (CH), 125.6 (CH), 127.6 (CH), 128.2 (CH), 128.4 (CH), 138.1 (CH), 141.9 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{21}\text{OBrNa}$, 331.0668; found, 331.0666.

2.4.3.22 [3-(2-Bromoethoxy)pent-4-yn-1-yl]benzene (**15b**).



In a vacuum dried 200 mL two-neck round-bottomed flask, 3-phenylpropionaldehyde (2.68 g, 20.0 mmol) was dissolved in dry Et_2O (56 mL), and the mixture was cooled to 0 °C under a nitrogen atmosphere. Ethynylmagnesium bromide solution in THF (0.5 M, 48.0 mL, 24.0 mmol) was added dropwise to the mixture, and the mixture was warmed to room temperature. After the mixture was stirred for 12 h, the reaction mixture was quenched by saturated NH_4Cl aq. and extracted with Et_2O three times. The combined organic layer was then dried over MgSO_4 . After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain the corresponding propargyl alcohol (1.95 g, 12.2 mmol, 61%) as a colorless oil.

In a vacuum dried 50 mL two-neck round-bottomed flask, the propargyl alcohol (1.95 g, 12.2 mmol) was added dropwise to a suspension of NaH (60% in mineral oil, washed with hexane three

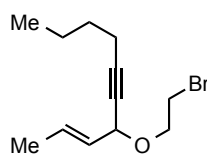
times under a nitrogen atmosphere, 0.54 g, 13.4 mmol) in THF (7.4 mL) at 0 °C under a nitrogen atmosphere. Then, the mixture was warmed to room temperature and stirred for 1 h. After the mixture was cooled to 0 °C, ethyl bromoacetate (2.45 g, 14.6 mmol) was added dropwise to the mixture. Then, the mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was quenched by saturated NH₄Cl aq. and extracted with Et₂O three times. The combined organic layer was then dried over MgSO₄. After filtration, the solvents were removed by evaporation. The corresponding crude ether was used to the next reaction without further purification.

In a vacuum dried 300 mL two-neck round-bottomed flask, the solution of the crude product in THF (30 mL) was added dropwise to a suspension of LiAlH₄ (0.51 g, 13.4 mmol) in THF (60 mL) at –30 °C under a nitrogen atmosphere. After the mixture was stirred for 16 h, the reaction mixture was quenched by MeOH (1.4 mL), then NaOH aq. (1 M, 0.5 mL) and H₂O (1.5 mL). After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain the corresponding reduction product (2.22 g, 10.9 mmol, 89%) as a colorless oil.

In a vacuum dried 100 mL two-neck round-bottomed flask, the reduction product (2.22 g, 10.9 mmol) and carbon tetrabromide (3.62 g, 10.9 mmol) were dissolved in dry THF (22 mL), and the mixture was cooled to 0 °C under a nitrogen atmosphere. Triphenylphosphine (2.85 g, 10.9 mmol) was added to the mixture, and the mixture was warmed to room temperature. After the mixture was stirred for 10 h, the solvents were removed by evaporation. The crude product was purified by flash column chromatography and bulb-to-bulb distillation to obtain the corresponding bromide **15b** (2.33 g, 8.73 mmol, 80%) as a colorless oil.

¹H NMR (392 MHz, CDCl₃, δ): 1.98–2.16 (m, 2H), 2.48 (d, *J* = 2.4 Hz, 1H), 2.81 (t, *J* = 7.6 Hz, 2H), 3.45–3.54 (m, 2H), 3.71 (dt, *J* = 6.5, 10.8 Hz, 1H), 4.02–4.08 (m, 2H), 7.18–7.22 (m, 3H), 7.27–7.31 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 30.2 (CH₂), 31.1 (CH₂), 36.9 (CH₂), 68.45 (CH₂), 68.51 (CH), 74.4 (C), 82.1 (CH), 125.9 (CH), 128.3 (CH), 128.4 (CH), 140.9 (C). HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₃H₁₅BrONa, 289.01985; found, 289.01991.

2.4.3.23 (*E*)-4-(2-Bromoethoxy)dec-2-en-5-yne [(*E*)-**15a**].



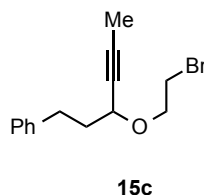
(*E*)-**15a**

(*E*)-**15a** was prepared as a colorless oil from the corresponding propargyl alcohol according to the procedure described above.

¹H NMR (392 MHz, CDCl₃, δ): 0.92 (t, *J* = 7.2 Hz, 3H), 1.37–1.56 (m, 4H), 1.75 (d, *J* = 6.7 Hz, 3H), 2.26 (dt, *J* = 1.9, 7.1 Hz, 2H), 3.48 (dt, *J* = 1.1, 6.7 Hz, 2H), 3.75 (dt, *J* = 6.6, 10.7 Hz, 1H), 3.90 (dt, *J* = 6.5, 10.4 Hz, 1H), 4.62 (d, *J* = 8.1 Hz, 1H), 5.52–5.59 (m, 1H), 5.87–5.96 (m, 1H). ¹³C NMR

(99 MHz, CDCl₃, δ): 13.5 (CH₃), 17.4 (CH₃), 18.3 (CH₂), 21.9 (CH₂), 30.2 (CH₂), 30.6 (CH₂), 67.2 (CH₂), 70.3 (CH), 76.8 (C), 88.1 (C), 128.3 (CH), 129.9 (CH). HRMS-EI (m/z): [M]⁺ calcd for C₁₂H₁₉OBr, 258.06193; found, 258.06186.

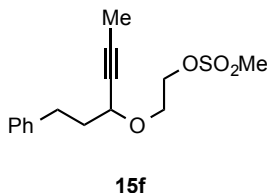
2.4.3.24 [3-(2-Bromoethoxy)pent-4-yn-1-yl]benzene (15c).



15c was prepared as a colorless oil from the corresponding propargyl alcohol according to the procedure described above.

¹H NMR (392 MHz, CDCl₃, δ): 1.87 (d, J = 2.4 Hz, 3H), 1.93–2.10 (m, 2H), 2.79 (t, J = 7.4 Hz, 2H), 3.45–3.53 (m, 2H), 3.68 (dt, J = 6.5, 11.1 Hz, 1H), 3.98–4.05 (m, 2H), 7.16–7.22 (m, 3H), 7.26–7.30 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 3.5 (CH₃), 30.4 (CH₂), 31.3 (CH₂), 37.3 (CH₂), 68.3 (CH₂), 69.1 (CH), 77.6 (C), 82.4 (C), 125.8 (CH), 128.3 (CH), 128.4 (CH), 141.3 (C). HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₄H₁₇BrONa, 303.03550; found, 303.03567.

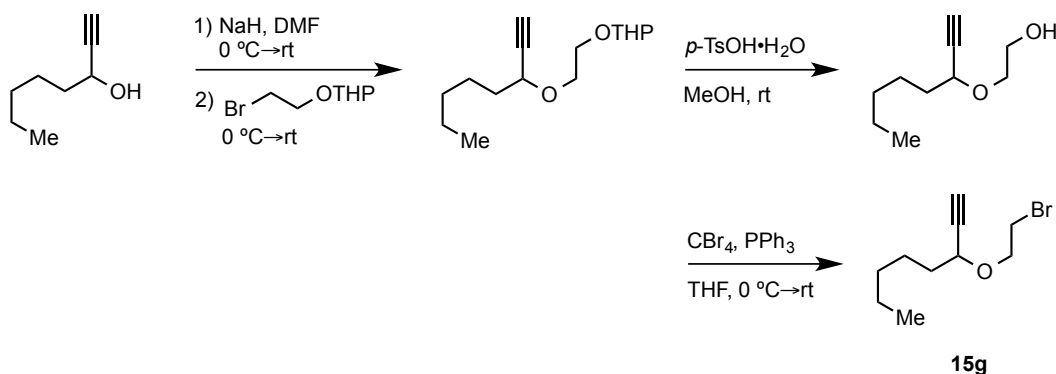
2.4.3.25 2-[(6-Methyl-1-phenylhept-4-yn-3-yl)oxy]ethyl methanesulfonate (15f).



15f was prepared as a colorless oil from the corresponding primary alcohol according to the procedure described above.

¹H NMR (392 MHz, CDCl₃, δ): 1.18 (d, J = 7.2 Hz, 6H), 1.90–2.08 (m, 2H), 2.55–2.66 (m, 1H), 2.77 (t, J = 7.9 Hz, 2H), 3.06 (s, 3H), 3.60–3.67 (m, 1H), 3.97 (ddd, J = 3.6, 5.2, 11.5 Hz, 1H), 4.05 (dt, J = 1.8, 6.5 Hz, 1H), 4.36–4.45 (m, 2H), 7.18–7.21 (m, 3H), 7.26–7.31 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 20.3 (CH), 22.8 (CH₃), 31.2 (CH₂), 37.2 (CH₂), 37.4 (CH₃), 65.9 (CH₂), 69.20 (CH), 69.24 (CH₂), 77.0 (C), 92.8 (C), 125.7 (CH), 128.2 (CH), 128.3 (CH), 141.1 (C). HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₇H₂₄O₄SNa, 347.12875; found, 347.12869.

2.4.3.26 Preparation of 3-(2-bromoethoxy)oct-1-yne (15g).



In a vacuum dried 200 mL two-neck round-bottomed flask, oct-1-yn-3-ol (3.79 g, 30.0 mmol) was added dropwise to a suspension of NaH (60% in mineral oil, washed with hexane three times under a nitrogen atmosphere, 1.58 g, 39.0 mmol) in DMF (60 mL) at 0 °C under a nitrogen atmosphere. Then, it was warmed to room temperature and stirred for 1 h. After the mixture was cooled to 0 °C, THP-protected bromoethanol (9.41 g, 45.0 mmol) was added dropwise. Then, the mixture was warmed to room temperature and stirred for 6 h. The reaction mixture was quenched by H₂O and extracted with EtOAc/Hexane (1:4) three times. The combined organic layer was washed with brine and dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain the corresponding ether (6.40 g, 25.2 mmol, 84%) as a colorless oil.

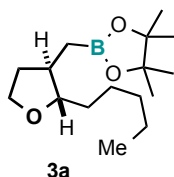
In an open 100 mL round-bottomed flask, the ether (6.40 g, 25.2 mmol) and *p*-toluenesulfonic acid monohydrate (0.24 g, 1.30 mmol) were dissolved in dry MeOH (50 mL) at room temperature under air. After the mixture was stirred for 2 h, the reaction mixture was quenched by saturated NaHCO₃ aq. and extracted with Et₂O three times. The combined organic layer was then dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain the corresponding alcohol (2.00 g, 11.8 mmol, 47%) as a colorless oil.

In a vacuum dried 100 mL two-neck round-bottomed flask, 2-(oct-1-yn-3-yloxy)ethan-1-ol (2.00 g, 11.8 mmol) and carbon tetrabromide (4.30 g, 13.0 mmol) were dissolved in dry THF (24 mL), and the mixture was cooled to 0 °C under a nitrogen atmosphere. Triphenylphosphine (3.41 g, 13.0 mmol) was added to the mixture, and the mixture was warmed to room temperature. After the mixture was stirred for 4 h, the solvents were removed by evaporation. The crude product was purified by flash column chromatography and bulb-to-bulb distillation to obtain the corresponding bromide **15g** (1.34 g, 5.74 mmol, 49%) as a colorless oil.

¹H NMR (392 MHz, CDCl₃, δ): 0.90 (t, *J* = 6.9 Hz, 3H), 1.26–1.38 (m, 4H), 1.43–1.50 (m, 2H), 1.66–1.81 (m, 2H), 2.45 (d, *J* = 2.0 Hz, 1H), 3.44–3.53 (m, 2H), 3.73 (dt, *J* = 6.4, 10.8 Hz, 1H), 4.04 (dt, *J* = 6.1, 10.6 Hz, 1H), 4.10 (td, *J* = 2.0, 6.7 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 13.9 (CH₃), 22.4 (CH₂), 24.7 (CH₂), 30.1 (CH₂), 31.3 (CH₂), 35.4 (CH₂), 68.5 (CH₂), 69.6 (CH), 73.9 (C), 82.4 (CH). HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₀H₁₇BrONa, 255.03550; found, 255.03607..

2.4.4 Borylation Product Characterization

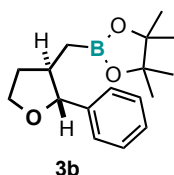
2.4.4.1 4,4,5,5-Tetramethyl-2-[(2-pentyltetrahydrofuran-3-yl)methyl]-1,3,2-dioxaborolane (**3a**).



The reaction was conducted with 118 mg (0.500 mmol) of **1a**. The product **3a** was obtained in 78% yield (110 mg, 0.391 mmol, colorless oil). The diastereoselectivity of **3a** was determined by ^1H NMR analysis (>95:5).

^1H NMR (392 MHz, CDCl_3 , δ): 0.73 (dd, $J = 9.6, 15.5$ Hz, 1H), 0.88 (t, $J = 6.7$ Hz, 3H), 0.97 (dd, $J = 5.2, 15.5$ Hz, 1H), 1.18–1.60 (m, 9H), 1.25 (s, 12H), 1.83–1.93 (m, 1H), 2.08–2.16 (m, 1H), 3.30 (dt, $J = 3.3, 7.7$ Hz, 1H), 3.76–3.84 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 14.0 (CH_3), 22.6 (CH_2), 24.7 (CH_3), 24.8 (CH_3), 26.2 (CH_2), 32.0 (CH_2), 34.1 (CH_2), 34.4 (CH_2), 40.1 (CH), 66.6 (CH_2), 83.0 (C), 86.4 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{31}\text{O}_3\text{BNa}$, 305.2259; found, 305.2260.

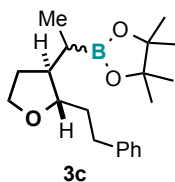
2.4.4.2 4,4,5,5-Tetramethyl-2-[(2-phenyltetrahydrofuran-3-yl)methyl]-1,3,2-dioxaborolane (**3b**).



The reaction was conducted with 121 mg (0.500 mmol) of **1b**. The product **3b** was obtained in 69% yield (100 mg, 0.347 mmol, colorless oil). The diastereoselectivity of **3b** was determined by ^1H NMR analysis (>95:5).

^1H NMR (399 MHz, CDCl_3 , δ): 0.80 (dd, $J = 9.6, 15.6$ Hz, 1H), 1.03 (dd, $J = 4.9, 15.8$ Hz, 1H), 1.19 (s, 6H), 1.20 (s, 6H), 1.71 (dq, $J = 8.6, 12.0$ Hz, 1H), 2.12–2.22 (m, 1H), 2.23–2.31 (m, 1H), 3.98–4.13 (m, 2H), 4.31 (d, $J = 8.2$ Hz, 1H), 7.23–7.36 (m, 5H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 13.2 (br, B–CH), 24.6 (CH_3), 24.8 (CH_3), 34.3 (CH_2), 44.1 (CH), 67.7 (CH_2), 83.0 (C), 88.3 (CH), 126.3 (CH), 127.3 (CH), 128.1 (CH), 142.0 (C). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{17}\text{H}_{25}\text{O}_3\text{B}$, 288.1897; found, 288.1911.

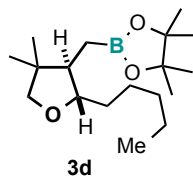
2.4.4.3 4,4,5,5-Tetramethyl-2-{1-[2-(2-phenylethyl)-tetrahydrofuran-3-yl]ethyl}-1,3,2-dioxaborolane (**3c**).



The reaction was conducted with 142 mg (0.500 mmol, 0.265 mmol, colorless oil) of (*E*)-**1c**. The product **3c** was obtained in 53% yield (87.4 mg). The product **3c** is a diastereomixture in term of the C–B bond, whereas the diastereomer ratio around C₂ and C₃ on the tetrahydrofuran ring was determined by ¹H NMR analysis (>95:5).

¹H NMR (392 MHz, CDCl₃, δ): 0.96 (d, *J* = 7.6 Hz, 1.5H), 0.98 (d, *J* = 7.2 Hz, 1.5H), 1.04–1.25 (m, 13H), 1.62–2.10 (m, 5H), 2.60–2.70 (m, 1H), 2.80–2.88 (m, 1H), 3.57–3.65 (m, 1H), 3.77–3.86 (m, 2H), 7.15–7.29 (m, 5H). ¹³C NMR (99 MHz, CDCl₃, δ): 12.9 (CH₃), 14.6 (CH₃), 19.4 (br, B–CH), 20.2 (br, B–CH), 24.61 (CH₃), 24.63 (CH₃), 24.69 (CH₃), 24.73 (CH₃), 30.7 (CH₂), 32.0 (CH₂), 32.79 (CH₂), 32.82 (CH₂), 37.0 (CH₂), 37.3 (CH₂), 46.4 (CH), 47.3 (CH), 66.7 (CH₂), 66.8 (CH₂), 82.6 (CH), 82.90 (C), 82.95 (CH), 83.00 (C), 125.5 (CH), 128.2 (CH), 128.3 (CH), 142.4 (C), 142.5 (C). HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₀H₃₁O₃BNa, 353.2259; found, 353.2257.

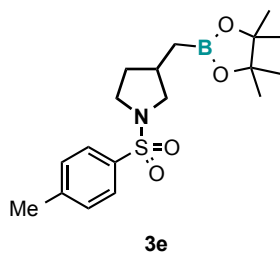
2.4.4.4 2-[(4,4-Dimethyl-2-pentyltetrahydrofuran-3-yl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3d**).



The reaction was conducted with 132 mg (0.500 mmol) of **1d**. The product **3d** was obtained in 82% yield (127 mg, 0.409 mmol, colorless oil). The diastereoselectivity of **3d** was determined using the corresponding alcohol prepared through oxidation of the boryl group by ¹H NMR analysis (90:10).

¹H NMR (392 MHz, CDCl₃, δ) 0.63 (dd, *J* = 7.8, 15.5 Hz, 1H), 0.77 (dd, *J* = 7.3, 15.5 Hz, 1H), 0.86–1.03 (m, 9H), 1.22–1.45 (m, 6H), 1.26 (s, 12H), 1.50–1.65 (m, 3H), 3.47–3.52 (m, 3H). ¹³C NMR (99 MHz, CDCl₃, δ): 8.41 (br, B–CH), 14.0 (CH₃), 21.2 (CH₃), 22.6 (CH₂), 24.8 (CH₃), 24.9 (CH₃), 25.1 (CH₂), 26.3 (CH₂), 32.1 (CH₂), 34.9 (CH₂), 41.7 (C), 49.7 (CH), 79.9 (CH₂), 83.1 (C), 85.8 (CH). HRMS-EI (*m/z*): [M–Me]⁺ calcd for C₁₇H₃₂BO₃, 295.2445; found, 295.2455.

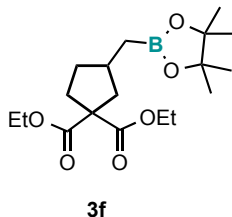
2.4.4.5 3-[(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-1-tosylpyrrolidine (3e).



The reaction was conducted with 159 mg (0.500 mmol) of **1e**. The product **3e** was obtained in 68% yield (125 mg, 0.342 mmol, colorless oil).

¹H NMR (392 MHz, CDCl₃, δ): 0.76 (d, *J* = 7.2 Hz, 2H), 1.21–1.43 (m, 13H), 1.92–1.98 (m, 1H), 2.12–2.20 (m, 1H), 2.43 (s, 3H), 2.73 (t, *J* = 9.2 Hz, 1H), 3.17–3.23 (m, 1H), 3.31–3.37 (m, 1H), 3.51 (dd, *J* = 7.2, 9.9 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.71 (t, *J* = 8.1 Hz, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 14.7 (br, B–CH), 21.4 (CH₃), 24.68 (CH₃), 24.72 (CH₃), 33.4 (CH₂), 34.7 (CH₂), 47.7 (CH₂), 54.9 (CH₂), 83.2 (C), 127.4 (CH), 129.5 (CH), 133.9 (C), 143.1 (C). HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₈H₂₈O₄NBNaS, 388.1724; found, 388.1724.

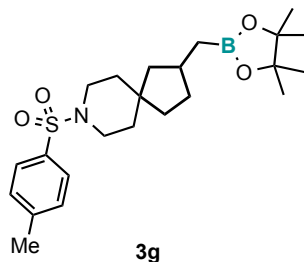
2.4.4.6 Diethyl 3-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]cyclopentane-1,1-dicarboxylate (3f).



The reaction was conducted with 153 mg (0.500 mmol) of **1f**. The product **3f** was obtained in 74% yield (131 mg, 0.370 mmol, colorless oil).

¹H NMR (392 MHz, CDCl₃, δ): 0.85 (dt, *J* = 7.5, 15.7 Hz, 1H), 0.89 (dt, *J* = 7.2, 15.6 Hz, 1H), 1.20–1.28 (m, 19H), 1.69 (dd, *J* = 10.3, 13.0 Hz, 1H), 1.90–1.93 (m, 1H), 2.07–2.17 (m, 2H), 2.27–2.34 (m, 1H), 2.50 (dd, *J* = 7.2, 13.0 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.17 (q, *J* = 7.2 Hz, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 14.0 (CH₃), 16.8 (br, B–CH₂), 24.7 (CH₃), 33.9 (CH₂), 34.3 (CH₂), 35.8 (CH), 42.8 (CH₂), 60.1 (C), 61.1 (CH), 82.9 (C), 172.8 (C). HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₈H₃₁O₆BNa, 377.2106; found, 377.2105.

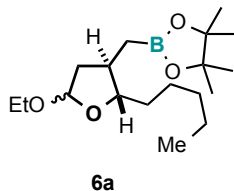
2.4.4.7 2-[(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-8-tosyl-8-azaspiro[4.5]decane (3g).



The reaction was conducted with 193 mg (0.500 mmol) of **1g**. The product **3g** was obtained in 90% yield (196 mg, 0.452 mmol, white solid).

^1H NMR (392 MHz, CDCl_3 , δ): 0.72–0.86 (m, 3H), 1.04–1.43 (m, 3H), 1.21 (s, 12 H), 1.48–1.63 (m, 5H), 1.71–1.81 (m, 1H), 1.96–2.08 (m, 1H), 2.43 (s, 3H), 2.88–2.99 (m, 4H), 7.31 (d, $J = 8.2$, 2H), 7.63 (d, $J = 8.7$ Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 17.7 (br, B– CH_2), 21.4 (CH_3), 24.6 (CH_3), 33.5 (CH_2), 34.6 (CH), 37.0 (CH_2), 37.4 (CH_2), 38.0 (CH_2), 40.0 (C), 43.7 (CH_2), 43.9 (CH_2), 46.8 (CH_2), 82.7 (C), 127.5 (CH), 129.4 (CH), 133.0 (C), 143.1 (C). HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{23}\text{H}_{36}\text{O}_4\text{NBNaS}$, 456.2350; found, 456.2354.

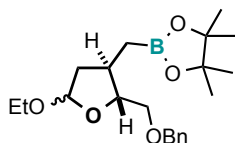
2.4.4.8 2-[(5-Ethoxy-2-pentyltetrahydrofuran-3-yl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6a).



The reaction was conducted with 140 mg (0.500 mmol) of **5a**. The product **6a** was obtained in 65% yield (106 mg, 0.325 mmol, colorless oil). The diastereomer ratio of **6a** around C_2 and C_3 on the tetrahydrofuran ring was determined by ^1H NMR analysis (>95:5). The product **6a** is a diastereomixture in term of the acetal moiety (C_5) due to the stereochemistry of the starting material.

^1H NMR (392 MHz, CDCl_3 , δ): 0.69–1.01 (m, 5H), 1.16–1.67 (m, 12H), 1.24 (s, 12 H), 1.78–1.88 (m, 0.5H), 2.09–2.25 (m, 1H), 2.38–2.45 (m, 0.5H), 3.37–3.47 (m, 1H), 3.50–3.56 (m, 1H), 3.69–3.78 (m, 1H), 5.02 (d, $J = 5.0$ Hz, 0.5H), 5.08 (dd, $J = 3.6, 5.8$ Hz, 0.5H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 13.96 (CH_3), 14.01 (CH_3), 15.1 (CH_3), 15.3 (CH_3), 22.5 (CH_2), 24.6 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 26.0 (CH_2), 26.1 (CH_2), 31.9 (CH_2), 32.0 (CH_2), 33.3 (CH_2), 35.6 (CH_2), 37.9 (CH), 39.5 (CH), 41.2 (CH_2), 41.4 (CH_2), 62.0 (CH_2), 62.8 (CH_2), 83.0 (C), 84.4 (CH), 87.4 (CH), 103.0 (CH), 103.1 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{18}\text{H}_{35}\text{O}_4\text{BNa}$, 349.2521; found, 349.2521.

2.4.4.9 2-{{2-(Benzyloxymethyl)-5-ethoxytetrahydrofuran-3-yl}methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6b).

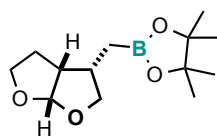


6b

The reaction was conducted with 165 mg (0.500 mmol) of **5b**. The product **6b** was obtained in 48% yield (91.0 mg, 0.242 mmol, colorless oil). The diastereomer ratio of **6b** around C₂ and C₃ on the tetrahydrofuran ring was determined by ¹H NMR analysis (90:10). The product **6b** is a diastereomixture in term of the acetal moiety (C₅) due to the stereochemistry of the starting material.

¹H NMR (392 MHz, CDCl₃, δ): 0.76–0.89 (m, 1H), 0.98–1.05 (m, 1H), 1.10–1.24 (m, 15H), 1.48–1.54 (m, 0.5H), 1.63–1.67 (m, 0.5H), 2.01–2.15 (m, 1H), 2.22–2.30 (m, 0.5H), 2.37–2.44 (m, 0.5H), 3.36–3.85 (m, 4H), 4.55–4.64 (m, 2.5H), 4.71 (d, *J* = 6.0 Hz, 0.5H), 5.07 (d, *J* = 5.0 Hz, 0.5H), 5.15 (dd, *J* = 3.1, 5.8 Hz, 0.5H), 7.26–7.38 (m, 5H). ¹³C NMR (99 MHz, CDCl₃, δ): 15.3 (CH₃), 15.4 (CH₃), 24.80 (CH₃), 24.83 (CH₃), 24.9 (CH₃), 35.3 (CH), 35.9 (CH), 41.0 (CH₂), 41.2 (CH₂), 62.3 (CH₂), 63.1 (CH₂), 71.2 (CH₂), 73.3 (CH₂), 73.4 (CH₂), 73.9 (CH₂), 83.2 (C), 83.3 (C), 83.9 (CH), 86.2 (CH), 103.7 (CH), 103.9 (CH), 127.0 (CH), 127.6 (CH), 127.75 (CH), 127.80 (CH), 128.4 (CH), 128.6 (CH), 138.47 (C), 138.53 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₂₁H₃₃O₅BNa, 399.2313; found, 399.2307.

2.4.4.10 2-{{(Hexahydrofuro[2,3-*b*]furan-3-yl)methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6c).

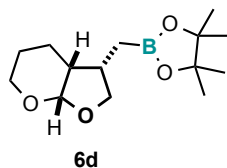


6c

The reaction was conducted with 127 mg (0.500 mmol) of **5c**. The product **6c** was obtained in 81% yield (103 mg, 0.405 mmol, colorless oil). The diastereomer ratio of **6c** around C₃ on the tetrahydrofuran ring was determined by ¹H NMR analysis (>95:5).

¹H NMR (392 MHz, CDCl₃, δ): 0.85 (d, *J* = 8.2 Hz, 2H), 1.25 (s, 12H), 1.75–1.91 (m, 2H), 2.43–2.54 (m, 1H), 2.81–2.88 (m, 1H), 3.34 (dd, *J* = 8.5, 11.2 Hz, 1H), 3.85 (dd, *J* = 6.3, 7.6 Hz, 2H), 3.95 (t, *J* = 7.9 Hz, 1H), 5.72 (d, *J* = 5.5 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 8.7 (br, B–CH₂), 24.57 (CH₃), 24.64 (CH₃), 25.1 (CH₂), 37.5 (CH), 46.3 (CH), 69.0 (CH₂), 73.8 (CH₂), 83.1 (C), 109.6 (CH). HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₁₃H₂₃O₄BNa, 277.1582; found, 277.1579.

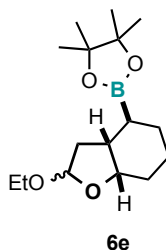
2.4.4.11 2-[(Hexahydro-4*H*-furo[2,3-*b*]pyran-3-yl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6d).



The reaction was conducted with 134 mg (0.500 mmol) of **5d**. The product **6d** was obtained in 75% yield (100 mg, 0.373 mmol, colorless oil). The diastereomer ratio of **6d** around C₃ on the tetrahydrofuran ring was determined by ¹H NMR analysis (94:6).

¹H NMR (392 MHz, CDCl₃, δ): 0.75–0.88 (m, 2H), 1.18–1.40 (m, 1H), 1.24 (s, 12H), 1.51–1.67 (m, 3H), 1.91–1.98 (m, 1H), 2.48–2.58 (m, 1H), 3.55–3.75 (m, 3H), 3.98 (t, *J* = 7.9 Hz, 1H), 5.30 (d, *J* = 3.7 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 8.38 (br, B–CH₂), 19.4 (CH₂), 23.3 (CH₂), 24.8 (CH₃), 36.7 (CH), 37.5 (CH), 60.9 (CH₂), 71.7 (CH₂), 83.3 (C), 102.1 (CH). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₄H₂₅O₄BNa, 291.1738; found, 291.1738.

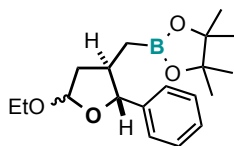
2.4.4.12 2-(2-Ethoxyoctahydrobenzofuran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6e).



The reaction was conducted with 125 mg (0.500 mmol) of **5e**. The product **6e** was obtained in 60% yield (89.0 mg, 0.300 mmol, colorless oil). The diastereomer ratio of **6e** around C₂ and C₃ on the tetrahydrofuran ring and the C–B bond on the cyclohexyl ring was determined by GC analysis (86:14). The product **6e** is a diastereomixture in term of the acetal moiety (C₅) due to the stereochemistry of the starting material.

¹H NMR (392 MHz, CDCl₃, δ): 0.78–0.85 (m, 0.5H), 1.07–1.23 (m, 15.5H), 1.30–1.68 (m, 6H), 1.74–2.21 (m, 3H), 3.40–3.50 (m, 1H), 3.73–3.83 (m, 1H), 3.87–3.95 (m, 0.5H), 4.07–4.09 (m, 0.5H), 5.07–5.21 (m, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 15.2 (CH₃), 15.3 (CH₃), 15.4 (CH₃), 20.5 (CH₂), 21.1 (CH₂), 21.5 (CH₂), 21.6 (CH₂), 23.1 (CH₂), 24.51 (CH₃), 24.53 (CH₃), 24.66 (CH₃), 24.73 (CH₃), 25.0 (CH₂), 25.9 (CH₂), 27.5 (CH₂), 28.8 (CH₂), 29.7 (CH₂), 29.8 (CH₂), 33.6 (CH₂), 33.7 (CH₂), 35.3 (CH), 36.9 (CH), 38.3 (CH), 38.4 (CH), 39.2 (CH₂), 40.7 (CH₂), 62.4 (CH₂), 63.2 (CH₂), 63.4 (CH₂), 63.5 (CH₂), 74.9 (CH), 77.5 (CH), 82.8 (C), 82.9 (C), 103.0 (CH), 103.5 (CH), 104.0 (CH), 105.1 (CH). HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₁₆H₂₉O₄BNa, 319.2051; found, 319.2059.

2.4.4.13 2-[(5-Ethoxy-2-phenyltetrahydrofuran-3-yl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6f**).

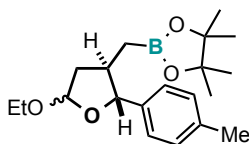


6f

The reaction was conducted with 142 mg (0.500 mmol) of **5f**. The product **6f** was obtained in 68% yield (113 mg, 0.341 mmol, colorless oil). The diastereomer ratio of **6f** around C₂ and C₃ on the tetrahydrofuran ring was determined by ¹H NMR analysis (>95:5). The product **6f** is a diastereomixture in term of the acetal moiety (C₅) due to the stereochemistry of the starting material.

¹H NMR (392 MHz, CDCl₃, δ): 0.71–1.03 (m, 2H), 1.16–1.31 (m, 15H), 1.61–1.66 (m, 0.5H), 1.81 (dt, *J* = 3.2, 12.3 Hz, 0.5H), 2.07–2.18 (m, 0.5H), 2.25 (dd, *J* = 6.9, 12.7 Hz, 0.5H), 2.40–2.51 (m, 0.5H), 2.62 (ddd, *J* = 5.5, 8.4, 13.7 Hz, 0.5H), 3.45–3.56 (m, 1H), 3.79–3.95 (m, 1H), 4.46 (dd, *J* = 9.0, 18.0 Hz, 1H), 5.17 (d, *J* = 5.5 Hz, 0.5H), 5.32 (dd, *J* = 3.7, 5.7 Hz, 0.5H), 7.26–7.39 (m, 5H). ¹³C NMR (99 MHz, CDCl₃, δ): 12.9 (br, B–CH₂), 15.2 (CH₃), 15.3 (CH₃), 24.57 (CH₃), 24.65 (CH₃), 24.77 (CH₃), 24.82 (CH₃), 41.3 (CH₂), 41.5 (CH₂), 42.0 (CH), 43.6 (CH), 62.7 (CH₂), 63.4 (CH₂), 83.0 (C), 83.1 (C), 86.5 (CH), 90.1 (CH), 103.4 (CH), 103.6 (CH), 126.8 (CH), 127.1 (CH), 127.4 (CH), 127.7 (CH), 128.1 (CH), 128.2 (CH), 140.3 (C), 142.0 (C). HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₉H₂₉O₄BNa, 355.2051; found, 355.2055.

2.4.4.14 2-[(5-Ethoxy-2-(*p*-tolyl)tetrahydrofuran-3-yl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6g**).



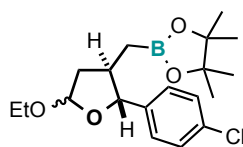
6g

The reaction was conducted with 149 mg (0.500 mmol) of **5g**. The product **6g** was obtained in 62% yield (107 mg, 0.309 mmol, colorless oil). The diastereomer ratio of **6g** around C₂ and C₃ on the tetrahydrofuran ring was determined by ¹H NMR analysis (>95:5). The product **6g** is a diastereomixture in term of the acetal moiety (C₅) due to the stereochemistry of the starting material.

¹H NMR (401 MHz, CDCl₃, δ): 0.68–1.01 (m, 2H), 1.16–1.30 (m, 15H), 1.57–1.64 (m, 0.5H), 1.79 (dt, *J* = 3.0, 12.3 Hz, 0.5H), 2.05–2.18 (m, 0.5H), 2.25 (dd, *J* = 6.6, 12.2 Hz, 0.5H), 2.33 (s, 3H), 2.40–2.49 (m, 0.5H), 2.62 (ddd, *J* = 5.5, 8.1, 13.5 Hz, 0.5H), 3.44–3.55 (m, 1H), 3.78–3.93 (m, 1H), 4.42 (dd, *J* = 9.2, 17.6 Hz, 1H), 5.16 (d, *J* = 5.1 Hz, 0.5H), 5.30 (dd, *J* = 4.0, 5.2 Hz, 0.5H), 7.09–7.15 (m, 2H), 7.24–7.27 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 12.8 (br, B–CH₂), 15.17 (CH₃), 15.22 (CH₃), 21.0 (CH₃), 24.5 (CH₃), 24.6 (CH₃), 24.7 (CH₃), 24.8 (CH₃), 41.3 (CH₂), 41.4 (CH₂), 41.9 (CH), 43.5 (CH), 62.6 (CH₂), 63.3 (CH₂), 82.9 (C), 83.0 (C), 86.3 (CH), 90.0 (CH), 103.2 (CH), 103.5 (CH),

126.7 (CH), 127.0 (CH), 128.79 (CH), 128.85 (CH), 137.0 (C), 137.2 (C), 138.9 (C). HRMS-ESI (m/z): [M+Na]⁺ calcd for C₂₀H₃₁O₄BNa, 369.2208; found, 369.2206.

2.4.4.15 2-{{2-(4-Chlorophenyl)-5-ethoxytetrahydrofuran-3-yl}methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6h).

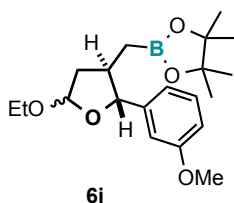


6h

The reaction was conducted with 160 mg (0.500 mmol) of **5h**. The product **6h** was obtained in 57% yield (106 mg, 0.288 mmol, colorless oil). The diastereomer ratio of **6h** around C₂ and C₃ on the tetrahydrofuran ring was determined by ¹H NMR analysis (>95:5). The product **6h** is a diastereomixture in term of the acetal moiety (C₅) due to the stereochemistry of the starting material.

¹H NMR (401 MHz, CDCl₃, δ): 0.68–1.01 (m, 2H), 1.16–1.30 (m, 15H), 1.57–1.64 (m, 0.5H), 1.79 (dt, *J* = 3.0, 12.3 Hz, 0.5H), 2.05–2.18 (m, 0.5H), 2.25 (dd, *J* = 6.6, 12.2 Hz, 0.5H), 2.33 (s, 3H), 2.40–2.49 (m, 0.5H), 2.62 (ddd, *J* = 5.5, 8.1, 13.5 Hz, 0.5H), 3.44–3.55 (m, 1H), 3.78–3.93 (m, 1H), 4.42 (dd, *J* = 9.2, 17.6 Hz, 1H), 5.16 (d, *J* = 5.1 Hz, 0.5H), 5.30 (dd, *J* = 4.0, 5.2 Hz, 0.5H), 7.09–7.15 (m, 2H), 7.24–7.27 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 12.8 (br, B–CH₂), 15.17 (CH₃), 15.22 (CH₃), 21.0 (CH₃), 24.5 (CH₃), 24.6 (CH₃), 24.7 (CH₃), 24.8 (CH₃), 41.3 (CH₂), 41.4 (CH₂), 41.9 (CH), 43.5 (CH), 62.6 (CH₂), 63.3 (CH₂), 82.9 (C), 83.0 (C), 86.3 (CH), 90.0 (CH), 103.2 (CH), 103.5 (CH), 126.7 (CH), 127.0 (CH), 128.79 (CH), 128.85 (CH), 137.0 (C), 137.2 (C), 138.9 (C). HRMS-ESI (m/z): [M+Na]⁺ calcd for C₂₀H₃₁O₄BNa, 369.2208; found, 369.2206.

2.4.4.16 2-{{5-Ethoxy-2-(3-methoxyphenyl)tetrahydrofuran-3-yl}methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6i).



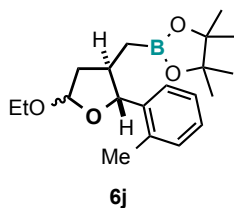
6i

The reaction was conducted with 156 mg (0.500 mmol) of **5i**. The product **6i** was obtained in 59% yield (105 mg, 0.290 mmol, colorless oil). The diastereomer ratio of **6i** around C₂ and C₃ on the tetrahydrofuran ring was determined by ¹H NMR analysis (>95:5). The product **6i** is a diastereomixture in term of the acetal moiety (C₅) due to the stereochemistry of the starting material.

¹H NMR (401 MHz, CDCl₃, δ): 0.71–1.05 (m, 2H), 1.17–1.31 (m, 15H), 1.58–1.64 (m, 0.5H), 1.80 (dt, *J* = 3.1, 12.2 Hz, 0.5H), 2.06–2.17 (m, 0.5H), 2.25 (dd, *J* = 6.4, 12.4 Hz, 0.5H), 2.40–2.50 (m, 0.5H), 2.62 (ddd, *J* = 5.5, 8.3, 13.5 Hz, 0.5H), 3.45–3.58 (m, 1H), 3.79–4.00 (m, 4H), 4.44 (dd, *J* =

9.2, 14.4 Hz, 1H), 5.18 (d, J = 4.8 Hz, 0.5H), 5.32 (dd, J = 3.8, 5.8 Hz, 0.5H), 6.79–6.83 (m, 1H), 6.92–6.97 (m, 2H), 7.21–7.26 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 13.0 (br, B–CH₂), 15.17 (CH₃), 15.19 (CH₃), 24.5 (CH₃), 24.6 (CH₃), 24.7 (CH₃), 24.8 (CH₃), 41.2 (CH₂), 41.3 (CH₂), 41.9 (CH), 43.5 (CH), 54.9 (CH₃), 55.0 (CH₃), 62.7 (CH₂), 63.3 (CH₂), 82.95 (C), 82.97 (C), 86.3 (CH), 89.9 (CH), 103.4 (CH), 103.6 (CH), 111.8 (CH), 111.9 (CH), 113.29 (CH), 113.33 (CH), 119.1 (CH), 119.4 (CH), 129.0 (CH), 129.1 (CH), 142.0 (C), 143.7 (C), 159.5 (C). HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{31}\text{O}_5\text{BNa}$, 385.2157; found, 385.2157.

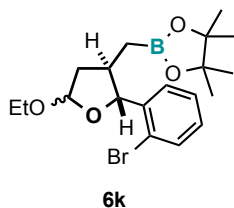
2.4.4.17 2-{{[5-Ethoxy-2-(*o*-tolyl)tetrahydrofuran-3-yl]methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6j).



The reaction was conducted with 150 mg (0.500 mmol) of **5j**. The product **6j** was obtained in 60% yield (104 mg, 0.301 mmol, colorless oil). The diastereomer ratio of **6j** around C₂ and C₃ on the tetrahydrofuran ring was determined by ^1H NMR analysis (92:8). The product **6j** is a diastereomixture in term of the acetal moiety (C₅) due to the stereochemistry of the starting material.

^1H NMR (396 MHz, CDCl_3 , δ): 0.74–1.00 (m, 2H), 1.11–1.30 (m, 15H), 1.60–1.67 (m, 0.5H), 1.78 (dt, J = 3.0, 12.4 Hz, 0.5H), 2.22–2.30 (m, 1H), 2.37 (s, 1.5H), 2.39 (s, 1.5H), 2.48–2.60 (m, 0.5H), 2.65 (ddd, J = 5.5, 8.3, 13.5 Hz, 0.5H), 3.45–3.54 (m, 1H), 3.78–3.91 (m, 1H), 4.84 (dd, J = 6.4, 9.2 Hz, 1H), 5.17 (d, J = 5.1 Hz, 0.5H), 5.31 (dd, J = 3.8, 5.7 Hz, 0.5H), 7.08–7.23 (m, 3H), 7.40 (d, J = 7.1 Hz, 0.5H), 7.52 (d, J = 7.9 Hz, 0.5H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 13.0 (br, B–CH₂), 15.1 (CH₃), 15.2 (CH₃), 19.4 (CH₃), 19.5 (CH₃), 24.5 (CH₃), 24.6 (CH₃), 24.7 (CH₃), 24.8 (CH₃), 41.4 (CH₂), 41.5 (CH₂), 42.0 (CH), 42.9 (CH), 62.6 (CH₂), 63.3 (CH₂), 82.2 (CH), 83.0 (C), 85.3 (CH), 103.3 (CH), 103.4 (CH), 126.0 (CH), 126.2 (CH), 126.6 (CH), 127.0 (CH), 127.3 (CH), 127.7 (CH), 129.8 (CH), 130.2 (CH), 135.6 (C), 136.2 (C), 137.9 (C), 139.6 (C). HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{20}\text{H}_{31}\text{O}_4\text{BNa}$, 369.2208; found, 369.2206.

2.4.4.18 2-{{[2-(2-Bromophenyl)-5-ethoxytetrahydrofuran-3-yl]methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6k).

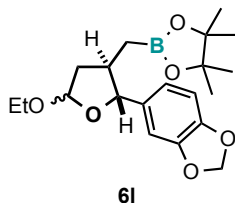


The reaction was conducted with 182 mg (0.500 mmol) of **5k**. The product **6k** was obtained in

48% yield (97.9 mg, 0.238 mmol, colorless oil). The diastereomer ratio of **6k** around C₂ and C₃ on the tetrahydrofuran ring was determined by ¹H NMR analysis (91:9). The product **6k** is a diastereomixture in term of the acetal moiety (C₅) due to the stereochemistry of the starting material.

¹H NMR (392 MHz, CDCl₃, δ): 0.85–1.31 (m, 17H), 1.67 (ddd, *J* = 3.8, 9.1, 13.2 Hz, 0.5H), 1.88 (dt, *J* = 3.4, 12.0 Hz, 0.5H), 2.10–2.26 (m, 1H), 2.43–2.53 (m, 0.5H), 2.60 (ddd, *J* = 5.5, 8.2, 13.5 Hz, 0.5H), 3.45–3.57 (m, 1H), 3.79–3.92 (m, 1H), 5.09 (t, *J* = 8.8 Hz, 1H), 5.20 (d, *J* = 4.7 Hz, 0.5H), 5.34 (dd, *J* = 3.1, 5.7 Hz, 0.5H), 7.07–7.13 (m, 1H), 7.26–7.34 (m, 1H), 7.45–7.52 (m, 1.5H), 7.61 (d, *J* = 7.8 Hz, 0.5H). ¹³C NMR (99 MHz, CDCl₃, δ): 13.4 (br, B–CH₂), 15.20 (CH₃), 15.25 (CH₃), 24.5 (CH₃), 24.6 (CH₃), 24.80 (CH₃), 24.82 (CH₃), 41.1 (CH₂), 41.2 (CH₂), 42.8 (CH), 44.0 (CH), 63.0 (CH₂), 63.3 (CH₂), 82.96 (C), 82.99 (C), 84.2 (CH), 87.3 (CH), 103.8 (CH), 103.9 (CH), 123.3 (C), 123.4 (C), 127.5 (CH), 127.6 (CH), 128.4 (CH), 128.7 (CH), 128.9 (CH), 129.5 (CH), 132.1 (CH), 132.5 (CH), 139.9 (C), 141.4 (C). HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₁₉H₂₈O₄BBrNa, 433.1156; found, 433.1160.

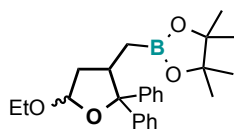
2.4.4.19 2-{{2-(Benzo[*d*][1,3]dioxol-5-yl)-5-ethoxytetrahydrofuran-3-yl}methyl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**6l**).



The reaction was conducted with 164 mg (0.500 mmol) of **5l**. The product **6l** was obtained in 52% yield (97.0 mg, 0.258 mmol, colorless oil). The diastereomer ratio of **6l** around C₂ and C₃ on the tetrahydrofuran ring was determined by ¹H NMR analysis (>95:5). The product **6l** is a diastereomixture in term of the acetal moiety (C₅) due to the stereochemistry of the starting material.

¹H NMR (392 MHz, CDCl₃, δ): 0.67–1.00 (m, 2H), 1.17–1.30 (m, 15H), 1.57–1.63 (m, 0.5H), 1.78 (dt, *J* = 3.0, 12.2 Hz, 0.5H), 2.02–2.12 (m, 0.5H), 2.23 (dd, *J* = 6.3, 12.5 Hz, 0.5H), 2.35–2.46 (m, 0.5H), 2.60 (ddd, *J* = 5.6, 8.3, 13.7 Hz, 0.5H), 3.44–3.55 (m, 1H), 3.78–3.90 (m, 1H), 4.38 (dd, *J* = 9.4, 16.6 Hz, 1H), 5.13 (d, *J* = 4.9 Hz, 0.5H), 5.28 (dd, *J* = 3.8, 5.6 Hz, 0.5H), 5.92–5.95 (m, 2H), 6.72–6.82 (m, 2H), 6.90 (dd, *J* = 1.4, 18.4 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 12.7 (br, B–CH₂), 15.1 (CH₃), 15.2 (CH₃), 24.5 (CH₃), 24.6 (CH₃), 24.7 (CH₃), 24.8 (CH₃), 41.2 (CH₂), 41.3 (CH₂), 41.8 (CH), 43.4 (CH), 62.6 (CH₂), 63.3 (CH₂), 82.98 (C), 83.01 (C), 86.3 (CH), 90.0 (CH), 100.7 (CH₂), 100.8 (CH₂), 103.2 (CH), 103.4 (CH), 107.0 (CH), 107.3 (CH), 107.5 (CH), 107.8 (CH), 120.5 (CH), 120.6 (CH), 134.1 (C), 135.9 (C), 147.0 (C), 147.1 (C), 147.6 (C), 147.7 (C). HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₀H₂₉O₆BNa, 399.195; found, 399.195.

2.4.4.20 2-[(5-Ethoxy-2,2-diphenyltetrahydrofuran-3-yl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6m).

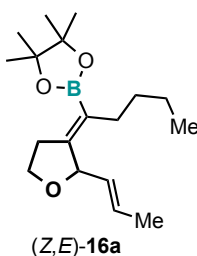


6m

The reaction was conducted with 181 mg (0.500 mmol) of **5m**. The product **6m** was obtained in 57% yield (116 mg, 0.284 mmol, colorless oil). The diastereomer ratio of **6m** around C₃ and C₅ on the tetrahydrofuran ring was determined by ¹H NMR analysis (58:42)

¹H NMR (392 MHz, CDCl₃, δ): 0.19 (dd, *J* = 12.6, 15.7 Hz, 0.58H), 0.60 (dd, *J* = 12.1, 16.1 Hz, 0.42H), 0.84 (t, *J* = 3.8 Hz, 0.58H), 0.88 (t, *J* = 4.0 Hz, 0.42H), 0.99 (t, *J* = 7.2 Hz, 1.74H), 1.20–1.22 (m, 12H), 1.32 (t, *J* = 7.2 Hz, 1.26H), 1.79 (ddd, *J* = 4.8, 7.6, 12.8 Hz, 0.42H), 1.85 (ddd, *J* = 4.7, 9.1, 12.9 Hz, 0.58H), 2.18–2.23 (m, 0.58H), 2.32 (quin, *J* = 6.5 Hz, 0.42H), 3.10–3.18 (m, 0.42H), 3.34–3.51 (m, 1.16H), 3.59–3.72 (m, 1H), 4.00–4.08 (m, 0.42H), 5.24 (t, *J* = 5.2 Hz, 0.42H), 5.43 (dd, *J* = 1.6, 5.2 Hz, 0.58H), 7.11–7.37 (m, 8H), 7.48–7.53 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 14.9 (CH₃), 15.5 (CH₃), 24.6 (CH₃), 24.9 (CH₃), 39.3 (CH₂), 40.2 (CH₂), 40.85 (CH), 40.92 (CH), 62.4 (CH₂), 64.2 (CH₂), 83.0 (C), 83.1 (C), 91.2 (C), 91.6 (C), 102.7 (CH), 103.3 (CH), 126.2 (CH), 126.3 (CH), 126.4 (CH), 126.6 (CH), 126.8 (CH), 127.0 (CH), 127.3 (CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 144.1 (C), 144.2 (C), 146.7 (C), 147.2 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₂₅H₃₃O₄BNa, 431.2364; found, 431.2368.

2.4.4.21 4,4,5,5-Tetramethyl-2-[(Z)-1-{2-[(E)-prop-1-en-1-yl]dihydrofuran-3(2H)-ylidene}pentyl]-1,3,2-dioxaborolane [(Z,E)-16a]



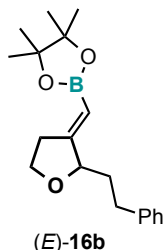
(Z,E)-16a

The reaction was conducted with 129.6 mg (0.50 mmol) of (*E*)-**15a**. The product (*Z,E*)-**16a** was obtained as a colorless oil in 80% yield (121.9 mg) with *E/Z* = <5:95.

¹H NMR (392 MHz, CDCl₃, δ): 0.87 (t, *J* = 7.0 Hz, 3H), 1.21–1.36 (m, 4H), 1.27 (s, 12H), 1.69 (dd, *J* = 1.3, 6.3 Hz, 3H), 2.04–2.08 (m, 2H), 2.66–2.74 (m, 1H), 2.87 (dt, *J* = 6.0, 16.5 Hz, 1H), 3.77 (dt, *J* = 7.8, 15.3 Hz, 1H), 3.97 (dt, *J* = 4.9, 8.1 Hz, 1H), 4.90 (d, *J* = 7.8 Hz, 1H), 5.40–5.46 (m, 1H), 5.72 (dq, *J* = 6.5, 15.3 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 14.1 (CH₃), 17.7 (CH₂), 22.9 (CH₂), 24.7 (CH₃), 24.9 (CH₃), 31.2 (CH₂), 32.0 (CH₂), 33.4 (CH₂), 66.9 (CH₂), 80.4 (CH), 82.9 (C), 128.2 (CH), 130.0 (CH), 154.8 (C). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₈H₃₁¹¹BO₃, 306.23696; found,

306.23633.

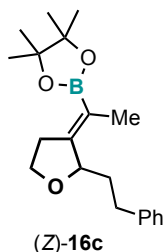
2.4.4.22 (E)-4,4,5,5-Tetramethyl-2-{{2-phenethyldihydrofuran-3(2H)-ylidene}methyl}-1,3,2-dioxaborolane [(E)-16b].



The reaction was conducted with 132.7 mg (0.50 mmol) of **15b**. The product (*E*)-**16b** was obtained as a white solid (m.p. = 49–51 °C) in 67% yield (105.1 mg) with *E/Z* = >95:5.

¹H NMR (392 MHz, CDCl₃, δ): 1.27 (s, 12H), 1.79–1.88 (m, 1H), 1.93–2.02 (m, 1H), 2.67–2.83 (m, 3H), 2.88–2.96 (m, 1H), 3.79 (td, *J* = 7.1, 8.6 Hz, 1H), 4.07 (td, *J* = 4.3, 8.3 Hz, 1H), 4.24–4.26 (m, 1H), 5.21 (q, *J* = 2.2 Hz, 1H), 7.15–7.21 (m, 3H), 7.25–7.29 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 24.79 (CH₃), 24.82 (CH₃), 31.6 (CH₂), 33.7 (CH₂), 36.2 (CH₂), 66.9 (CH₂), 81.4 (CH), 82.8 (C), 106.9 (br, B–CH), 125.6 (CH), 128.2 (CH), 128.4 (CH), 142.0 (C), 167.8 (C). HRMS-EI (*m/z*): [M]⁺ calcd for C₁₉H₂₇¹¹BO₃, 314.20532; found, 314.20569.

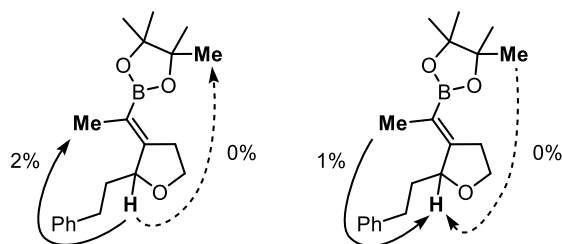
2.4.4.23 (Z)-4,4,5,5-Tetramethyl-2-{1-[2-phenethyldihydrofuran-3(2H)-ylidene]ethyl}-1,3,2-dioxaborolane [(Z)-16c].



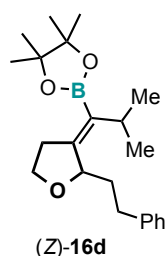
The reaction was conducted with 138.8 mg (0.50 mmol) of **15c**. The product (*Z*)-**16c** was obtained as a colorless oil in 74% yield (119.1 mg) with *E/Z* = <5:95.

¹H NMR (392 MHz, CDCl₃, δ): 1.26 (s, 12H), 1.65 (s, 3H), 1.74–1.84 (m, 1H), 1.86–1.94 (m, 1H), 2.64–2.73 (m, 2H), 2.76–2.84 (m, 1H), 2.89–2.96 (m, 1H), 3.81 (q, *J* = 7.7 Hz, 1H), 4.02 (td, *J* = 5.0, 8.3 Hz, 1H), 4.56 (d, *J* = 9.0 Hz, 1H), 7.15–7.22 (m, 3H), 7.25–7.29 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 16.8 (CH₃), 24.7 (CH₃), 24.9 (CH₃), 31.9 (CH₂), 33.3 (CH₂), 34.5 (CH₂), 66.8 (CH₂), 79.2 (CH), 82.9 (C), 116.5 (br, B–C), 125.6 (CH), 128.2 (CH), 128.4 (CH), 142.1 (C), 158.3 (C). HRMS-EI (*m/z*): [M]⁺ calcd for C₂₀H₂₉¹¹BO₃, 328.22097; found, 328.22089.

The product configuration was determined by ¹H NMR nOe experiment. The results were summarized as following schemes. A solid curved arrow indicates the observed nOe.



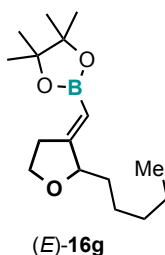
2.4.4.24 (Z)-4,4,5,5-Tetramethyl-2-{2-methyl-1-[2-phenethyldihydrofuran-3(2H)-ylidene]propyl}-1,3,2-dioxaborolane [(Z)-16d].



The reaction was conducted with 162.2 mg (0.50 mmol) of the corresponding sulfonate **15d**. The product (Z)-**15d** was obtained as a colorless oil in 47% yield (83.4 mg) with *E/Z* = 7:93.

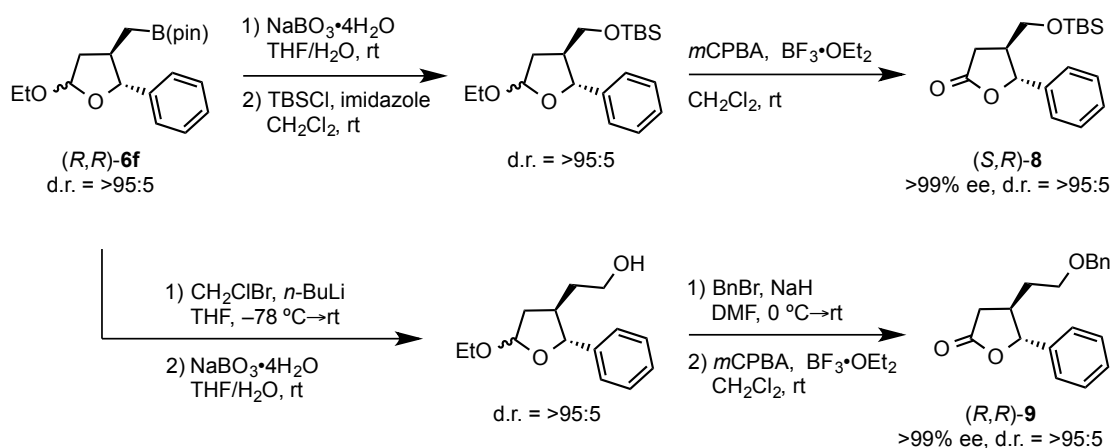
¹H NMR (392 MHz, CDCl₃, δ): 1.02 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.27 (s, 12H), 1.80–1.86 (m, 2H), 2.39 (septet, *J* = 6.7 Hz, 1H), 2.61–2.73 (m, 2H), 2.74–2.85 (m, 2H), 3.82 (dt, *J* = 7.8, 16.0 Hz, 1H), 3.98 (dt, *J* = 5.2, 8.2 Hz, 1H), 4.59 (t, *J* = 5.4 Hz, 1H), 7.15–7.22 (m, 3H), 7.24–7.29 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 22.1 (CH₃), 24.7 (CH₃), 24.9 (CH₃), 31.7 (CH), 32.0 (CH₂), 32.9 (CH₂), 36.1 (CH₂), 66.5 (CH₂), 78.7 (CH), 82.7 (C), 125.6 (CH), 128.2 (CH), 128.4 (CH), 142.2 (C), 152.7 (C). HRMS-EI (*m/z*): [*M*]⁺ calcd for C₂₂H₃₃¹¹BO₃, 356.25267; found, 356.25177..

2.4.4.25 (E)-4,4,5,5-Tetramethyl-2-{[2-pentyldihydrofuran-3(2H)-ylidene]methyl}-1,3,2-dioxaborolane [(E)-16g].

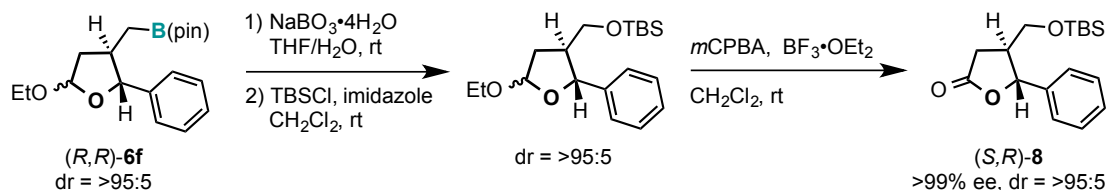


¹H NMR (392 MHz, CDCl₃, δ): 0.88 (t, *J* = 6.9 Hz, 3H), 1.22–1.34 (m, 16H), 1.37–1.55 (m, 3H), 1.60–1.69 (m, 1H), 2.67–2.77 (m, 1H), 2.87–2.94 (m, 1H), 3.75 (td, *J* = 6.8, 8.4 Hz, 1H), 4.03 (td, *J* = 3.9, 8.3 Hz, 1H), 4.20–4.22 (m, 1H), 5.19 (q, *J* = 2.1 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 14.0 (CH₃), 22.5 (CH₂), 24.78 (CH₃), 24.80 (CH₃), 25.2 (CH₂), 31.8 (CH₂), 33.6 (CH₂), 34.6 (CH₂), 66.8 (CH₂), 82.3 (CH), 82.8 (C), 106.6 (br, B–CH), 168.2 (C). HRMS-EI (*m/z*): [*M*]⁺ calcd for C₁₆H₂₉¹¹BO₃, 280.22097; found, 280.22228.

2.4.5 Synthetic Application Procedures of Borylation Products



2.4.5.1 (4*S*,5*R*)-4-[[*tert*-Butyldimethylsilyl]oxy]methyl]-5-(3-methoxyphenyl)dihydrofuran-2(3*H*)-one [(*S*,*R*)-8].



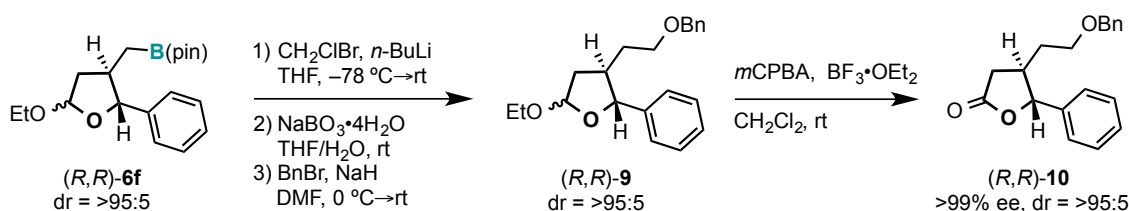
The optically active organoboron compound **(R,R)-6f** was prepared from the corresponding chiral allyl alcohol **(R)-7f**.³⁹ In a reaction vial, **(R,R)-6f** (166 mg, 0.500 mmol) was dissolved in THF/ H_2O (1:1, 2.00 mL). $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ (308 mg, 2.00 mmol) was then added at room temperature. After stirred for 2 hours, the reaction mixture was extracted three times with EtOAc, dried over MgSO_4 , and filtered. The crude mixture was purified by flash column chromatography (SiO_2 , ethyl acetate/hexane, 10:90–50:50) to afford the corresponding alcohol as a colorless oil.

The corresponding alcohol and imidazole (68.1 mg, 0.500 mmol) was dissolved in dry CH_2Cl_2 (1.00 mL) under a nitrogen atmosphere. TBS chloride (90.4 mg, 0.600 mmol) was then added to the solution at room temperature. After stirred for 16 hours, the reaction mixture was passed through a short silica gel column eluting with Et₂O/ CH_2Cl_2 (50:50). The crude mixture was purified by flash column chromatography (SiO_2 , ethyl acetate/hexane, 2:98–5:95) to afford the corresponding silyl ether (151 mg, 0.450 mmol, 89 %, 2 steps) as a colorless oil.

The oxidation of the acetal moiety was performed according to the literature procedure.⁴⁸ *m*-CPBA (356 mg, 1.34 mmol) was added to a stirred solution of the corresponding silyl ether in CH_2Cl_2 (3.00 mL), at room temperature followed by the addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (127 mg, 0.890 mmol). After 2 hours, the reaction mixture was quenched by the addition of aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution and extracted three times with CH_2Cl_2 . The combined organic layer was washed with aqueous NaHCO_3 three times, brine. The solution was dried over MgSO_4 . After filtration, the solvent was removed by evaporation under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2 , ethyl acetate/hexane, 4:96–12:88) to afford the corresponding lactone **(S,R)-8** (73.7 mg, 0.240 mmol, 54%) as a colorless oil.

^1H NMR (392 MHz, CDCl_3 , δ): 0.08 (s, 3H), 0.09 (s, 3H), 0.92 (s, 9H), 2.54–2.71 (m, 3H), 3.69 (d, $J = 3.9$ Hz, 2H), 5.38 (d, $J = 5.1$ Hz, 1H), 7.31–7.42 (m, 5H). ^{13}C NMR (99 MHz, CDCl_3 , δ): –5.6 (CH_3), 18.2 (C), 25.7 (CH_3), 30.9 (CH_2), 46.4 (CH), 61.4 (CH_2), 82.7 (CH), 125.5 (CH), 128.4 (CH), 128.7 (CH), 139.0 (C), 176.3 (C). HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{17}\text{H}_{26}\text{O}_3\text{NaSi}$, 329.1543; found, 329.1543. $[\alpha]_{\text{D}}^{21.1}$ –6.48 (c 1.1 in CHCl_3 , >99% ee). Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 3/97, 0.5 mL/min, 40 °C, (*S,R*)-isomer: $t_{\text{R}} = 20.15$ min., (*R,S*)-isomer: $t_{\text{R}} = 21.19$ min.

2.4.5.2 (4*R*,5*R*)-4-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-5-(3-methoxyphenyl)dihydrofuran-2(3*H*)-one [(*R,R*)-10].



In an oven-dried reaction vial, (*R,R*)-**6f** (166 mg, 0.500 mmol) and bromochloromethane (129 mg, 0.500 mmol) were dissolved in dry THF (3.00 mL) in nitrogen atmosphere. After the mixture was cooled to –78 °C, a solution of *n*-BuLi in hexane (1.60 M, 469 μL , 0.750 mmol) was added dropwise. The mixture was stirred at –78 °C for 10 min, and then stirred at room temperature for 2 hours. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl solution and extracted three times with Et_2O . The combined organic layer was dried over Na_2SO_4 . After filtration, the resulting crude material was submitted to the subsequent reaction without further purification. In a reaction vial, the crude material of above reaction was dissolved in THF/ H_2O (1:1, 3.00 mL). $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ (308 mg, 2.00 mmol) was then added at room temperature. After stirred for 15 hours, the reaction mixture was extracted with Et_2O . The organic layer was dried over MgSO_4 . After filtration, the crude mixture was purified by flash column chromatography (SiO_2 , ethyl acetate/hexane, 10:90–50:50) to afford the corresponding alcohol (106 mg, 0.480 mmol, 96%, 2 steps) as a colorless oil.

A solution of the alcohol (113 mg, 0.480 mmol) in DMF (2.00 mL) was added to a suspension of NaH (60 wt.%, 28.8 mg, 0.720 mmol) in DMF at 0 °C. Benzyl bromide (86.0 μL , 0.720 mmol) was then added and the reaction mixture was stirred for 2 hours at room temperature. The reaction mixture was quenched by addition of water, extracted with Et_2O three times, the combined organic layer was dried over MgSO_4 followed by filtration. The crude mixture was purified by flash column chromatography (SiO_2 , diethyl ether/hexane, 0:100–10:90) to afford the corresponding benzyl ether (*R,R*)-**9** (108 mg, 0.330 mmol, 69%) as a colorless oil.

Oxidation of acetal moiety was performed according to the literature procedure.⁴⁸ *m*-CPBA (263 mg, 0.990 mmol) was added to a solution of the benzyl ether (108.3 mg, 0.330 mmol) in CH_2Cl_2 (2.00 mL) at room temperature followed by the addition of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (93.70 mg, 0.660 mmol). After 1 hour, the reaction mixture was quenched by addition of aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and extracted three times with CH_2Cl_2 . The combined organic layer was washed three times with aqueous NaHCO_3 solution, and

brine, dried over MgSO_4 , and filtered. The crude mixture was purified by flash column chromatography (SiO_2 , ethyl acetate/hexane, 3:97–15:85) to afford the corresponding lactone (*R,R*)-**10** (76.9 mg, 0.260 mmol, 79%) as a white solid.

^1H NMR (392 MHz, CDCl_3 , δ): 1.70–1.79 (m, 1H), 1.88–1.96 (m, 1H), 2.41 (dd, $J = 9.6, 17.1$ Hz, 1H), 2.55–2.65 (m, 1H), 2.79 (dd, $J = 8.2, 17.2$ Hz, 1H), 3.47 (t, $J = 5.9$, 2H), 4.41 (s, 2H), 5.07 (d, $J = 7.8$ Hz, 1H), 7.25–7.40 (m, 10H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 31.9 (CH_2), 35.6 (CH_2), 42.5 (CH), 68.0 (CH_2), 73.2 (CH_2), 86.7 (CH), 126.3 (CH), 127.8 (CH), 127.9 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 138.0 (C), 138.2 (C), 176.4 (C). HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{19}\text{H}_{20}\text{O}_3\text{Na}$, 319.1305; found, 319.1305. $[\alpha]_{\text{D}}^{17.8} -17.65$ (c 1.0 in CHCl_3 , >99% ee). Daicel CHIRALPAK® AY-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*R,R*)-isomer: $t_{\text{R}} = 59.97$ min., (*S,S*)-isomer: $t_{\text{R}} = 44.19$ min. The compound (*R,R*)-**10** was further recrystallized from CH_2Cl_2 /Hexane (1:1) to prepare crystals for single crystal XRD analysis.

Data for Single Crystal X-ray Structural Analysis

Single crystal X-ray structural analyses were carried out on a Rigaku R-Axis RAPID diffractometer using graphite monochromated $\text{Cu-K}\alpha$ radiation. The structure was solved by direct methods and expanded using Fourier techniques. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. All calculations were performed using the CrystalStructure crystallographic software package except for refinement, which was performed using SHELXL-97.⁴⁹

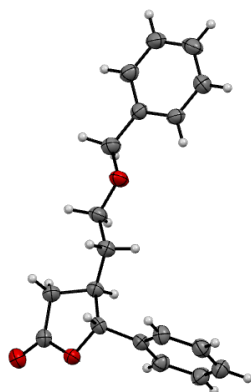
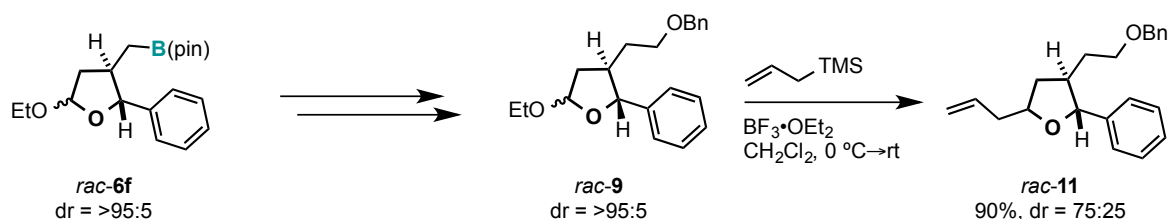


Fig. S2.1 ORTEP structure of (*R,R*)-**10**. Thermal ellipsoids are drawn at the 50% probability level.

Table S2.1. Summary of X-ray crystallographic data for (*R,R*)-**10**

CCDC Name	1528041
Empirical Formula	C ₁₉ H ₂₀ O ₃
Formula Weight	296.37
Crystal System	monoclinic
	0.806 × 0.162 ×
Crystal Size / mm	0.082
<i>a</i> / Å	17.9303(8)
<i>b</i> / Å	6.8625(3)
<i>c</i> / Å	13.4226(6)
β / °	99.456(3)
<i>V</i> / Å ³	1629.17(12)
Space Group	C2 (#5)
<i>Z</i> value	4
<i>D</i> _{calc} / g cm ⁻³	1.208
Temperature / K	123.15
2 θ _{max} / °	136.5
μ (Cu-K α) / cm ⁻¹	6.478
No. of Reflections	Total: 8873
Measured	Unique: 2845 (<i>R</i> _{int} = 0.0400)
No. of Observations (All reflections)	2858
Residuals: <i>R</i> ₁ (<i>I</i> > 2.00 σ (<i>I</i>))	0.0395
Residuals: <i>wR</i> ₂ (All reflections)	0.1104
Goodness of Fit Indicator (GOF)	1.170
Maximum Peak in Final Diff. Map / Å ³	0.19 e-
Minimum Peak in Final Diff. Map / Å ³	-0.21 e-
Flack Parameter	0.04

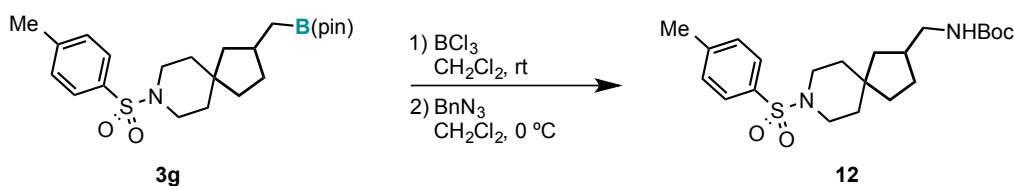
2.4.5.3 Experimental Procedure of Allylation of 9.



The racemic lactol ether **9** was prepared from **6f** according to the procedure described above. The allylation of acetal moiety was performed according to the literature procedure.⁵⁰ In an oven-dried reaction vial, a solution of the lactol ether **9** (65.3 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was treated with allyltrimethylsilane (91.4 mg, 0.8 mmol) and then cooled to $-78\text{ }^\circ\text{C}$. After treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (31.2 mg, 0.22 mmol), the reaction mixture was warmed to room temperature over 2 hours. The reaction mixture was quenched by the addition of saturated aqueous NaHCO_3 solution, extracted three times with CH_2Cl_2 , dried over MgSO_4 , and filtered. The crude mixture was purified by flash column chromatography (SiO_2 , ethyl acetate/hexane, 3:97–10:90) to afford the corresponding **11** (57.9 mg, 0.18 mmol, 90 %) as a colorless oil. The product was obtained as a diastereomixture and the diastereomer ratio for C_5 was determined by ^1H NMR analysis.

^1H NMR (392 MHz, CDCl_3 , δ): 1.18–1.25 (m, 0.25H), 1.40–1.48 (m, 0.25H), 1.57–1.66 (m, 1H), 1.77–1.87 (m, 1.75H), 1.90–1.97 (m, 0.75H), 2.08–2.16 (m, 0.75H), 2.22–2.39 (m, 1.25H), 2.43–2.53 (m, 1H), 3.41 (t, $J = 6.7$, 2H), 4.17 (dt, $J = 6.4$, 13.1 Hz, 0.75H), 4.27–4.47 (m, 3.25H), 5.06–5.16 (m, 2H), 5.80–5.94 (m, 1H), 7.24–7.35 (m, 10H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 31.6 (CH_2), 32.0 (CH_2), 37.1 (CH_2), 39.0 (CH_2), 40.6 (CH_2), 40.8 (CH_2), 44.3 (CH), 46.2 (CH), 68.9 (CH_2), 69.0 (CH_2), 72.8 (CH_2), 77.7 (CH), 78.9 (CH), 86.4 (CH), 87.1 (CH), 116.99 (CH_2), 117.04 (CH_2), 126.46 (CH), 126.52 (CH), 127.5 (CH), 127.6 (CH), 128.2 (CH), 128.3 (CH), 134.6 (CH), 134.8 (CH), 138.3 (C), 141.5 (C), 142.2 (C). HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{22}\text{H}_{26}\text{O}_2\text{Na}$, 345.1825; found, 345.1825.

2.4.5.4 Experimental Procedure of Amination of 3g.

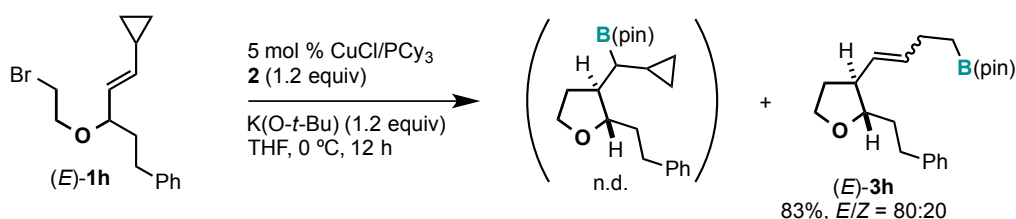


The amination of the boryl group was performed according to the literature procedure.⁵¹ In an oven-dried reaction vial, a solution of BCl_3 in CH_2Cl_2 (1.00 M, 1.85 mL, 1.85 mmol) was added under nitrogen atmosphere. The solution of **3g** (160 mg, 0.370 mmol) in CH_2Cl_2 (2.20 mL) was added to the reaction mixture at room temperature. After 4 hours, the volatile materials were removed under reduced pressure, and dry CH_2Cl_2 (2.20 mL) was added to the resultant product. The reaction vial was cooled to $0\text{ }^\circ\text{C}$, and benzyl azide (148 mg, 1.11 mmol) was added to the mixture. After stirred for 16 hours at $0\text{ }^\circ\text{C}$, the reaction mixture was quenched by adding aqueous NaOH solution (2.00 M), extracted three times with EtOAc , dried over Na_2SO_4 , and filtered. The crude material was then

purified by flash column chromatography (SiO₂, EtOAc/CH₂Cl₂ 0:100–50:50) to obtain the corresponding amine **12** (109 mg, 71%) as a colorless oil.

¹H NMR (392 MHz, CDCl₃, δ): 0.89 (dd, *J* = 9.6, 12.3 Hz, 1H), 1.14–1.26 (m, 1H), 1.28–1.42 (m, 2H), 1.48–1.64 (m, 5H), 1.72–1.80 (m, 1H), 2.02–2.12 (m, 1H), 2.44 (s, 3H), 2.44–2.56 (m, 2H), 2.84–2.93 (m, 2H), 2.99–3.01 (m, 2H), 3.75 (s, 2H), 7.22–7.33 (m, 7H), 7.63 (d, *J* = 8.2 Hz, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 21.4 (CH₃), 29.2 (CH₂), 36.5 (CH₂), 37.0 (CH₂), 37.8 (CH₂), 38.9 (CH), 40.2 (CH), 42.4 (CH₂), 43.6 (CH₂), 44.0 (CH₂), 54.1 (CH₂), 55.2 (CH₂), 126.8 (CH), 127.5 (CH), 127.9 (CH), 128.3 (CH), 129.5 (CH), 133.0 (C), 140.3 (C), 143.2 (C). HRMS-ESI (*m/z*): [M+H]⁺ calcd for C₂₄H₃₃O₂N₂S, 413.2257; found, 413.2257.

2.4.6 Radical clock experiment



Copper chloride (2.5 mg, 0.02500 mmol) and bis(pinacolato)diboron (**2**) (152 mg, 0.600 mmol), PCy₃ (8.3 mg, 0.025 mmol) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a Teflon-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (0.400 mL) and K(O-*t*-Bu)/THF (1.00 M, 0.600 mL, 0.600 mmol) were added in the vial through the rubber septum using a syringe. After stirring for 30 min at 0 °C, **(E)-1h** (173. mg, 0.500 mmol) was added to the mixture at 0 °C. After stirred for 12 hours, the reaction mixture was passed through a short silica gel (Φ: 10 mm, height of the silica-gel column: 30 mm) eluting with Et₂O. The crude material was purified by flash column chromatography (SiO₂, Et₂O/hexane, typically 0:100–10:90) to give the corresponding borylation product **(E)-3h** (147 mg, 0.415 mmol, 83%, *E/Z* = 80:20) as a colorless oil. The *E/Z* ratio was determined by ¹H NMR analysis.

¹H NMR (392 MHz, CDCl₃, δ): 0.82–0.90 (m, 2.5H), 1.229 (s, 12H), 1.234 (m, 3H), 1.66–1.93 (m, 3.75H), 2.05–2.23 (m, 4H), 2.34 (quint, *J* = 8.5 Hz, 1H), 2.59–2.86 (m, 2.75H), 3.41–3.49 (m, 1.25H), 3.84–3.92 (m, 2.5H), 5.17 (t, *J* = 10.3 Hz, 0.25H), 5.28 (dd, *J* = 8.5, 15.3 Hz, 1H), 5.47 (dt, *J* = 7.2, 10.9 Hz, 1H), 5.55 (dt, *J* = 6.5, 15.4 Hz, 1H), 7.15–7.21 (m, 3.75H), 7.25–7.29 (m, 2.5H). ¹³C NMR (99 MHz, CDCl₃, δ): 10.7 (br, B–CH₂), 11.0 (br, B–CH₂), 22.0 (CH₂), 24.7 (CH₃), 26.7 (CH₂), 32.7 (CH₂), 32.8 (CH₂), 33.6 (CH₂), 33.9 (CH₂), 35.7 (CH₂), 35.8 (CH₂), 43.2 (CH), 48.7 (CH), 66.9 (CH₂), 67.1 (CH₂), 82.86 (C), 82.93 (C), 83.1 (CH), 83.6 (CH), 125.5 (CH), 128.18 (CH), 128.29 (CH), 128.33 (CH), 128.9 (CH), 129.0 (CH), 133.5 (CH), 133.8 (CH), 142.2 (C), 142.3 (C). HRMS-ESI (*m/z*): [M+Na]⁺ calcd for C₂₂H₃₃O₃BNa, 379.2415; found, 379.2409.

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Chapter 3

Copper(I)-Catalyzed Regioselective Hydroboration of Aliphatic Terminal Alkenes

Abstract A Markovnikov hydroboration of alkyl-substituted terminal alkenes has been developed by the ligand-controlled regioselectivity of the copper(I)-catalyzed hydroboration with a diboron reagent. We found that a bulky bisphosphine-copper(I) catalyst system shows high regioselectivity to afford secondary alkylboronates from the corresponding terminal alkenes (branch/linear = 92:8–97:3).

3.1 Introduction

Since Harbert C. Brown reported the first example of hydroboration of alkenes with borane reagent, hydroboration reactions became the most fundamental and useful methods to prepare various organoboron compounds.^{1,2} In particular, the resulting alkylboronates have been recognized as versatile building blocks in synthetic organic chemistry because the C–B bond can be transformed into various functional groups in stereospecific manner.^{3–6} Generally, non-catalytic or catalytic hydroborations of terminal alkenes show *anti*-Markovnikov regioselectivity to afford primary alkylboronates (Fig. 3.1a).^{2,7–13} On the other hand, rhodium(I)-catalyzed Markovnikov hydroborations of styrene-type terminal alkenes utilizing a substrate controlled regioselectivity have been achieved (Fig. 3.1b).^{14–19} Furthermore, regioselectivity of hydroboration can be controlled by directing group such as amide moiety.^{20–22} Although great efforts have been devoted to controlling the regioselectivity of transition-metal-catalyzed hydroboration of terminal alkenes, no practical method for Markovnikov hydroboration of alkyl-substituted terminal alkenes have been reported.²³

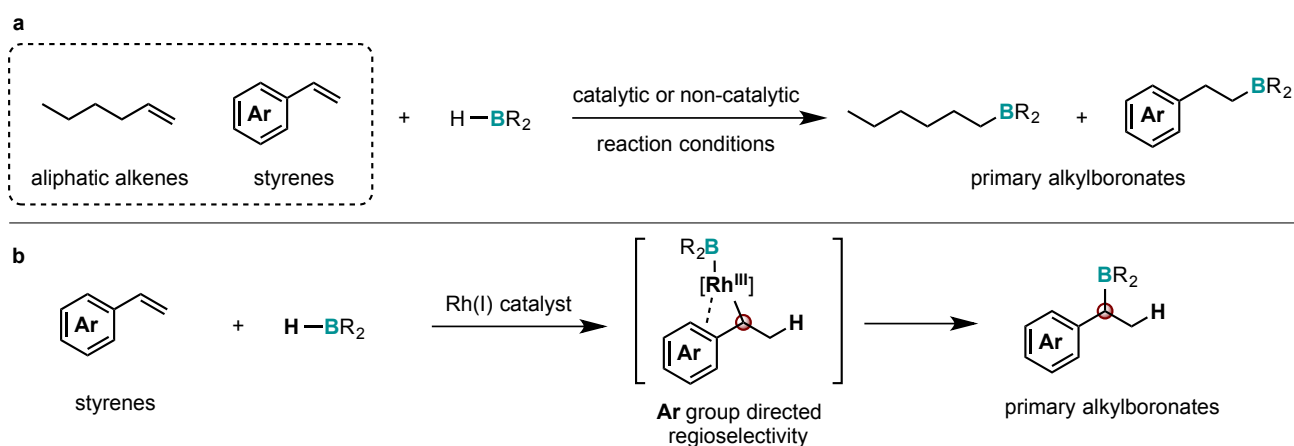


Fig. 3.1 a) *anti*-Markovnikov hydroboration of alkenes. b) Markovnikov hydroboration of styrenes.

In 2013, our group reported the first example of copper(I)-catalyzed hydroboration of unactivated aliphatic terminal alkenes giving the corresponding primary alkylboronates which can be called anti-Markovnikov hydroboration products.²⁴ The mechanism involves the reaction between borylcopper(I) active species and terminal carbon–carbon double bonds selectively to afford secondary alkylcopper(I) intermediate when Xantphos was used as a ligand (Fig. 3.2). Moreover, the previous report suggested that the regioselectivity of copper(I)-catalyzed hydroboration of the terminal alkenes are drastically changed by choosing the ligand. Recently several groups reported that the regioselectivity in borylcupration of the terminal alkenes can be controlled by the ligand. The level of the regioselectivity of the borylcupration step and the yields of hydroboration products, however, were not sufficient.^{25–28} In this work, we conducted the further investigation of the catalytic system to achieve Markovnikov hydroboration of aliphatic alkenes with high reactivity and regioselectivity.

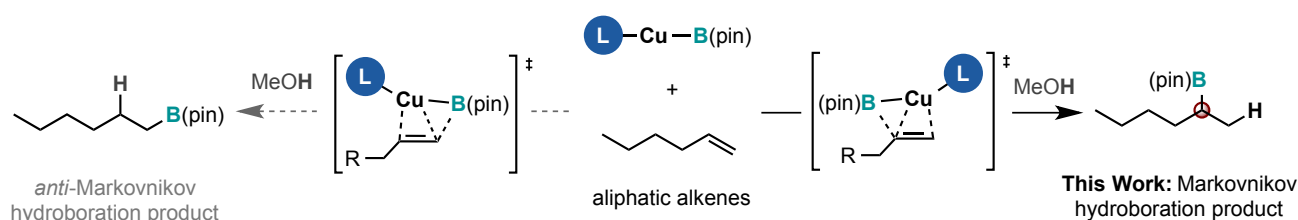


Fig. 3.2 Ligand-controlled regioselectivity of borylcopper(I)-mediated hydroboration of aliphatic terminal alkenes.

3.2 Result and Discussion

The copper(I)-catalyzed hydroboration of **1a** with bis(pinacolato)diboron (**2**) using Xantphos gave the primary alkylboronate **4a** in a high yield with excellent *anti*-Markovnikov regioselectivity (**4a**: 97%, **3a/4a** = 2:98, entry 1) as we previously reported.²⁴ Use of dppp and dppf resulted in lower regioselectivity, and primary alkylboronate **4a** was still obtained as the major product (**3a/4a** = 36:64, entry 2, **3a/4a** = 27:73, entry 3), whereas, dppe ligand furnished trace amounts of hydroboration products **3a** and **4a** (**3a/4a** = 51:49, entry 4). Dppbz ligand featuring a small bite-angle and a rigid backbone showed moderate Markovnikov regioselectivity with high substrate conversion (**3a**: 59%, **3a/4a** = 68:32, entry 5). We also tested the NHC ligand such as IPr•HCl. Although this system showed good Markovnikov regioselectivity, the conversion was low (**3a**: 14%, **3a/4a** = 85:15, entry 6).²⁵ The use of Cy-Xantphos that was reported by Fu and co-workers exhibited sluggish reactivity under our reaction conditions (**3a**: 1%, **3a/4a** = 85:15, entry 7).²⁶ The reaction without ligand resulted in low conversion, but moderate branch selectivity was emerged (**3a**: 3%, entry 8).²⁸ We then optimized the substituents on the phosphorus atoms of dppbz ligand because the regioselectivity would be raised by the small bite-angle of bisphosphine ligands (Fig. 3.3). Ligands **L1** and **L2**, which have bulky substituents, *tert*-butyl or trimethyl silyl groups at 3,5-position of phenyl rings, also exhibited high reactivity, but the regioselectivity was slightly higher than that of using dppbz (**3a**: 69%, **3a/4a** = 78:22, entry 9; **3a**: 61%, **3a/4a** = 75:25, entry 10).²⁹ Finally, we found that the reaction using a ligand **L3**

bearing 2-methyl-phenyl moieties on both phosphorus atoms gave **3a** in a high yield with excellent Markovnikov regioselectivity (**3a**: 82%, **3a/4a** = 97:3, entry 11).³⁰

Table 3.1 Optimization of borylsubstitution selective reaction of **1a**.^a

entry	ligand	yield of 3a (%) ^b	yield of 4a (%) ^b	3a/4a ^b
1	Xantphosdppp	2	97	2:98
2	dppf	31	54	36:64
3	dppp	9	25	27:73
4	dppe	1	<1	51:49
5	dppbz	59	28	68:32
6	IPr•HCl	14	3	85:15
7	Cy-Xatphos	1	<1	85:15
8	-	3	<1	82:18
9	L1	69	19	78:22
10	L2	61	20	75:25
11	L3	82	3	97:3

^aConditions: CuCl (0.025 mmol), ligand (0.025 mmol), **1a** (0.5 mmol), bis(pinacolato)diboron (**2**) (0.6 mmol), and K(O-*t*-Bu) (0.6 mmol) in THF (1.0 mL) at -10 °C. ^bDetermined by GC analysis of the crude reaction mixture using an internal standard.

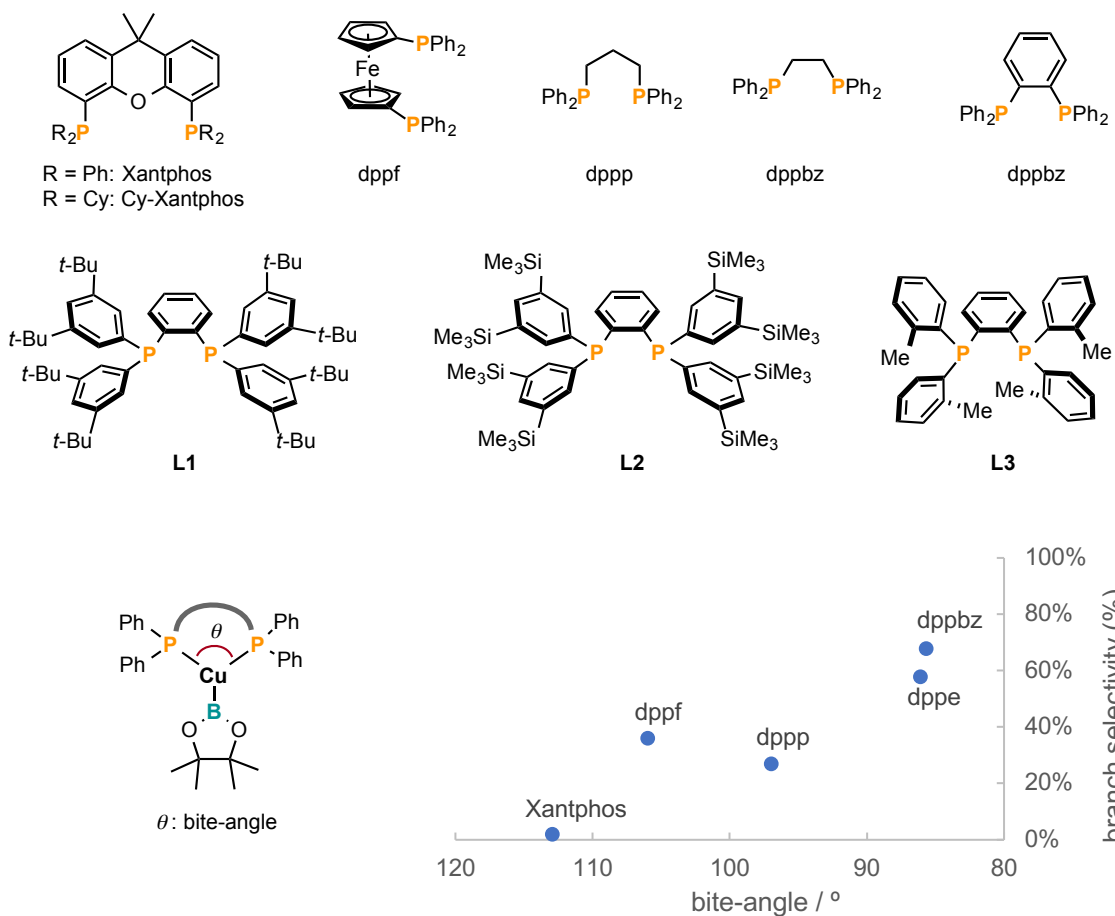
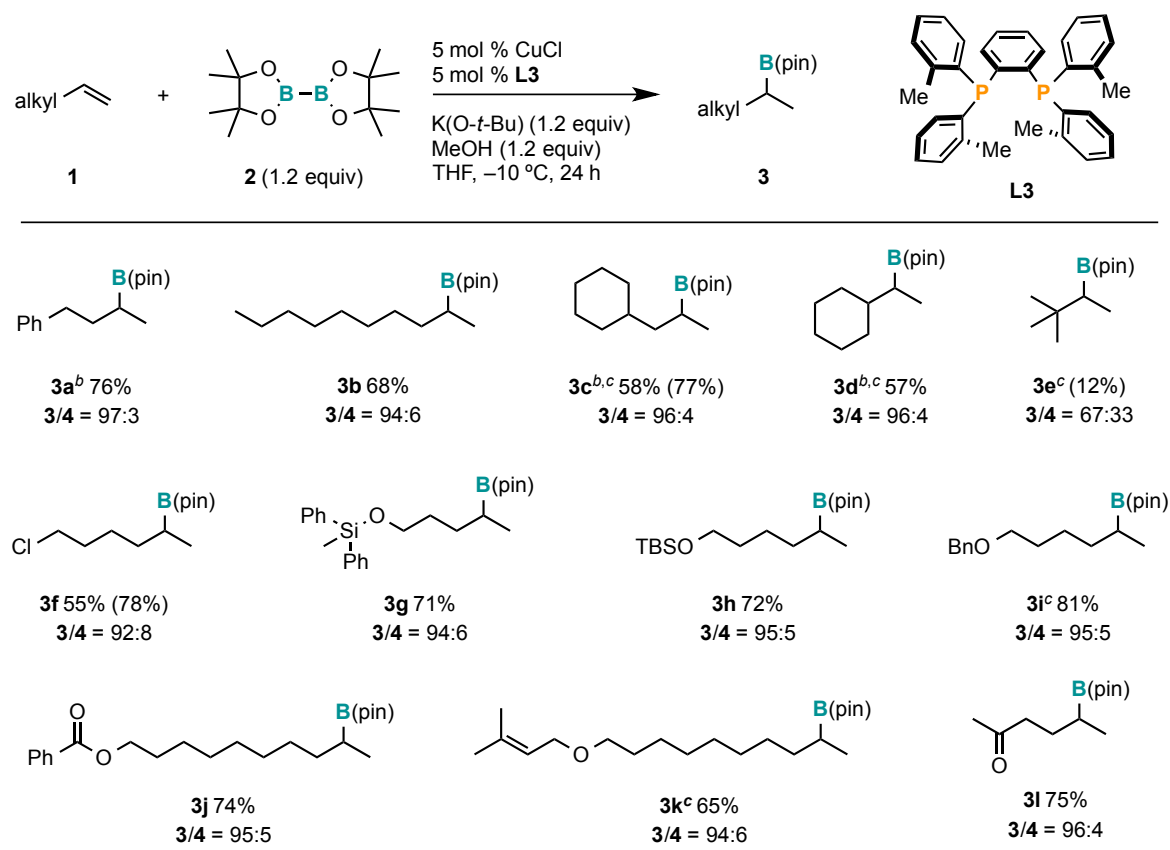


Fig. 3.3 Bite-angle dependent regioselectivity of hydroboration [bite-angle of borylcopper(I) complexes were calculated by B3PW91/cc-pVDZ gas phase 298 K].

Having the optimized reaction conditions, we next investigated the substrate compatibility of the Markovnikov hydroboration of various aliphatic terminal alkenes (Table 3.2). We first examined substrates **1a–e** only consisted of carbon and hydrogen atoms. The corresponding products **3a** and **3b** were obtained in good yields with high regioselectivity (**3a**: 76%, **3/4** = 97:3, **3b**: 68%, **3/4** = 94:6). This catalyst system was applicable to terminal alkene **1c** bearing a bulky substituent such as cyclohexyl group (58%, **3/4** = 96:4). Moreover, vinyl cyclohexane (**1d**), which is more steric congested terminal alkene than **1c**, was successfully converted to the corresponding product **3d** without a loss of the regioselectivity (57%, **3/4** = 96:4). However, the reaction of the highly steric congested terminal alkene **1e** was resulted in a low yield and moderate regioselectivity (12%, **3/4** = 67:33). Next, we tested a variety of terminal alkenes containing functional groups (**1f–k**). Slightly reducing the regioselectivity was observed when terminal alkene **1f** bearing alkyl chloride moiety was used as a substrate (55%, **3/4** = 92:8). We found that our Markovnikov hydroboration reaction allowed the various functional groups such as silyl ethers **1g** and **1h**, benzyl ethers **3i**, benzoyl ester **1j**, internal alkene **1k** and ketone **1l** to afford the corresponding products in good yields with excellent regioselectivity (**3g–3l**: 65–81% yield, **3/4** = >94:6).

Table 3.2 Substrate scope for Markovnikov hydroboration of aliphatic alkenes **1**.^a



^aConditions: **1** (0.5 mmol), CuCl (0.025 mmol), **L2** (0.025 mmol), **2** (0.6 mmol), K(O-*t*-Bu) (0.6 mmol), THF (1.0 mL), -10 °C. Isolated yield. NMR yield is shown in the parenthesis. Regioselectivity was determined by ¹H NMR analysis of the crude reaction mixture using an internal standard. ^bDetermined by GC analysis of the crude material. ^cReaction time was 48 h.

In order to confirm the reaction mechanism, we conducted the several experiments (Fig. 3.4). The use of MeOD instead of MeOH gave the corresponding 1-deuterated product with excellent regioselectivity (**3c-D**: 54%, **3/4** = 96:4, Fig. 3.4a). It suggests that this hydroboration reaction proceeds through regioselective borylcupration of terminal alkene followed by protonation of the alkylcopper(I) intermediate with the alcohol (Fig. 3.2). As another possible reaction pathway, we considered the diboration/proto-deborylation pathway. In 2011, Fernández and co-workers reported that Lewis base catalyzed diboration reaction of terminal alkenes to give the corresponding 1,2-bis(boronates) products.³¹ Furthermore, Morken and co-workers have proposed chemoselective activation of the terminal boryl moiety of 1,2-bis(boronates) compounds.^{32,33} To check these plausible deborylation pathway, we conducted the proto-deborylation reaction of 1,2-bis(boronates) **5** as a substrate for the copper(I)-alkoxide catalyst (Fig. 3.4b). As a result, the protonated product **3a** was not detected and the substrate **5** was fully recovered. Thus, the possibility that the diboration–transmetalation event precedes the borylcupration of terminal alkenes can be ruled out.

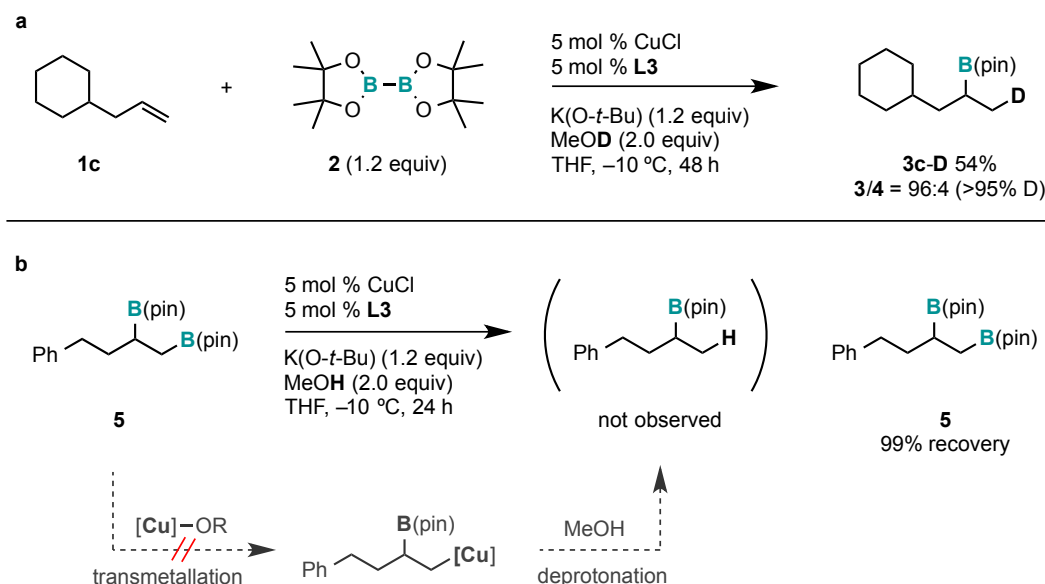


Fig. 3.4 a) Deuteration experiment with MeOD. b) Protodeborylation of diboration product **5**.

On the basis of these experiments, we propose the following catalytic cycle (Fig. 3.5). The borylcopper(I) active species **B** and terminal alkene **1** form the copper(I)-alkene complex **C** followed by regioselective borylcupration of the carbon-carbon double bond to afford the alkylcopper(I) intermediate **D** where the copper moiety is introduced at the 2-position, whereas the boron moiety is introduced at the 1-position. Protonation of the intermediate **D** with alcohol gives the product **3** and reproduces the copper(I) alkoxide **A**. Transition state models of the insertion step from **C** to **D** suggest the regioselectivity of our hydroboration reaction (Fig. 3.6). The favored transition state **TS-b** would be free from steric congestion between an alkyl chain of the substrate **1** and *ortho*-methyl-phenyl moiety in ligand **L3**, thus producing Markovnikov hydroboration product **3**. In contrast, the disfavored

transition state **TS-I** would be destabilized because of steric repulsion between an alkyl chain of the substrate **1** and *ortho*-methyl-phenyl moiety of **L3**.

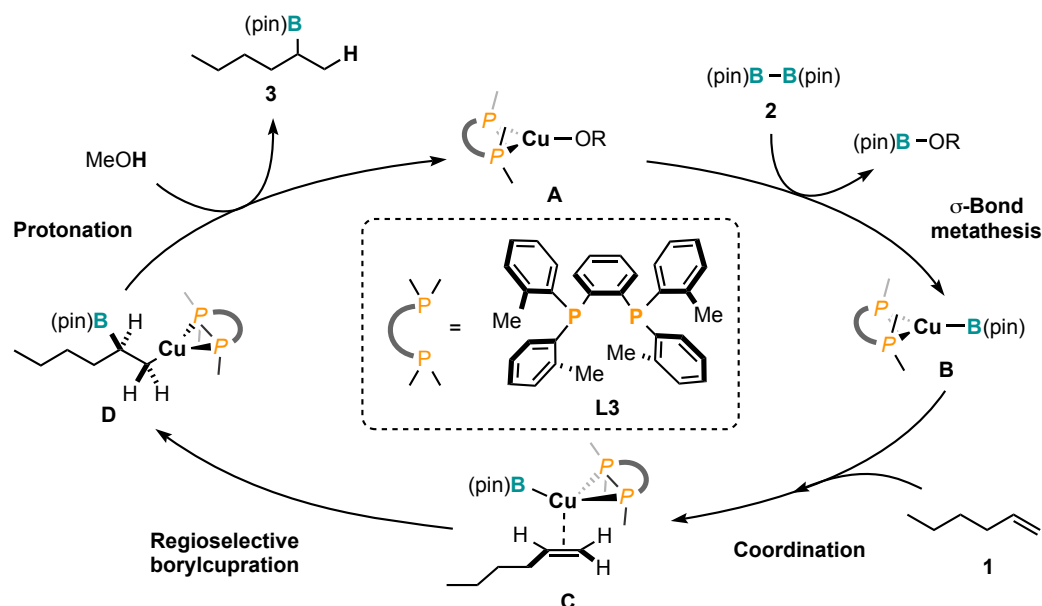


Fig. 3.5 Proposed catalytic cycle for copper(I)-catalyzed hydroboration of aliphatic terminal alkenes.

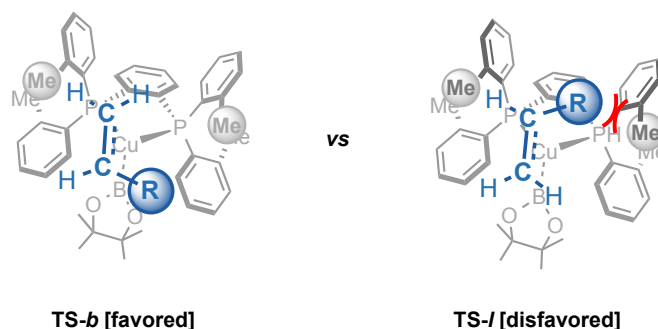


Fig. 3.6 Plausible reaction pathways for borylative radical cyclization and allylic borylation.

3.3 Conclusion

In conclusion, we have achieved the copper(I)-catalyzed highly regioselective Markovnikov hydroboration of alkyl-substituted terminal alkenes. We found that a bisphosphine ligand bearing a narrow bite-angle, a rigid backbone and a sterically bulky substituent in the proximal region to the copper(I) center is effective for regioselective borylcupration of terminal carbon-carbon double bond to give the Markovnikov hydroboration products. This reaction can be recognized as a complementary method to classical *anti*-Markovnikov hydroborations of terminal alkenes.

3.4 Experimental

3.4.1 General

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4A). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^1H : 400 MHz, ^{13}C : 100 MHz and ^{11}B : 127 MHz). Tetramethylsilane (^1H), CDCl_3 (^{13}C) and $\text{BF}_3\cdot\text{OEt}_2$ (^{11}B) were employed as the external standards, respectively. Infrared (IR) spectra were recorded on a JASCO FT/IR-4600 spectrometer. CuCl (ReagentPlus® grade, 224332-25G, $\geq 99\%$) and $\text{K}(\text{O}-t\text{-Bu})$ / THF (1.0 M, 328650-50ML) were purchased from Sigma-Aldrich Co. and used as received. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with a ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and a FID detector. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University.

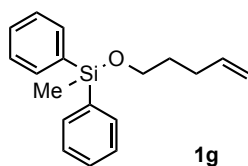
3.4.2 General Experimental Procedure

Copper chloride (2.5 mg, 0.025 mmol) and bis(pinacolato)diboron (**2**) (152.4 mg, 0.60 mmol), **L2** (12.6 mg, 0.025 mmol) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a teflon-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (0.4 mL) and $\text{K}(\text{O}-t\text{-Bu})/\text{THF}$ (1.0 M, 0.6 mL, 0.6 mmol) were added in the vial through the rubber septum using a syringe. The reaction mixture was stirred at room temperature and cooled down to $-10\text{ }^\circ\text{C}$. After stirring for 15 min, **1a** (74.5. mg, 0.50 mmol) and methanol were added dropwise to the mixture. After the reaction was complete, the reaction mixture was passed through a silica gel column (radius: 10 mm, height of the column: 30 mm) eluting with Et_2O . The crude material was purified by flash column chromatography (SiO_2 , CH_2Cl_2 /pentane, typically 0:100–40:60) to give the corresponding borylation product **3a** as a colorless oil.

3.4.3 Substrate preparation

The substrates for asymmetric borylation **1a–1f** and **1l** were purchased from commercial suppliers.

3.4.3.1 Methyl(pent-4-en-1-yloxy)diphenylsilane (**1g**).

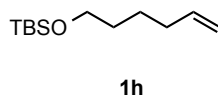


1g was prepared from 4-penten-1-ol according to the standard silylation procedure.

^1H NMR (392 MHz, CDCl_3 , δ): 0.64 (s, 3H), 1.67 (dt, $J = 7.1, 14.4$ Hz, 2H), 2.12 (q, $J = 7.0$ Hz,

2H), 3.71 (t, $J = 6.5$ Hz, 2H), 4.91–5.03 (m, 2H), 5.78 (ddt, $J = 6.7, 10.3, 17.1$ Hz, 1H), 7.35–7.43 (m, 6H), 7.59 (d, $J = 7.2$ Hz, 4H). ^{13}C NMR (99 MHz, CDCl_3 , δ): –3.1 (CH_3), 30.0 (CH_2), 31.7 (CH_2), 62.8 (CH_2), 114.6 (CH_2), 127.8 (CH), 129.7 (CH), 134.3 (CH), 136.1 (C), 138.2 (CH). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{18}\text{H}_{22}\text{OSi}$, 282.14399; found, 282.14461.

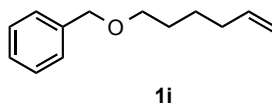
3.4.3.2 *tert*-Butyl(hex-5-en-1-yloxy)dimethylsilane (**1h**).³⁴



1h was prepared from 5-hexen-1-ol according to the standard silylation procedure.

^1H NMR (392 MHz, CDCl_3 , δ): 0.05 (s, 6H), 0.89 (s, 9H), 1.39–1.47 (m, 2H), 1.50–1.57 (m, 2H), 2.06 (q, $J = 7.2$ Hz, 2H), 3.61 (t, $J = 6.5$ Hz, 2H), 4.92–5.03 (m, 2H), 5.81 (ddt, $J = 6.7, 10.3, 17.1$ Hz, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): –5.3 (CH_3), 18.3 (C), 25.2 (CH_2), 25.9 (CH_3), 32.3 (CH_2), 33.6 (CH_2), 63.0 (CH_2), 114.4 (CH_2), 138.8 (CH). HRMS–EI (m/z): $[\text{M}-\text{CH}_3]^+$ calcd for $\text{C}_{11}\text{H}_{23}\text{OSi}$, 199.15182; found, 199.15114.

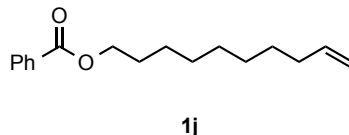
3.4.3.3 [(Hex-5-en-1-yloxy)methyl]benzene (**1i**).³⁵



1i was prepared from 5-hexen-1-ol according to the standard benzyl protection procedure.

^1H NMR (392 MHz, CDCl_3 , δ): 1.44–1.52 (m, 2H), 1.60–1.67 (m, 2H), 2.04–2.10 (m, 2H), 3.48 (t, $J = 6.5$ Hz, 2H), 4.50 (s, 2H), 4.93–5.03 (m, 2H), 5.81 (ddt, $J = 6.7, 10.3, 17.1$ Hz, 1H), 7.26–7.37 (m, 5H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 25.3 (CH_2), 29.1 (CH_2), 33.4 (CH_2), 70.0 (CH_2), 72.6 (CH_2), 114.4 (CH_2), 127.0 (CH), 127.3 (CH), 127.4 (C), 128.1 (CH), 138.5 (CH). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{13}\text{H}_{18}\text{O}$, 190.13576; found, 190.13523.

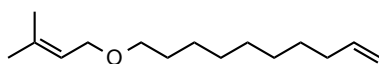
3.4.3.4 Dec-9-en-1-yl benzoate (**1j**).³⁶



1j was prepared from 9-decen-1-ol according to the standard benzoate protection procedure.

^1H NMR (392 MHz, CDCl_3 , δ): 1.31–1.48 (m, 10H), 1.76 (dt, $J = 7.1$ Hz, 14.4 Hz, 2H), 2.04 (q, $J = 6.9$ Hz, 2H), 4.32 (t, $J = 6.7$ Hz, 2H), 4.91–5.02 (m, 2H), 5.81 (ddt, $J = 6.7, 10.2, 17.1$ Hz, 1H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.54–7.58 (m, 1H), 8.03–8.06 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 25.9 (CH_2), 28.6 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 33.7 (CH_2), 65.0 (CH_2), 114.1 (CH_2), 128.2 (CH), 129.4 (CH), 130.4 (C), 132.7 (CH), 139.0 (CH), 166.5 (C). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{17}\text{H}_{24}\text{O}_2$, 260.17763; found, 260.17723.

3.4.3.5 10-[(3-Methylbut-2-en-1-yl)oxy]dec-1-ene (1k).



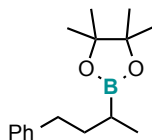
1k

1k was prepared from 9-decen-1-ol according to the standard etherification procedure.

^1H NMR (392 MHz, CDCl_3 , δ): 1.29–1.41 (m, 10H), 1.54–1.61 (m, 2H), 1.67 (s, 3H), 1.74 (s, 3H), 2.03 (q, $J = 7.0$ Hz, 2H), 3.40 (t, $J = 6.9$ Hz, 2H), 3.94 (d, $J = 6.9$ Hz, 2H), 4.91–5.02 (m, 2H), 5.33–5.38 (m, 1H), 5.81 (ddt, $J = 6.9, 10.5, 17.1$ Hz, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 17.9 (CH_3), 25.7 (CH_3), 26.1 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 29.4 (CH_2), 29.7 (CH_2), 33.7 (CH_2), 67.1 (CH_2), 70.2 (CH_2), 114.0 (CH_2), 121.3 (CH), 136.4 (C), 139.0 (CH). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{28}\text{O}$, 224.21401; found, 224.21380.

3.4.4 Borylation Product Characterization

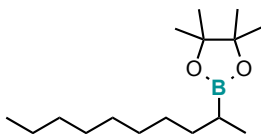
3.4.4.1 4,4,5,5-Tetramethyl-2-(4-phenylbutan-2-yl)-1,3,2-dioxaborolane (3a).³⁷



3a

^1H NMR (392 MHz, CDCl_3 , δ): 1.01–1.11 (m, 4H), 1.25 (s, 12H), 1.54–1.63 (m, 1H), 1.74–1.83 (m, 1H), 2.56–2.67 (m, 2H), 7.14–7.20 (m, 3H), 7.25–7.28 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 15.4 (CH_3), 16.8 (br, B–CH), 24.7 (CH_3), 24.8 (CH_3), 35.3 (CH_2), 82.9 (C), 125.5 (CH), 128.2 (CH), 128.4 (CH), 143.0 (C). ^{11}B NMR (127 MHz, CDCl_3 , δ): 34.2. FT-IR (neat): $\nu_{\text{max}} = 2976, 1370, 1315, 1145, 699\text{ cm}^{-1}$. HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{16}\text{H}_{25}\text{BO}_2$, 260.19476; found, 260.19437.

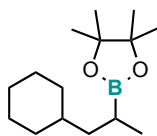
3.4.4.2 2-(Decan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3b).



3b

^1H NMR (392 MHz, CDCl_3 , δ): 0.88 (t, $J = 6.7$ Hz, 3H), 0.95–1.01 (m, 4H), 1.20–1.29 (m, 25H), 1.40–1.46 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 14.1 (CH_3), 15.5 (CH_3), 16.8 (br, B–CH), 22.7 (CH_2), 24.67 (CH_3), 24.71 (CH_3), 29.0 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 31.9 (CH_2), 33.2 (CH_2), 82.7 (C). ^{11}B NMR (127 MHz, CDCl_3 , δ): 34.3. FT-IR (neat): $\nu_{\text{max}} = 2923, 1370, 1312, 1144, 860\text{ cm}^{-1}$. HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{16}\text{H}_{33}\text{BO}_2$, 268.25736; found, 268.25827.

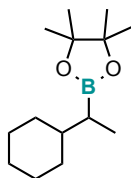
3.4.4.3 2-(1-Cyclohexylpropan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3c).



3c

^1H NMR (392 MHz, CDCl_3 , δ): 0.74–0.89 (m, 2H), 0.93 (d, $J = 7.3$ Hz, 3H), 1.06–1.40 (m, 20H), 1.60–1.70 (m, 4H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 14.1 (br, B–CH), 15.7 (CH_3), 24.7 (CH_3), 26.4 (CH_2), 26.5 (CH_2), 26.7 (CH_2), 33.1 (CH_2), 33.6 (CH_2), 36.5 (CH), 40.8 (CH_2), 82.7 (C). ^{11}B NMR (127 MHz, CDCl_3 , δ): 34.3. FT-IR (neat): $\nu_{\text{max}} = 2920, 1369, 1312, 1144, 861\text{ cm}^{-1}$. HRMS–EI (m/z): $[\text{M}]^+$ calcd for, $\text{C}_{15}\text{H}_{29}\text{BO}_2$, 252.22606; found, 252.22711.

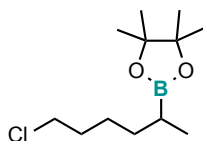
3.4.4.4 2-(1-Cyclohexylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3d).³⁸



3d

^1H NMR (392 MHz, CDCl_3 , δ): 0.86–1.40 (m, 22H), 1.62–1.75 (m, 5H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 12.5 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 26.69 (CH_2), 26.75 (CH_2), 31.8 (CH_2), 32.7 (CH_2), 40.4 (CH), 82.7 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, CDCl_3 , δ): 34.1. FT-IR (neat): $\nu_{\text{max}} = 2921, 1358, 1310, 1143, 863\text{ cm}^{-1}$. HRMS–EI (m/z): $[\text{M}]^+$ calcd for, $\text{C}_{14}\text{H}_{27}\text{BO}_2$, 238.21041; found, 238.21127.

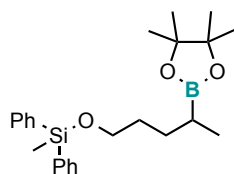
3.4.4.5 2-(6-Chlorohexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3f).³⁸



3f

^1H NMR (392 MHz, CDCl_3 , δ): 0.86–1.40 (m, 22H), 1.62–1.75 (m, 5H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 12.5 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 26.69 (CH_2), 26.75 (CH_2), 31.8 (CH_2), 32.7 (CH_2), 40.4 (CH), 82.7 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, CDCl_3 , δ): 34.1. FT-IR (neat): $\nu_{\text{max}} = 2921, 1358, 1310, 1143, 863\text{ cm}^{-1}$. HRMS–EI (m/z): $[\text{M}]^+$ calcd for, $\text{C}_{14}\text{H}_{27}\text{BO}_2$, 238.21041; found, 238.21127.

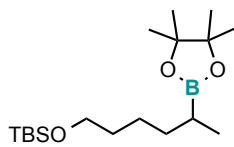
3.4.4.6 Methyldiphenyl{[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl]oxy}silane (3g).



3g

^1H NMR (392 MHz, CDCl_3 , δ): 0.63 (s, 3H), 0.93–1.01 (m, 4H), 1.22–1.50 (m, 14H), 1.55–1.64 (m, 2H), 3.68 (t, $J = 7.0$ Hz, 2H), 7.34–7.43 (m, 6H), 7.58–7.60 (m, 4H). ^{13}C NMR (99 MHz, CDCl_3 , δ): –3.0 (CH_3), 15.5 (CH_3), 16.7 (br, B–CH), 24.6 (CH_3), 24.7 (CH_3), 29.2 (CH_2), 31.9 (CH_2), 63.8 (CH_2), 82.7 (C), 127.7 (CH), 129.6 (CH), 134.3 (CH), 136.2 (C). ^{11}B NMR (127 MHz, CDCl_3 , δ): 34.1. FT-IR (neat): $\nu_{\text{max}} = 2928, 1315, 1145, 1118, 736\text{ cm}^{-1}$. HRMS–EI (m/z): $[\text{M}]^+$ calcd for, $\text{C}_{24}\text{H}_{35}\text{BO}_3\text{Si}$, 410.24485; found, 410.24413.

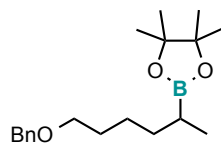
3.4.4.7 *tert*-Butyldimethyl{[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexyl]oxy}silane (3h).



3h

^1H NMR (392 MHz, CDCl_3 , δ): 0.04 (s, 6H), 0.89 (s, 9H), 0.95–1.07 (m, 4H), 1.23–1.54 (m, 18H), 3.59 (t, $J = 6.5$ Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): –5.3 (CH_3), 15.5 (CH_3), 16.9 (br, B–CH), 18.3 (C), 24.68 (CH_3), 24.72 (CH_3), 25.2 (CH_2), 26.0 (CH_3), 33.0 (CH_2), 33.1 (CH_2), 63.3 (CH_2), 82.7 (C). ^{11}B NMR (127 MHz, CDCl_3 , δ): 34.2. FT-IR (neat): $\nu_{\text{max}} = 2929, 1313, 1145, 1097, 834\text{ cm}^{-1}$. HRMS–EI (m/z): $[\text{M}-\text{CH}_3]^+$ calcd for $\text{C}_{17}\text{H}_{36}\text{BO}_3\text{Si}$, 327.25268; found, 327.25236.

3.4.4.8 2-[6-(Benzyloxy)hexan-2-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3i).

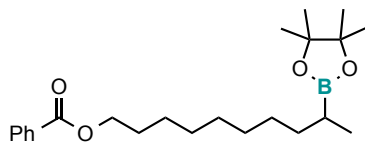


3i

^1H NMR (392 MHz, CDCl_3 , δ): 0.94–1.07 (m, 4H), 1.23–1.51 (m, 16H), 1.57–1.65 (m, 2H), 3.46 (t, $J = 6.7$ Hz, 2H), 4.50 (s, 2H), 7.25–7.34 (m, 5H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 15.4 (CH_3), 16.9 (br, B–CH), 24.61 (CH_3), 24.65 (CH_3), 25.4 (CH_2), 29.9 (CH_2), 32.9 (CH_2), 70.4 (CH_2), 72.7 (CH_2), 82.7 (C), 127.3 (CH), 127.4 (CH), 128.2 (CH), 138.7 (C). ^{11}B NMR (127 MHz, CDCl_3 , δ): 34.2. FT-IR (neat): $\nu_{\text{max}} = 3064, 1369, 1313, 1144, 697\text{ cm}^{-1}$. HRMS–EI (m/z): $[\text{M}]^+$ calcd for, $\text{C}_{19}\text{H}_{31}\text{BO}_3$,

318.23662; found, 318.23709.

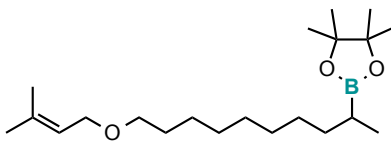
3.4.4.9 9-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)decyl benzoate (3j).



3j

^1H NMR (392 MHz, CDCl_3 , δ): 0.95–1.01 (m, 4H), 1.23–1.47 (m, 24H), 1.76 (dt, $J = 7.1$ Hz, 14.4 Hz, 2H), 4.31 (t, $J = 6.7$ Hz, 2H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.53–7.58 (m, 1H), 8.03–8.06 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 15.4 (CH_3), 16.8 (br, B–CH), 24.60 (CH_3), 24.64 (CH_3), 25.9 (CH_2), 28.6 (CH_2), 28.8 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 29.7 (CH_2), 33.1 (CH_2), 65.0 (CH_2), 82.6 (C), 128.2 (CH), 129.4 (CH), 130.4 (C), 132.6 (CH), 166.5 (C). ^{11}B NMR (127 MHz, CDCl_3 , δ): 34.2. FT-IR (neat): $\nu_{\text{max}} = 2924, 1720, 1273, 1145, 713\text{ cm}^{-1}$. HRMS–EI (m/z): $[\text{M}]^+$ calcd for, $\text{C}_{23}\text{H}_{37}\text{BO}_4$, 388.27849; found, 388.27830.

3.4.4.10 4,4,5,5-Tetramethyl-2-{10-[(3-methylbut-2-en-1-yl)oxy]decan-2-yl}-1,3,2-dioxaborolane (3k).



3k

^1H NMR (392 MHz, CDCl_3 , δ): 0.95–1.03 (m, 4H), 1.24–1.46 (m, 24H), 1.53–1.60 (m, 2H), 1.67 (s, 3H), 1.74 (s, 3H), 3.39 (t, $J = 7.0$ Hz, 2H), 3.94 (d, $J = 6.7$ Hz, 2H), 5.33–5.38 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 15.4 (CH_3), 16.8 (br, B–CH), 17.9 (CH_3), 24.58 (CH_3), 24.61 (CH_3), 25.7 (CH_3), 26.1 (CH_2), 28.8 (CH_2), 29.36 (CH_2), 29.45 (CH_2), 29.68 (CH_2), 29.72 (CH_2), 33.1 (CH_2), 67.1 (CH_2), 70.3 (CH_2), 82.6 (C), 121.3 (CH), 136.4 (C). ^{11}B NMR (127 MHz, CDCl_3 , δ): 34.2. FT-IR (neat): $\nu_{\text{max}} = 2925, 1370, 1313, 1144, 859\text{ cm}^{-1}$. HRMS–EI (m/z): $[\text{M}]^+$ calcd for, $\text{C}_{21}\text{H}_{41}\text{BO}_3$, 352.31487; found, 352.31532.

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Chapter 4

Computational Design of Chiral Bisphosphine Ligand for Copper(I)-Catalyzed Enantioselective Markovnikov Hydroboration of Aliphatic Terminal Alkenes

Abstract Discovery of an optimal chiral ligand in a transition-metal-catalyzed asymmetric reaction is often time-consuming and high-cost process even if the detail of reaction mechanism has already been known. Although modern computational analysis has achieved the stereoselectivity prediction, there are still scarcely examples of the attempt to design chiral ligand with combination of the computational and experimental method for further improvement of the stereoselectivity. Herein, we established a systematic chiral ligand design method utilizing the computational and experimental evaluation sequence for enantioselective Markovnikov hydroboration of aliphatic terminal alkenes. The newly developed a three-hindered quadrant P-chirogenic bisphosphine ligand that is designed in accordance with design direction from computational study performed the Markovnikov hydroboration of aliphatic terminal alkenes with high enantioselectivity (up to 99% ee).

4.1 Introduction

Asymmetric catalysis is one of the most sophisticated molecular systems established by scientists.¹ After beginning of this research field in 1960's, the discovery of optimal chiral catalyst for asymmetric reactions has been highly depending on experimental trial and error. This conventional method is time-consuming and expensive process especially in the case of asymmetric catalysis. Although recent high throughput screening technique can improve the discovery efficiency⁵⁻⁷, when the catalyst structures are complicated and their synthesis is laborious, the preparation of the catalyst library is then a great bottleneck. Moreover, in the point of achievement of very high enantioselectivity, it is the less likely that a better catalyst can be found by chance through screening from the chiral catalyst library or structure modification of the present catalyst without any rational guidance for the selectivity improvement. Recent development of density functional theory (DFT) calculations enables us to get information of the possible reaction paths including intermediates and transition-state structures, and the modern methods including dispersion correlation reaches a level of high accuracy in terms of stereoselectivity prediction in organic reactions.⁸⁻¹⁵ Whereas, the multidimensional analysis using steric parameters and properties of organic compounds for asymmetric reactions have successfully developed.¹⁶⁻¹⁹ However, there is still scarce example where the computational results were effectively utilized for the rational design for enantioselective catalyst.²⁰⁻²³ Our basic motivation is to conduct a design of a new asymmetric catalyst by utilizing combination of DFT calculations and experimental

evaluations (Fig. 4.1).



Fig. 4.1 Assistant tools for organic reaction development.

As the target reaction, we focus on the regio- and enantioselective transformations of aliphatic terminal alkenes (α -olefins), which are feedstock chemicals obtained by petrochemicals. Their asymmetric functionalization with high selectivity (>95% ee) remains challenging because of their small steric demand and small electronic differentiation between the terminal and internal carbons.^{24–36} Among them, we adopted asymmetric hydroboration reactions of aliphatic terminal alkenes with copper(I)-catalyst as a target of our catalyst design project (Fig. 4.2). It is well-known that hydroboration of terminal alkenes proceeds in *anti*-Markovnikov regioselectivity under both uncatalyzed- and catalyzed reaction conditions.^{37,38} In contrast to this, development of Markovnikov hydroboration is a long-standing issue. In 1989, Hayashi and co-workers realized the first enantioselective Markovnikov hydroboration of styrene substrates with the chiral rhodium catalyst^{39–41} to provide enantioenriched secondary alkylboronates which are versatile intermediates in organic chemistry.^{42,43} For aliphatic terminal alkenes, even under uncatalyzed nor catalyzed conditions, achieving the high Markovnikov selectivity have been difficult. In 2016, we first reported that an achiral copper(I)-catalyst containing bulky 1,2-bis(diarylphosphino)benzene ligand provides racemic secondary alkylboronates with Markovnikov regioselectivity.^{44–48} During the course of our study, an enantioselective Markovnikov hydroboration of aliphatic terminal alkenes has been reported by Aggarwal and co-workers with the chiral rhodium(III) catalyst and an asymmetrical diboron reagent⁵¹, and very recently, Shi and co-workers reported copper(I)-catalyzed reaction with chiral NHC ligands.⁵² However, there was still room for improvement of the enantioselectivity or regioselectivity: for example, the reaction of 4-phenylbut-1-ene resulted in 80% ee, *branch* / *linear* = 98:2⁵¹ and 96% ee, *branch* / *linear* = 80:20⁵², respectively.

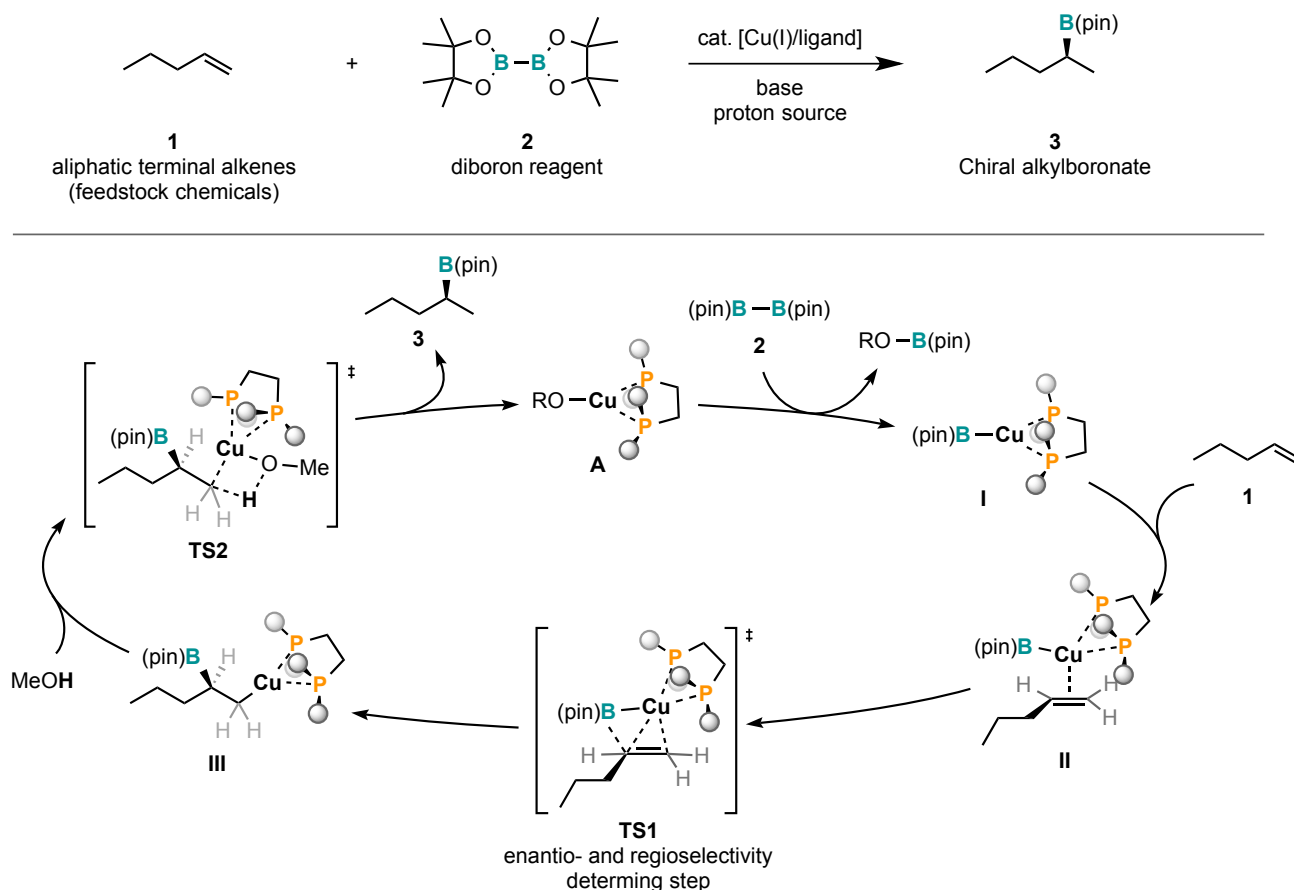


Fig. 4.2 Enantioselective Markovnikov hydroboration with copper(I)-catalyst and diboron reagent.

To establish the computational study-assisted ligand design sequence, we must seek the ideal phosphine ligand preparation system possessing synthetic and structure modularity on substituents on phosphorus atoms to reflect the design directions obtained by DFT calculations as well as the rigid core scaffold to avoid the drastic structure change on the alternation of the substituents on the phosphorus atoms. We thus employed P-chirogenic 2,3-bis(phosphino)quinoxaline ligand system because they were easily prepared by stepwise coupling of chiral phosphine module (CP), achiral phosphine module (AP) into 2,3-dichloroquinoxaline (Fig. 4.3).^{53–56}

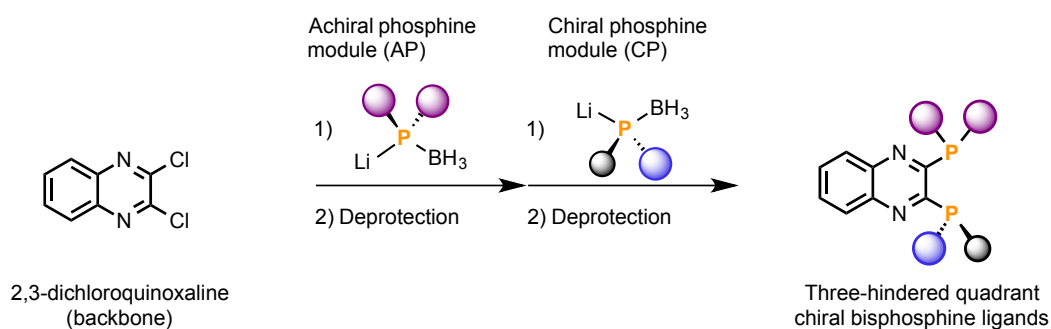


Fig. 4.3 High modularity of QuinoxP* ligand system.

Given the target reaction and ligand preparation procedure, we planned the ligand design work flow utilizing combination of computational and experimental analysis and evaluation (Fig. 4.4): (i) pick up a chiral ligand with moderate selectivity from initial screening of a ligand library; (ii) evaluate ligand about the regio- and enantioselectivity in the borylation of an aliphatic terminal alkene; (iii) if the selectivity was not sufficient, calculate the borylation reaction with the ligand, followed by confirming the validity of the calculations by comparing the experimental and calculated selectivities, and a design direction is obtained by quadrant-by-quadrant structure analysis of the transition states as output; (iii) synthesize the new generation chiral ligand by the modular coupling of CP and AP and 2,3-dichloroquinoxaline core; (iv) go back the experiment evaluation step and the ligand is then tested in the borylation. Through these iterative cycles, we finally reached a new bulky ligand that shows the unprecedentedly high enantio- and regioselectivity (99% ee, *br/l* = 92:8) in the enantioselective Markovnikov borylation of aliphatic terminal alkenes.

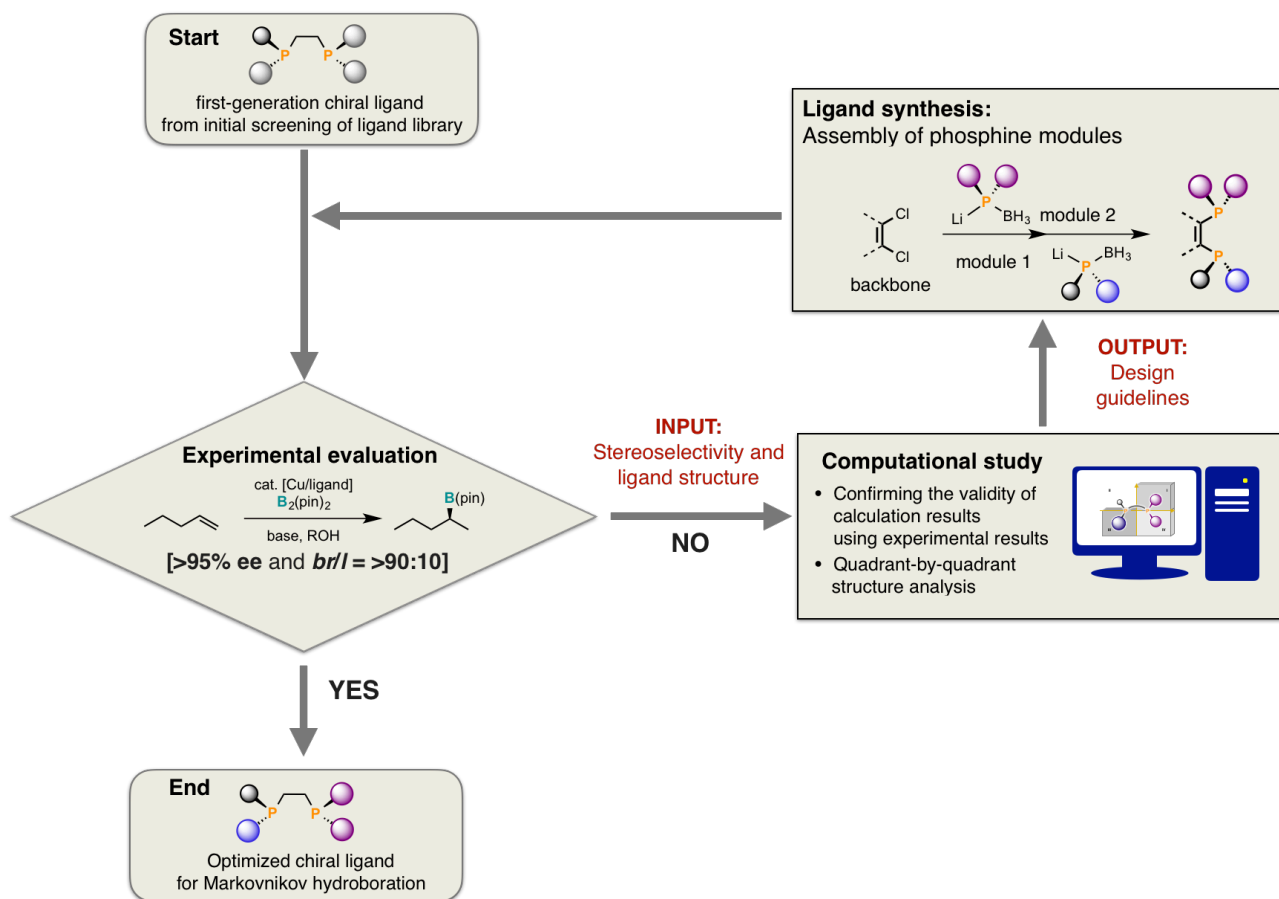


Fig. 4.4 High-performance chiral ligand design work flow for copper(I)-catalyzed Markovnikov hydroboration.

4.2 Result and Discussion

We began our studies by screening of commercially available chiral ligands (Table 4.1) in the reaction of **1a** with using copper(I) chloride, stoichiometric diboron **2**, K(O-*t*-Bu) and methanol as the proton source. The ferrocene-type chiral bisphosphine ligands were not suitable to proceed the hydroboration reaction due to the low reactivity and stereoselectivity [entry 1: 3% (**3a**); entry 2: 7% (**3a**), **3/4** = 83:17; entry 3: 31% (**3a**), **3/4** = 42:58, –52% ee]. As the previous report (Chapter 3)⁴⁴, the 1,2-bis(phosphino)arene type chiral ligands such as (*R,R*)-Me-Duphos and (*R,R*)-*i*-Pr-Duphos showed high reactivity [entry 4: 41% (**3a**), **3/4** = 46:54, –59% ee; entry 5: 48% (**3a**), **3/4** = 56:44, –73% ee]. However, the reactivity at low temperature was low, when the reaction using (*R,R*)-*i*-Pr-Duphos was conducted [entry 6, 7% (**3a**), **3/4** = 64:36]. The use of a chiral monophosphine ligand (*R*)-MOP gave the racemic secondary alkylboronate **3** in low yield [entry 7, 16% (**3a**), **3/4** = 71:29, 0% ee]. (*S*)-DTBM-Segphos, which is reported as a high selective ligand for the copper(I)-catalyzed enantioselective borylation of aliphatic aldehydes⁵⁷, resulted in low enantioselectivity although aliphatic aldehydes can be structural analog of aliphatic terminal alkenes [entry 8, 32% (**3a**), **3/4** = 86:14, 8% ee]. The P-chirogenic bisphosphine ligands afforded the linear product with high selectivity and low enantioselectivity for the branched product **3** [entry 9, 11% (**3a**), **3/4** = 27:73, –18% ee; entry 10, 24% (**3a**), **3/4** = 15:85, –29% ee]. Then, we found that the reaction with a *C*₂ symmetrical P-chirogenic bisphosphine ligand, (*S,S*)-QuinoxP* showed high reactivity and moderate enantioselectivity, the undesired linear product **4a** was also obtained as the major product [entry 11: 24% (**3a**), **3/4** = 24:76, 73% ee (*S*)-**3a**].⁵⁴ Next, in order to improve the selectivities, we modified the steric demanding of the catalyst. The use of more hindered *C*₁ symmetrical three-hindered quadrant P-chirogenic bisphosphine ligand, (*S*)-3H-QuinoxP* [(*S*)-Quinox-*t*Bu₃],⁵⁶ inverted the regioselectivity and improved the enantioselectivity to give the branched product as the major product [entry 12: 55% (**3a**), **3/4** = 65:35, 87% ee (*S*)-**3a**] (Fig. 4.5). Further reaction conditions optimization revealed that a cationic copper(I) salt [Cu(MeCN)₄]BF₄ is good copper(I) precursor to conduct the reaction at exceedingly low temperature for high regioselectivity (Fig. 4.6). This experimental catalyst investigation indicated that three-hindered quadrant chiral bisphosphine ligand would be more suitable for regio- and enantioselective recognition of aliphatic terminal alkenes.

Table 4.1 Initial ligand screening for enantioselective Markovnikov hydroboration **1a**.^a

entry	chiral ligand	temp (°C)	time (h)	yield of 3a (%) ^b	3/4 ^b	ee of 3a (%) ^c
1	(<i>R,S</i>)-Josiphos	-10	48	3	-	-
2	(<i>R_pR_p</i>)-Mandyphos	-10	72	7	83:17	-
3	(<i>R,R</i>)-Et-Ferrotane	-10	48	31	42:58	-52
4	(<i>R,R</i>)-Me-Duphos	-10	24	41	46:54	-59
5	(<i>R,R</i>)- <i>i</i> -Pr-Duphos	rt	24	48	56:44	-73
6	(<i>R,R</i>)- <i>i</i> -Pr-Duphos	0	24	7	64:36	-
7	(<i>R</i>)-MOP	rt	72	16	71:29	0
8	(<i>S</i>)-DTMB-Segphos	-10	48	32	86:14	8
9	(<i>R,R,S,S</i>)-Tangphos	-10	48	11	27:73	-18
10	(<i>R,R,S,S</i>)-Duanphos	-10	48	8	15:85	-29
11	(<i>S,S</i>)-QuinoxP*	-10	24	24	24:76	73
12	(<i>S</i>)-Quinox- <i>t</i> Bu ₃	-10	24	55	65:35	87

^aConditions: **1a** (0.25 mmol), Cu(I) salt (0.0125 mmol), ligand (0.0125 mmol), **2** (0.3 mmol) and K(O-*t*-Bu) (0.3 mmol) in THF (0.5 mL). ^bDetermined by GC analysis with an internal standard using the crude material. ^cDetermined by HPLC analysis after oxidation of **3a**. ^d3 mol % catalyst loading.

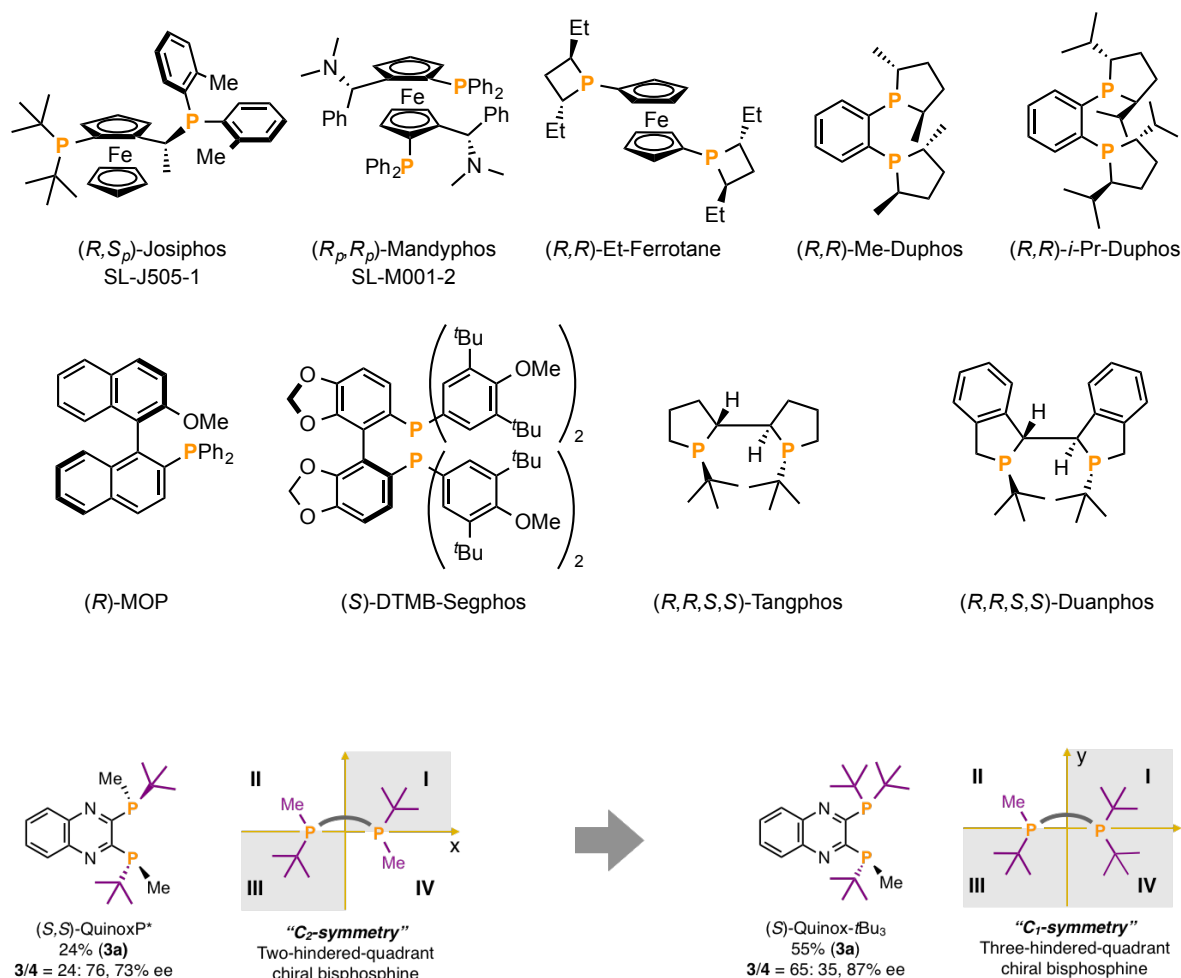


Fig. 4.5 Comparison between *C*₂-symmetric chiral ligand and *C*₁-symmetric chiral ligand.

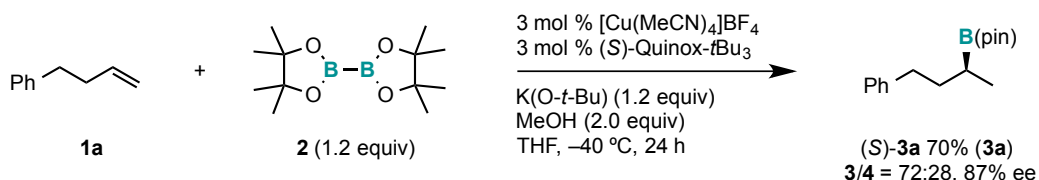


Fig. 4.6 Optimized reaction conditions at -40°C for (S)-Quinox-*t*Bu₃.

To understand this stereoselectivity of the *first generation* of the chiral ligand (S)-Quinox-*t*Bu₃, we carried out the computational study with the method including the dispersion correlation [ω B97XD/SDD for Cu atom, 6-311G(d,p) for other atoms, gas phase].⁵⁸ First, we compared the experimental and computational results of regio- and enantioselectivity to check validity of the calculation method and basis set. The reaction between (pin)B–Cu/(S)-Quinox-*t*Bu₃ and 1-butene was employed as a model reaction. In the case of the addition reaction between a C₁ symmetrical borylcopper(I) complex and a mono-substituted terminal alkene, the eight routes are necessary to consider for understanding the stereoselectivity (Fig. 4.7a): two reaction pathways (A_{branch} and D_{branch}) are the routes for the major enantiomer (S)-**3**, which was obtained with (S)-Quinox-*t*Bu₃ another two reaction pathways (B_{branch} and C_{branch}) are the routes for the minor enantiomer (R)-**3** and the other four paths are routes for the linear product **4** (A_{linear}, B_{linear}, C_{linear} and D_{linear}). The activation energy values of the transition states given by the DFT calculation (Fig. 4.7b) indicated; (i) path D_{branch} for the major enantiomer (S)-**3** is the most favorable reaction route [$+13.1$ (0.0) kcal/mol], (ii) path A_{linear} is the most favorable route for the linear product **4** [$+13.7$ (+0.6) kcal/mol], (ii) path B_{branch} is a major pathway for the production of the minor enantiomer (R)-**3** [$+14.5$ (+1.4) kcal/mol]. The activation barriers of the other pathways [TS-A_{branch}: $+15.0$ (+1.9) kcal/mol, TS-C_{branch}: $+16.0$ (+2.9) kcal/mol, TS-B_{linear}: $+16.0$ (+2.9) kcal/mol, TS-C_{linear}: $+15.6$ (+2.5) kcal/mol, TS-D_{linear}: $+16.8$ (+3.7) kcal/mol] would be too high to contribute the product selectivity. The enantio- and regioselectivity estimated from the calculated activation energy values of borylcupration of the carbon-carbon double bond were significantly matched with the experimental result of **1a** (predicted values: 83% ee, $3/4 = 76:24$, experimental values: 87% ee, $3/4 = 72:28$). This excellent matching between computational and experimental results convinced us to believe the calculations of the copper(I)-catalyzed Markovnikov hydroboration of aliphatic terminal alkenes.

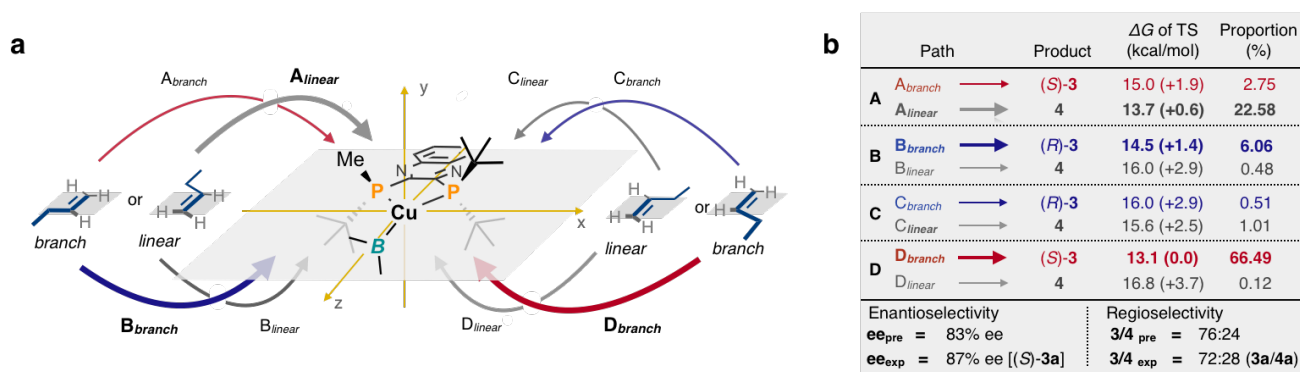


Fig. 4.7 **a**) Eight possible reaction routes for branched product **3** and linear product **4**. **b**) Activation energy values by density functional theory (DFT) calculations [ω B97XD/SDD for Cu atom, 6-311G(d,p) for other atoms, gas phase, 298 K].

We then tried to extract important structural factors that affect the regio- and enantioselectivity by an analysis of steric congestions for each quadrant, i.e., a “*quadrant-by-quadrant analysis*” of the following three important transition states for the stereoisomers: TS- D_{branch} for (S)-**3** (66.49%) (Fig. 4,8a), TS- B_{branch} for (R)-**3** (6.06%) (Fig. 4.8b), and TS- A_{linear} for **4** (22.58%) (Fig. 4.8c). The most favorable transition state structure TS- D_{branch} revealed that the pinacolato boryl moiety [B(pin)] moiety inclining in direction of the vacant quadrant **II** renders the rigid chiral space suitable for recognition of the prochiral carbon–carbon double bond by avoiding the steric repulsion between the methyl group in the boryl group and the alkyl chain of 1-butene {H4 (1-butene) – H6 [B(pin)] = 3.08 Å} (Fig. 4,8a). In contrast, TS- B_{branch} , which affords the minor enantiomer, would be destabilized by the steric congestion between the alkyl chain of 1-butene and the methyl group in the B(pin) moiety, evident from the short distance between H4 (1-butene) and H6 [B(pin)] (2.29 Å) (Fig. 4,8b). Strain in this structure should also arise from the steric interaction between a methyl group in the B(pin) moiety and the *tert*-butyl group of the ligand in quadrant **I** {H7 [B(pin)] – H9 (chiral ligand) = 2.09 Å}. Additionally, the *tert*-butyl group in quadrant **III** and the alkyl chain of 1-butene are relatively close in TS- B_{branch} [H5 (1-butene) – H11 (chiral ligand) = 2.34 Å]. The difference of the activation energy values between TS- D_{branch} and TS- A_{linear} is relatively small (+0.6 kcal/mol). The steric congestion between the *tert*-butyl groups of the ligand in quadrants **III** and **IV** with the B(pin) moiety in TS- A_{linear} distorts the transition state {H7 [B(pin)]– H12 (chiral ligand) = 2.28 Å and H7 [B(pin)]–H13 (chiral ligand) = 2.37 Å} (Fig. 4,8c). A structural comparison of TS- D_{branch} and TS- B_{branch} suggests that the steric demand in quadrants **I** and **III** plays a major and a minor role for the enantioselectivity, respectively. In contrast, according to a structural comparison of TS- D_{branch} and TS- A_{linear} , the steric congestion in quadrants **III** and **IV** significantly affects the regioselectivity (Fig. 4,8d).

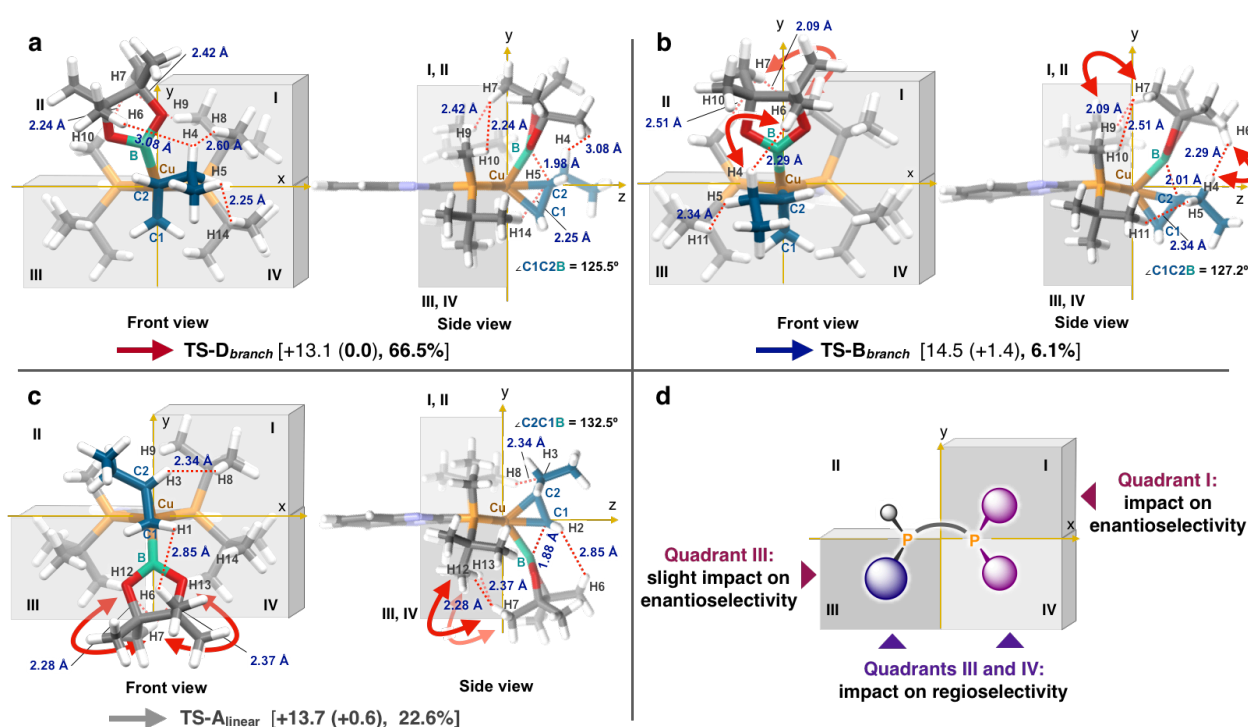


Fig. 4.8 a) Structure analysis of TS-D_{branch}. b) Structure analysis of TS-B_{branch}. c) Structure analysis of TS-A_{linear}. d) Design direction by quadrant-by-quadrant structure analysis for higher stereoselectivity.

To confirm the reaction pathway through the favorable transition state of borylcupration TS-D_{branch} of the copper(I)-catalyzed hydroboration of aliphatic terminal alkenes, the DFT calculation including the protonation of the alkylcopper(I) intermediate was carried out (Fig 4.9). The borylcupration step of a carbon–carbon double bond of an aliphatic terminal alkene at least requires +13.7 kcal/mol because the copper(I)-alkene π -complex **II-D** is thermodynamically unstable compared to the borylcopper(I) specie **I** (+4.9 kcal/mol). As the alkylcopper(I) intermediate **III-D** is significantly stabilized after the transition state (–28.5 kcal/mol), the borylcupration step should be irreversible pathway. Subsequently, protonation of the alkylcopper(I) by methanol was calculated to determine whether the intermediate provide the product in reasonable activation energy. The transition state TS_{pro} from the alkylcopper(I) **III-D** could not be found because of steric congestion between the substituents of phosphine and B(pin) moiety. Thus, the conformational isomer **III-D**_{rot} which is slightly unstable than **III-D** was found to be an intermediate for the protonation of the carbon–copper(I) bond in the reasonable energy value (+11.0 kcal/mol).

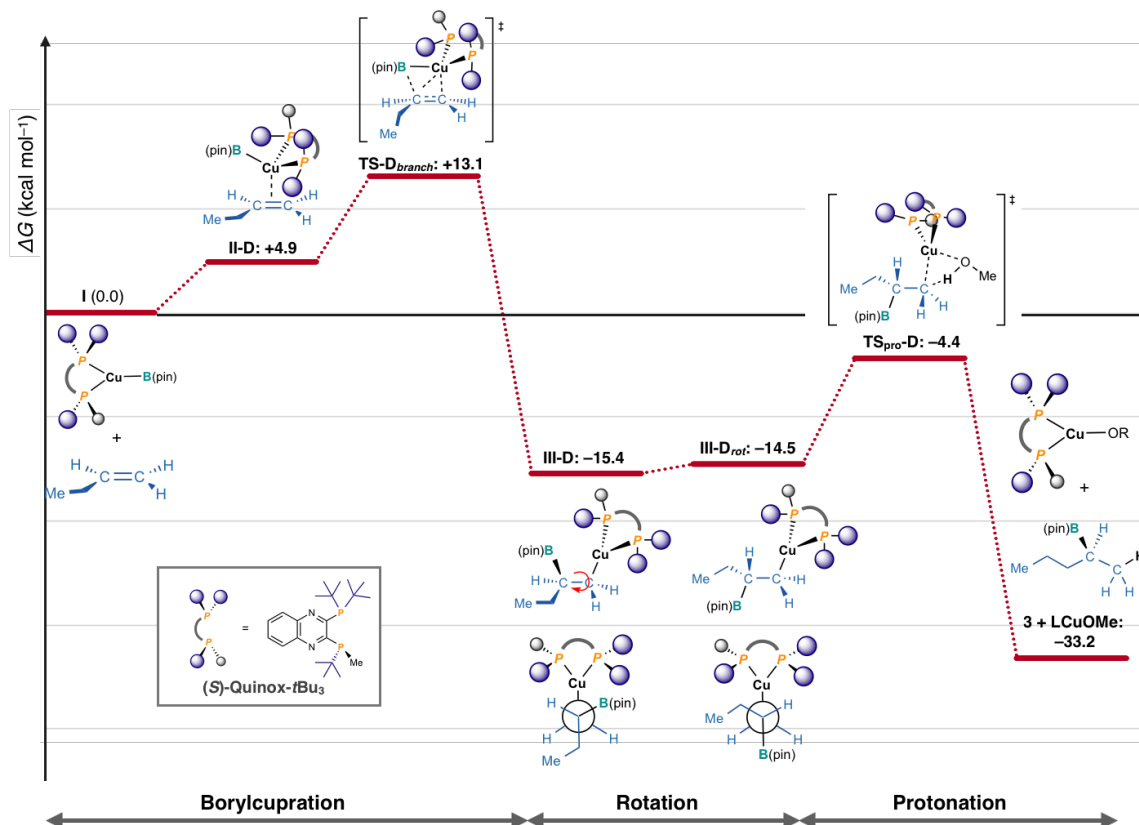
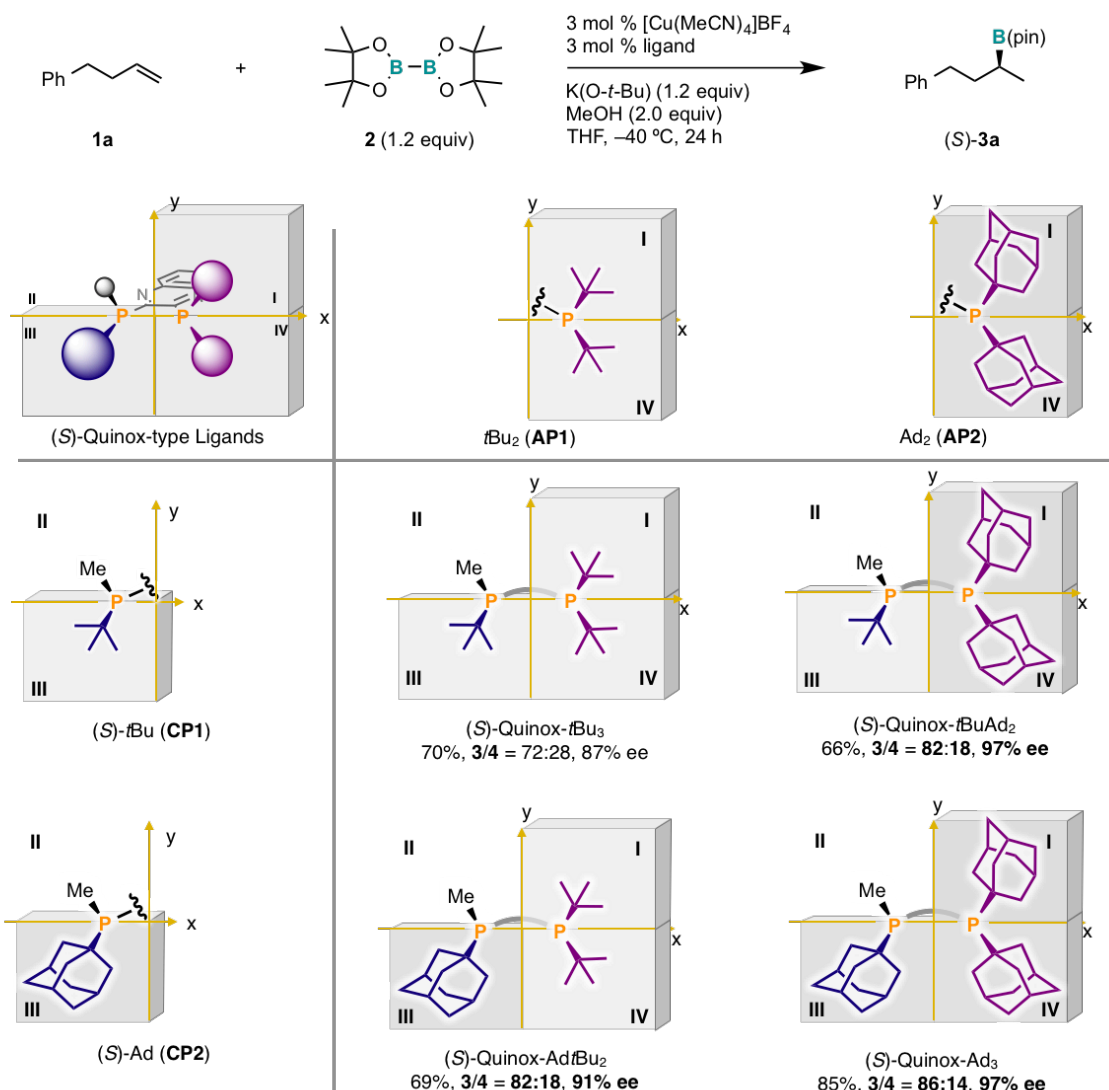


Fig. 4.9 Reaction coordinate for copper(I)-catalyzed hydroboration with (S)-Quinox-*t*Bu₃.

To achieve higher enantioselectivity and regioselectivity than (S)-Quinox-*t*Bu₃, we synthesized several Quinox-type three-hindered-quadrants chiral bisphosphine ligands via a stepwise modular synthesis using an electrophilic quinoxaline core with the corresponding phosphine modules (**APs** and **CPs**) on the basis of the design guidelines derived from the computational study (Table 4.2). The chiral bisphosphine ligand (S)-Quinox-Ad*t*Bu₂, consisting of a chiral adamantyl methylphosphino [(S)-Ad: **CP2**] and di-*tert*-butyl phosphino modules (*t*Bu₂: **AP1**), is bulkier than (S)-Quinox-*t*Bu₃ in quadrant **III**, and exhibited slightly higher regioselectivity and enantioselectivity than (S)-Quinox-*t*Bu₃ (69%, 91% ee, **3/4** = 82:18). This improvement of the selectivities upon the structural modification from (S)-Quinox-*t*Bu₃ to (S)-Quinox-Ad*t*Bu₂ is thus consistent with the structural analysis (Fig. 4.8d). The use of the chiral ligand (S)-Quinox-*t*BuAd₂, which bears chiral *tert*-butyl methylphosphino modules [(S)-*t*Bu: **CP1**] and sterically demanding adamantyl groups (Ad₂: **AP2**) in quadrants **I** and **IV** dramatically improved the enantioselectivity (66%, 97% ee, **3/4** = 82:18), while the regioselectivity remained similar to that of (S)-Quinox-Ad*t*Bu₂, which is again consistent with the structural analysis (Fig. 4.8d). (S)-Quinox-Ad₃, which was synthesized by combining phosphine modules **CP2** and **AP2**, afforded excellent enantioselectivity and good regioselectivity (85%, 97% ee, **3/4** = 86:14). These selectivity improvements are clearly consistent with the DFT-derived guidelines for the design of chiral bisphosphine ligands (Fig. 4.8d). Nevertheless, the regioselectivity could still be improved.

Table 4.2 Ligand synthesis and experimental evaluation of three-hindered quadrant bisphosphine ligands.^a



^aConditions: **1a** (0.5 mmol), Cu(I) salt (0.015 mmol), ligand (0.015 mmol), **2** (0.3 mmol) and K(O-*t*-Bu) (0.6 mmol) in THF (1.0 mL) at -40 °C. Yield and regioselectivity of **3a** were determined by GC analysis with an internal standard using the crude material. Optical purity of **3a** was determined by HPLC analysis after oxidation of **3a**.

To gather more detailed information in order to further improve the enantioselectivity and the regioselectivity of the *second-generation* of the chiral bisphosphine ligand (S)-Quinox-Ad₃, we conducted DFT calculations on the borylcupration step of the terminal alkene in the presence of (S)-Quinox-Ad₃ (Fig. 4.10). According to the activation energy values of the transition states, the predicted enantioselectivity and regioselectivity were adequately matched with the experimental results (predicted values: 99.6% ee, 3/4 = 90:10; experimental values: 97% ee, 3/4 = 86:14, Fig. 4.10b). The transition state TS-D'_{branch}, which provides the major enantiomer (S)-**3** is the most favorable reaction pathway (+12.3 kcal/mol), while TS-B'_{branch}, which provides the minor enantiomer (R)-**3** was effectively destabilized [+17.4 (+5.1) kcal/mol] by the bulkier adamantyl substituents in quadrants **I** and **IV** as compared to (S)-Quinox-*t*Bu₃ [TS-B_{branch} = +14.5 (+1.4) kcal/mol] (Fig. 4.8b). Similarly, TS-A'_{linear} was also slightly destabilized [+13.8 (+1.5) kcal/mol] by changing the *tert*-butyl groups in

(*S*)-Quinox-*t*Bu₃ to adamantyl group in (*S*)-Quinox-Ad₃. While TS-C_{branch} [+16.0 (+2.9) kcal/mol] for (*S*)-Quinox-*t*Bu₃ scarcely contributed to the product ratio, TS-C'_{branch} [+15.9 (+3.6) kcal/mol] became the lowest pathway for the minor enantiomer (*R*)-**3**.

Subsequently, we carried out the quadrant-by-quadrant structural analysis of two important unfavorable pathways, i.e., TS-C'_{branch} and TS-A'_{linear}. In TS-C'_{branch}, steric congestion was observed between the B(pin) and adamantyl moieties in quadrants **III** and **IV** (Fig. 4.11a). The steric interaction in quadrant **III** should exert a more pronounced influence on the activation barrier of TS-C'_{branch} than that in quadrant **IV**, as the B(pin) moiety is inclined in direction of quadrant **III** to avoid the steric interaction with the alkyl chain of 1-butene and the ligand in quadrant **I** {H15 [B(pin)] – H18 (chiral the ligand) = 2.02 Å}. In TS-A'_{linear} (Fig. 4.11b), the adamantyl groups of (*S*)-Quinox-Ad₃ in quadrants **III** and **IV** should interact more effectively with the B(pin) group relative to the *tert*-butyl group of (*S*)-Quinox-*t*Bu₃, which is reflected in the larger energy difference between TS-D'_{branch} and TS-A'_{linear} [(*S*)-Quinox-Ad₃: +1.5 kcal/mol] compared to that between TS-D_{branch} and TS-A_{linear} [(*S*)-Quinox-*t*Bu₃: +0.6 kcal/mol] {H7 [B(pin)] – H12 (chiral ligand) = 2.67 Å, H7 [B(pin)] – H13 (chiral ligand) = 2.31 Å, H7 [B(pin)] – H19 (chiral ligand) = 2.39 Å, H16 [B(pin)] – H18 (chiral ligand) = 2.22 Å, H17 [B(pin)] – H18 (chiral ligand) = 2.23 Å and H15 [B(pin)] – H19 (chiral ligand) = 1.97 Å}. It should also be noted that the adamantyl groups in (*S*)-Quinox-Ad₃ are sterically more demanding around the remote domain of the reaction center in quadrants **III** and **IV**, which is more effective than the *tert*-butyl groups in the first-generation ligand (*S*)-Quinox-*t*Bu₃ for the control of the steric strain between the ligand and B(pin) moiety.

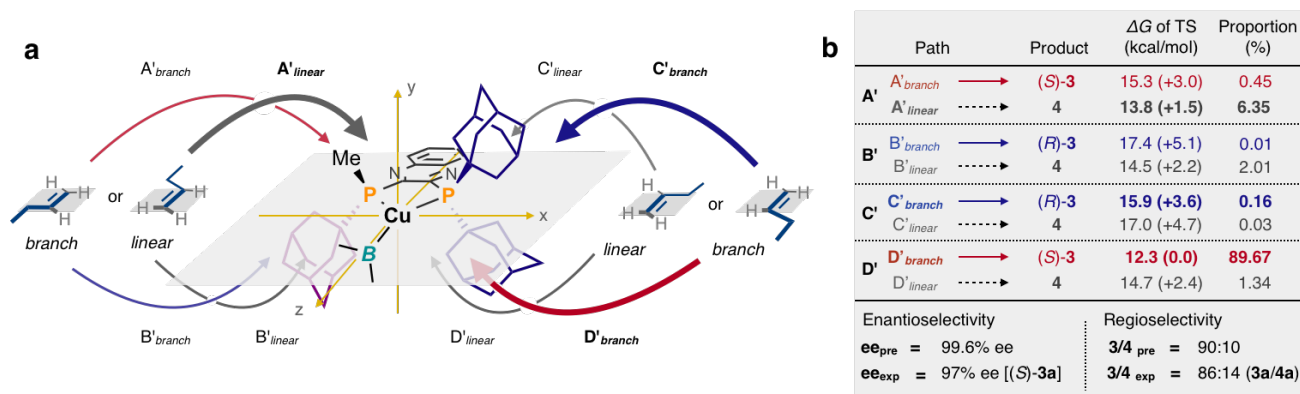


Fig. 4.10 a) Eight possible reaction routes for branched product **3** and linear product **4**. b) Activation energy values by density functional theory (DFT) calculations [ω B97XD/SDD for Cu atom, 6-311G(d,p) for other atoms, gas phase, 298 K].

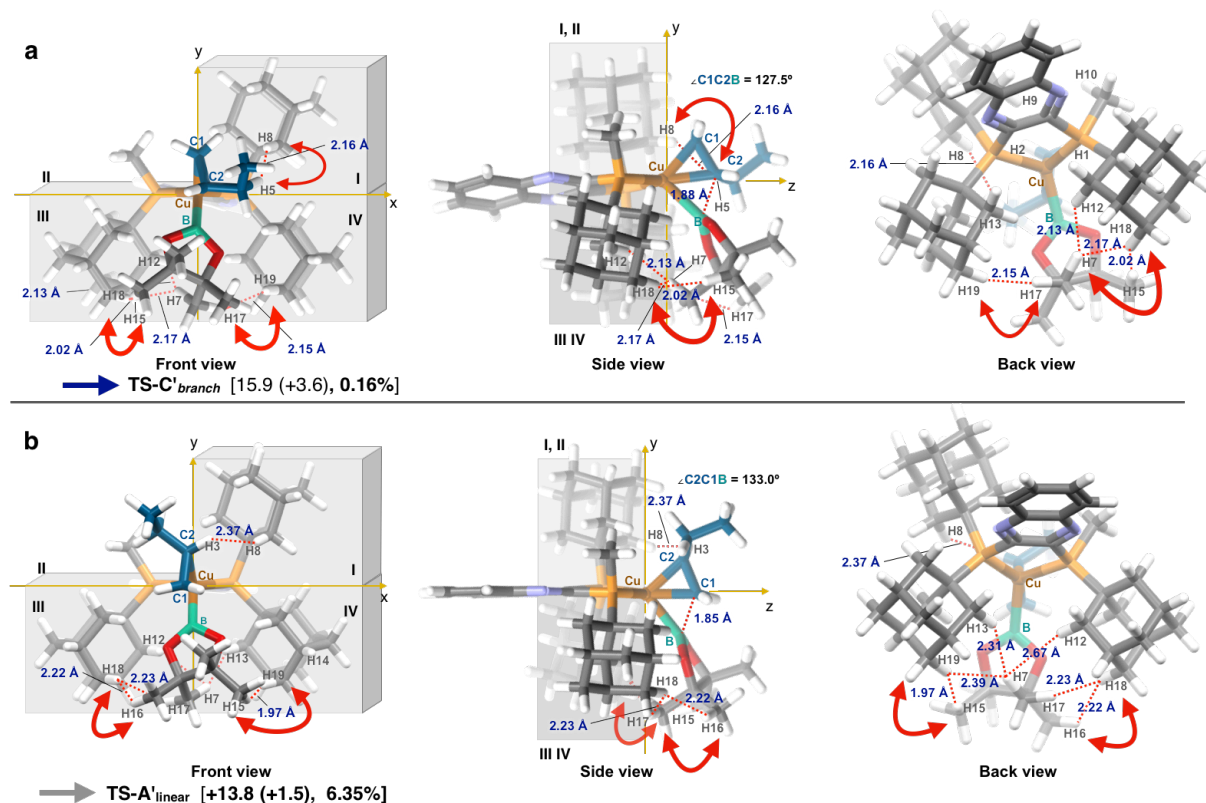


Fig. 4.11 Ligand-controlled regioselectivity of borylcopper(I)-mediated hydroboration of aliphatic terminal alkenes.

From the quadrant-by-quadrant structural analysis of the *second-generation* chiral ligand (*S*)-Quinox-Ad₃ (Fig. 4.11a and 4.11b), we obtained the design guidelines for the improvement of the stereoselectivity (Fig. 4.12). We anticipated that the introduction of a substituent that exerts bulk in the remote domain of the reaction center compared to that of the adamantyl group in quadrant **III** should destabilize TS-C'_{branch}, while the introduction of a sterically highly demanding substituent in the remote domain should destabilize TS-A'_{linear}. Therefore, we focused on the *tert*-octyl group, which is bulkier than the 1-adamantyl group according to the steric parameters in a quantitative structure-activity relationship (QSAR).^{59–61} The Charton value (*v*), which corresponds to Taft's steric parameter correlated with the van der Waals radii, of the *tert*-octyl group is larger than that of the 1-adamantyl group (*tert*-butyl: 1.24; 1-adamantyl: 1.33; *tert*-octyl: 1.74). Furthermore, the Sterimol parameter B5 of the *tert*-octyl group, which reflects the long-range steric bulk, is larger than that of the 1-adamantyl group (*tert*-butyl: B5 = 3.17; 1-adamantyl: B5 = 3.49; *tert*-octyl: B5 = 4.54). Based on these considerations, we identified (*S*)-Quinox-*t*OctAd₂, which contains a *tert*-octyl group in quadrant **III** as the optimal chiral ligand. (*S*)-Quinox-*t*OctAd₂ exhibited almost perfect enantioselectivity and high regioselectivity to afford the desired Markovnikov hydroboration product in high yield (92% for **3a**, 99% ee, **3/4** = 92:8).⁶² This enantioselectivity was higher than the value of the previous report [Rh: 80% ee⁵¹; Cu: 96% ee⁵²].

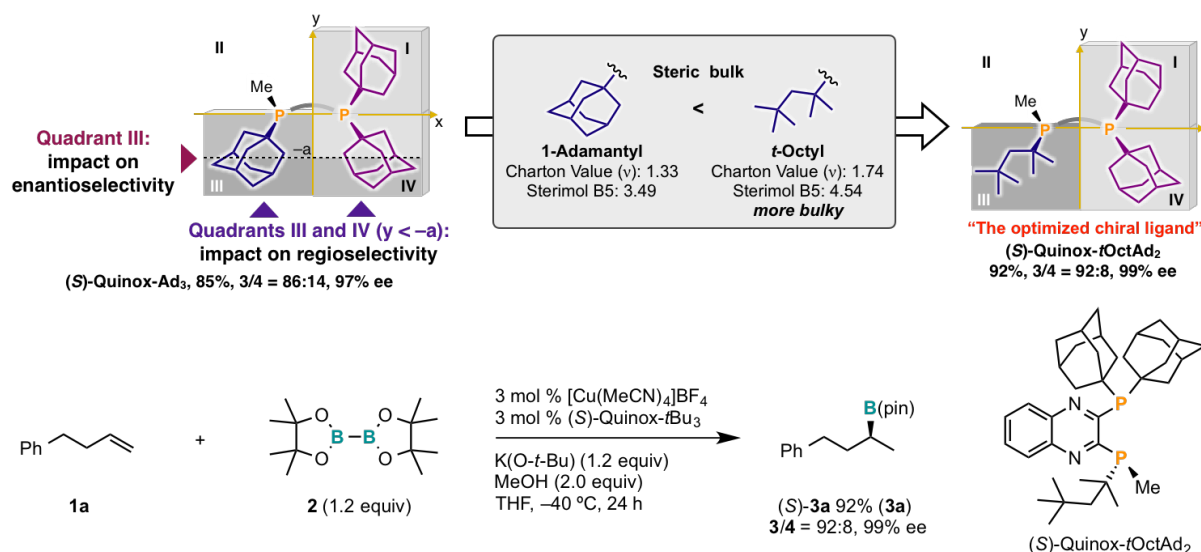


Fig. 4.12 Design guidelines from the quadrant-by-quadrant structural analysis and optimized high-performance chiral bisphosphine ligand (S)-Quinox-tOctAd₂.

The DFT calculation of hydroboration reaction pathway through the favorable transition state of borylcupration TS-D'_{branch} of the copper(I)-catalyzed hydroboration of aliphatic terminal alkenes, with (S)-Quinox-Ad₃ was conducted (Fig 4.13). As similar to that of (S)-Quinox-tBu₃ (Fig 4.9), the borylcupration TS-D'_{branch} of a terminal alkene would be irreversible at least under low temperature (+28.5 kcal/mol). Furthermore, the bond rotation of the carbon–carbon bond respectively bearing the copper(I) and boron atom in the alkylcopper(I) intermediate would be required to proceed the protonation of the alkylcopper(I) intermediate III-D'. The energy barrier of TS_{pro-D'} was reasonable value to provide the Markovnikov hydroboration product (S)-3 and regenerate the copper(I) alkoxide complex (+7.9 kcal/mol).

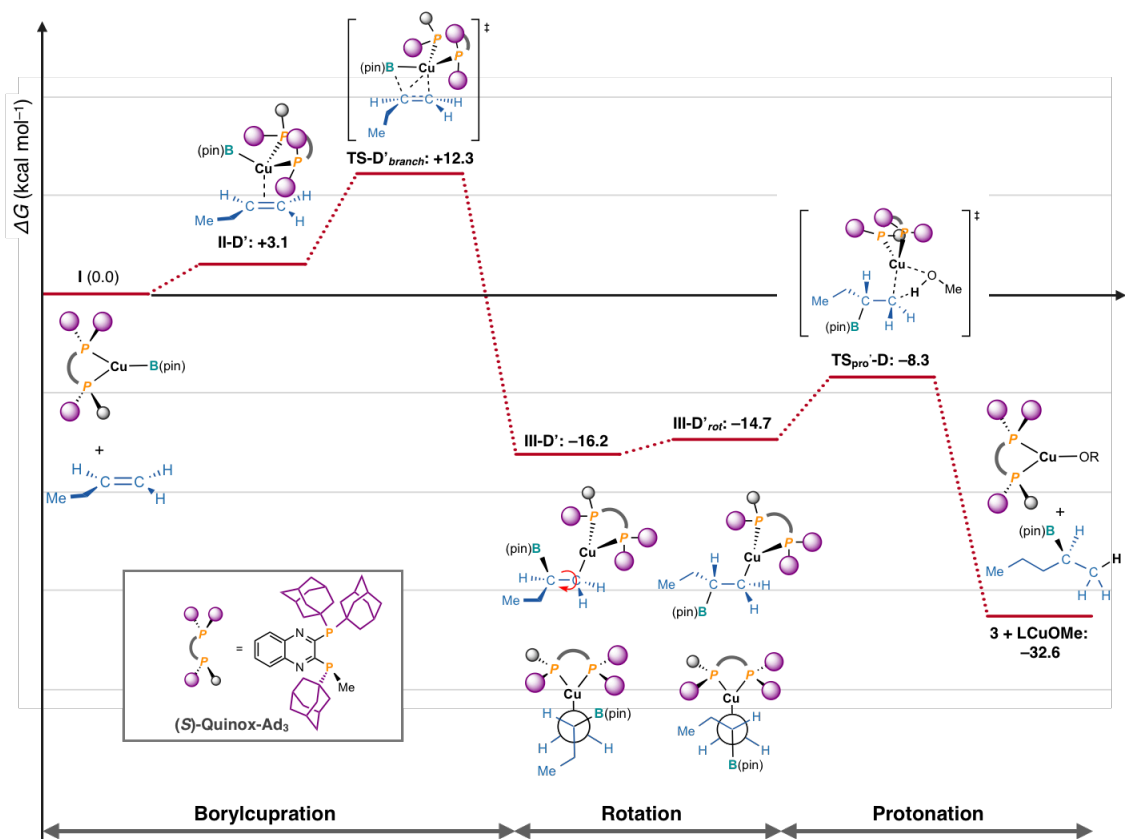
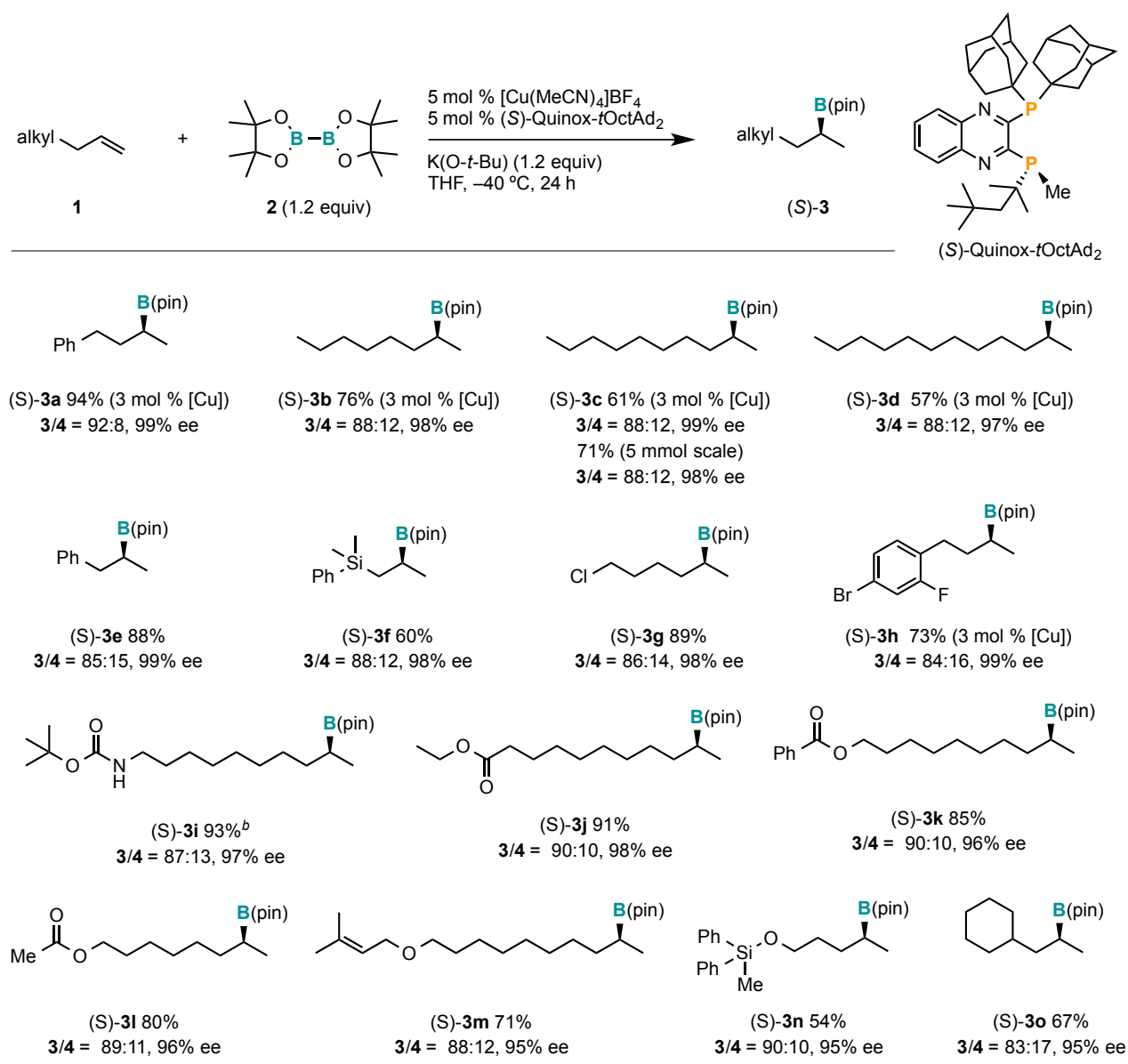


Fig. 4.13 Reaction coordinate for copper(I)-catalyzed Markovnikov hydroboration with (*S*)-Quinox-Ad₃.

With (*S*)-Quinox-*t*OctAd₂ as the optimized chiral bisphosphine ligand for the enantioselective Markovnikov hydroboration of terminal aliphatic alkenes, we examined the substrate scope (Table 4.3). The reactions of aliphatic terminal alkenes (**1a–e**), including α -olefins such as 1-octene (**1b**), 1-decene (**1c**), and 1-dodecene (**1d**), afforded the corresponding secondary alkylboronates (*S*)-**3a–e** with high regioselectivity and excellent enantioselectivity [(*S*)-**3a**: 94%, **3/4** = 92:8, 99% ee; (*S*)-**3b**: 76%, **3/4** = 88:12, 98% ee; (*S*)-**3c**: 61%, **3/4** = 89:11, 99% ee; (*S*)-**3d**: 57%, **3/4** = 88:12, 97% ee; (*S*)-**3e**: 88%, **3/4** = 85:15, 99% ee]. This is the first example for a catalyst that promotes the Markovnikov borylation of α -olefins in high selectivity (> 97% ee) [Rh: (*S*)-**3c**, 80% ee⁵¹; Cu: (*S*)-**3d**, 91% ee⁵²]. The reactivity and stereoselectivity were not affected by large-scale reaction conditions [(*S*)-**3c**: 71%, **3/4** = 89:11, 98% ee]. We also conducted reactions with terminal alkenes that contained functional groups. The reaction of allylsilane **1f** afforded product (*S*)-**3f** with high regioselectivity and enantioselectivity (60%, **3/4** = 93:7, 98% ee). Secondary alkylboronates containing halide moieties were obtained in high yield with moderate regioselectivity and excellent enantioselectivity [(*S*)-**3g**: 89%, **3/4** = 86:14, 98% ee; (*S*)-**3h**: 73%, **3/4** = 84:16, 99% ee], whereas the reaction of substrates bearing oxygen atoms as functional groups or a bulky alkyl substituent resulted in slightly lower, but still sufficiently high enantioselectivity (>95% ee) [(*S*)-**3i**: 93%, **3/4** = 87:13, 97% ee; (*S*)-**3j**: 91%, **3/4** = 90:10, 98% ee; (*S*)-**3k**: 85%, **3/4** = 90:10, 96% ee; (*S*)-**3l**: 80%, **3/4** = 89:11, 96% ee; (*S*)-**3n**: 71%, **3/4** = 88:12, 95% ee; (*S*)-**3m**: 54%, **3/4** = 90:10, 95% ee; (*S*)-**3o**: 67%, **3/4** = 83:17, 95% ee].

Table 4.3 Substrate screening of enantioselective Markovnikov hydroboration of aliphatic terminal alkenes.^a



^aConditions: **1** (0.5 mmol), [Cu(MeCN)₄]BF₄ (0.025 mmol), (S)-Quinox-tOctAd₂ (0.025 mmol), **2** (0.6 mmol) and K(O-*t*-Bu) (0.6 mmol) in THF (1.0 mL) at -40 °C. Isolated yield. Regioselectivities (3/4) were determined by the gas chromatography (GC) analysis using the crude material. Enantioselectivities (% ee) were determined by the high-pressure liquid chromatography (HPLC) analysis with a chiral column.

^bAt -10 °C.

2-Methyl-branched alkanols are versatile intermediates for the synthesis of natural products such as insect pheromones, chiral saturated carboxylic acids found in glycolipids, and related natural products (Fig. 4.14a).^{63–66} Conventional synthetic procedures for methyl-branched alkyl chains often require stoichiometric amounts of optically active starting materials. The potential utility of our enantioselective Markovnikov hydroboration was demonstrated on the synthesis of the enantioenriched 2-methyl-alkanol (S)-**5** from an octene mixture that included 1-octene (**1c**), *cis*- and *trans*-2-octene, as well as *cis*- and *trans*-4-octene, which can be considered as a model substrate for a petrochemical feedstock obtained from a cracking process, where the isomers are difficult to separate (Fig. 4.14b). This catalytic system only reacted with the terminal alkene to provide the borylation

product (*S*)-**3b** with good regioselectivity (**3/4** = 89:11), while the internal alkenes were recovered almost quantitatively. Other borylation products that could have been potentially generated from internal alkenes were not detected. The minor linear product **4b** was removed from the crude material by column chromatography to give the corresponding (*S*)-**3b** as a pure form. The subsequent homologation of (*S*)-**3b** was accomplished by a treatment with an oxidant, which furnished chiral 2-methyl-branched alkanol (*R*)-**5** in good yield with excellent enantioselectivity (89% over two steps, 98% ee). This study thus provides a high-performance catalyst for the enantioselective Markovnikov hydroboration of aliphatic terminal alkenes, and a successful example for a computationally assisted study in chiral-ligand design.

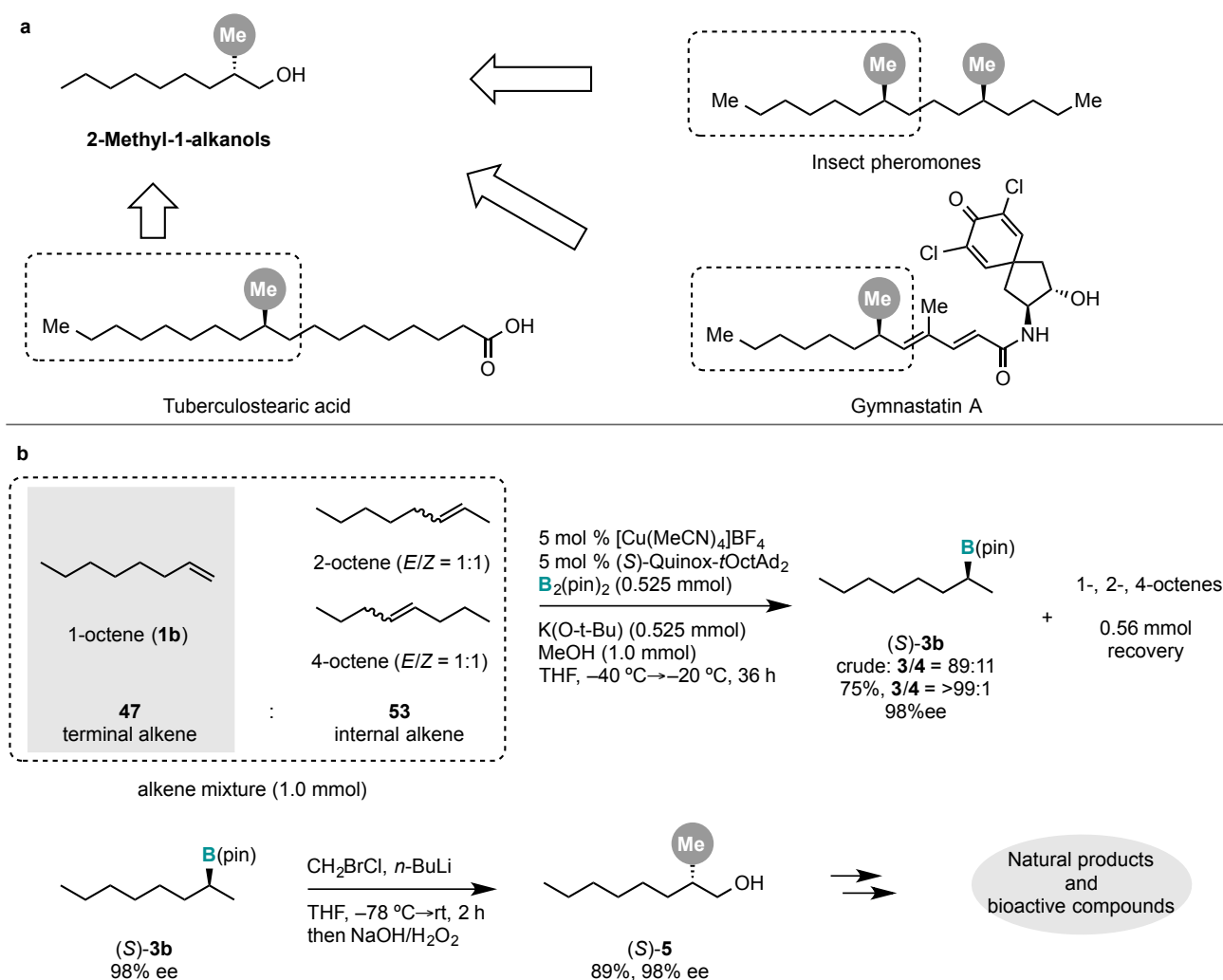


Fig. 4.14 **a**) Chiral 2-methyl alkanols as versatile intermediates for natural products or bioactive compounds bearing chiral-methyl branched moieties. **b**) The synthesis of 2-methyl-alkanol (*S*)-**5** via the enantioselective Markovnikov hydroboration of a mixture of octenes.

4.3 Conclusion

In conclusion, we have developed an enantioselective copper(I)-catalyzed Markovnikov hydroboration of aliphatic terminal alkenes. The rational catalyst design strategy based on quadrant-by-quadrant optimization with experimental and DFT calculation results as well as the steric parameters in QSAR led us to an optimal C_1 symmetric chiral bisphosphine ligand, (*S*)-Quinox-*t*OctAd₂. The key of the success should be modularity of quinoxaline based ligand structure and introduction of the steric demanding in the appropriate position around the reaction site (quadrant **I** and **III** for the enantioselectivity and quadrant **III** and **IV** for the regioselectivity). The optimized bisphosphine ligand exhibited broad range of the substrate scope for terminal aliphatic alkenes and good functional group tolerance to give various secondary chiral alkylboronate with high regioselectivity and excellent enantioselectivity (>95% ee). We anticipated that this success will pave the way for new generation asymmetric catalysis.

4.4 Experimental

4.4.1 General

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4A). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^1H : 400 MHz, ^{13}C : 100 MHz, ^{31}P : 160 MHz). Tetramethylsilane (^1H), CDCl_3 (^{13}C) and H_3PO_4 in D_2O (^{31}P) were employed as the external standards, respectively. CuCl (ReagentPlus® grade, 224332-25G, $\geq 99\%$) and $\text{K}(\text{O}-t\text{-Bu})/\text{THF}$ (1.0 M, 328650-50ML) were purchased from Sigma-Aldrich Co. and used as received. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with a ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and a FID detector. HPLC analyses with chiral stationary phase were carried out using a Hitachi LaChrome Elite HPLC system with a L-2400 UV detector. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University. Single crystal X-ray structural analyses were carried out on a Rigaku R-Axis RAPID diffractometer using graphite monochromated $\text{Mo-K}\alpha$ radiation. The structure was solved by direct methods and expanded using Fourier techniques. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. All calculations were performed using the CrystalStructure crystallographic software package except for refinement, which was performed using SHELXL-97.

4.4.2 General Experimental Procedure

4.4.2.1 Procedure for the Enantioselective Hydroboration of **1a** with CuCl (Table 4.1).

Copper chloride (1.2 mg, 0.0125 mmol), bis(pinacolato)diboron (**2**) (76.2 mg, 0.30 mmol) and chiral ligand (0.0125 mmol) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a TeflonTM-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (0.20 mL) and $\text{K}(\text{O}-t\text{-Bu})/\text{THF}$ (1.00 M, 0.30 mL, 0.30 mmol) were added in the vial through the rubber septum using a syringe. After stirring for 30 min, **1a** (33.0 mg, 0.25 mmol) and methanol (0.0404 mL, 1.0 mmol) were added to the mixture. After the reaction was complete, the reaction mixture was passed through a short silica gel (Φ : 10 mm, height of the silica-gel column: 30 mm) eluting with Et_2O . The yield and regioselectivity of **3a** were determined by GC analysis with an internal standard using the crude material. The crude material was treated with $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ as an oxidant for the boryl group in $\text{THF}/\text{H}_2\text{O}$ (1:1). The mixture was stirred at room temperature. After the reaction complete, the reaction mixture was extracted with Et_2O and dried over MgSO_4 . The solvents were removed under reduced pressure. The crude material was purified by flash column chromatography (SiO_2 , $\text{EtOAc}/\text{hexane}$, 0:100–20:80) to give the corresponding alcohol as a colorless oil.

4.4.2.2 Procedure for the Enantioselective Hydroboration of **1** with [Cu(MeCN)₄]BF₄ (Fig. 4.6, Fig. 4.12, Table 4.2 and Table 4.3, Table S4.1).

[Cu(MeCN)₄]BF₄ (4.7 mg, 0.015 mmol), bis(pinacolato)diboron (**2**) (152.4 mg, 0.60 mmol) and chiral ligand (0.015 mmol) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a TeflonTM-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (0.40 mL) and K(O-*t*-Bu)/THF (1.00 M, 0.60 mL, 0.60 mmol) were added in the vial through the rubber septum using a syringe. After stirring for 30 min at -40 °C, **1** (0.50 mmol) and methanol (0.0404 mL, 1.0 mmol) were added to the mixture at -40 °C. After the reaction was complete, the reaction mixture was passed through a short silica gel (Φ: 10 mm, height of the silica-gel column: 30 mm) eluting with Et₂O. The regioselectivity of **3** was determined by GC analysis. The crude material was purified by flash column chromatography (SiO₂, Et₂O/hexane, typically 0:100–3:97) to give the corresponding alkylboronate (*S*)-**3**. The enantioselectivity was determined by HPLC after the stereospecific derivatization of the boryl group.

Table S4.1 Evaluation of three-hindered quadrant bisphosphine ligands.

3 mol % $[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ 3 mol % Chiral bisphosphine ligand (pin)B–B(pin) (1.2 equiv) K(O-<i>t</i>-Bu) (1.2 equiv) MeOH (2.0 equiv) THF, –40 °C, 24 h		Ph-CH=CH-CH₃ 1a		Ph-CH₂-CH₂-CH₂-CH₂-B(pin) (S)-3a	Ph-CH₂-CH₂-CH₂-CH₂-B(pin) 4a
Achiral phosphine synthetic modules $\text{H}_3\text{B}-\text{P}(\text{tBu})_2$ AP1-BH₃ (tBu₂) $\text{H}_3\text{B}-\text{P}(\text{Ad})_2$ AP2-BH₃ (Ad₂)					
Chiral phosphine synthetic modules (R)-CP1-BH₃ (tBu) <i>t</i>-Bu^a: $\nu = 1.24$ B1 = 2.60 B5 = 3.17 (R)-CP2-BH₃ (Ad) 1-Ad^a: $\nu = 1.33$ B1 = 3.16 B5 = 3.49 (R)-CP3-BH₃ (tOct) $\nu = 1.74$ B1 = 2.60 B5 = 4.54		(S)-Quinox-tBu₂ 70%, 3/4 = 72:28 87% ee	(S)-Quinox-tBuAd₂ 66%, 3/4 = 82:18 97% ee	(S)-Quinox-AdtBu₂ 69%, 3/4 = 82:18 91% ee	(S)-Quinox-Ad₃ 85%, 3/4 = 86:14 97% ee
		(S)-Quinox-tOcttBu₂ 77%, 3/4 = 81:19 94% ee	(S)-Quinox-tOctAd₂ 92%, 3/4 = 92:8 99% ee		

^aAll steric parameters are literature values^{59–61}. ν : Charton's value; B1: Sterimol B1 parameter; B5: Sterimol parameter.

4.4.3 Phosphine ligand preparation

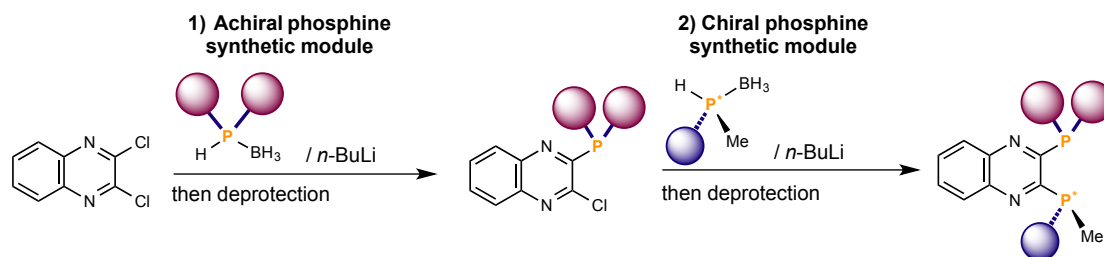
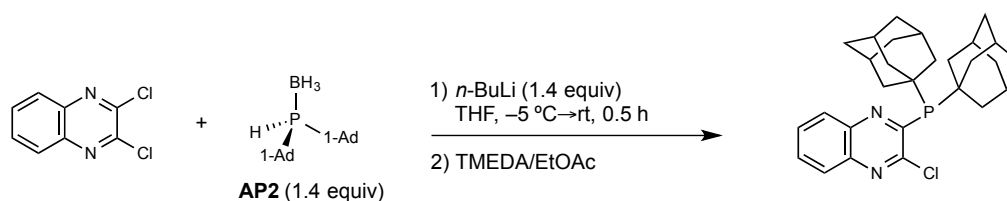


Fig. S4.1 General synthetic scheme of modular synthesis of chiral bisphosphine ligand.

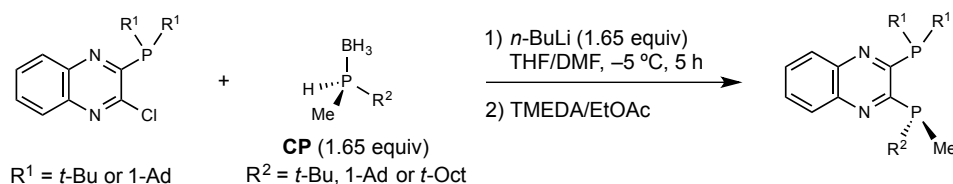
4.4.3.1 Preparation of 2-[(diadamantan-1-yl)phosphanyl]-3-chloroquinoxaline.



The nucleophilic phosphination was performed according to the literature procedure⁵⁶. A hexane solution of *n*-BuLi (1.64 M, 1.68 mmol, 1.02 mL) was added to a solution of (1-Ad)₂PH•BH₃ (1.68 mmol, 531 mg) in dry THF (3.6 mL) at −5 °C under nitrogen atmosphere. After the addition of THF (4.0 mL), the resulting solution was added to a solution of 2,3-dichloroquinoxaline (1.2 mmol, 239 mg) in THF (4.8 mL) at 0 °C. Then, the mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was quenched by H₂O and the mixture was extracted with *n*-hexane three times. The combined organic layer was then dried over Na₂SO₄. After filtration, the solvents were removed under reduced pressure. TMEDA (1.2 mL) and EtOAc (2.4 mL) was added to the residual oil at room temperature. After stirring for 3 h, the reaction mixture was diluted with EtOAc and washed with 1.5 M aqueous HCl solution, water and brine subsequently. The organic layer was dried over Na₂SO₄. After filtration, the solutions solvents were removed under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, Et₂O/hexane, 0:100–2:98) to give the corresponding phosphine as a yellow solid (0.93 mmol, 434 mg, 78%).

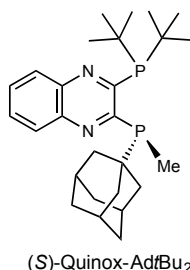
¹H NMR (392 MHz, CDCl₃, δ): 1.68 (br-s, 12H), 1.87–2.03 (br-m, 12H), 2.12–2.25 (br-m, 6H), 7.77–7.83 (m, 2H), 7.99–8.04 (m, 2H), 8.18–8.23 (m, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 28.8 (d, *J* = 9.4 Hz, CH), 36.9 (s, CH₂), 39.2 (d, *J* = 22.6 Hz, C), 41.3 (d, *J* = 12.2 Hz, CH₂), 128.3 (CH), 129.5 (CH), 129.8 (CH), 131.2 (CH), 140.3 (C), 141.1 (C), 153.8 (d, *J* = 37.6 Hz, C), 159.5 (d, *J* = 33.8 Hz, C). ³¹P NMR (160 MHz, CDCl₃, δ): 26.1. HRMS-EI (*m/z*): [M]⁺ calcd for C₂₈H₃₄N₂PCl, 464.2148; found, 464.2146. mp 209 °C.

4.4.3.2 General procedure for the phosphination of 2-phosphanyl-3-chloroquinoxaline.



The bisphosphine was synthesized according to the literature procedure.⁵⁶ A hexane solution of *n*-BuLi (1.55 M, 1.65 equiv) was added to a solution of the chiral phosphine–borane complex **CP** (>99% ee, 1.65 equiv) in dry THF (1.2 M) at 0 °C under nitrogen atmosphere. The resulting solution was added to a suspension of the corresponding 2-phosphanyl-3-chloroquinoxaline in DMF (0.19 M) at –5 °C. After stirring for 5 h, the reaction was quenched by H₂O and the mixture was extracted with EtOAc twice. The combined organic layer was washed with brine and dried over Na₂SO₄. After filtration, the solvents were removed by evaporation under reduced pressure. TMEDA/EtOAc (1:2) (0.07 M) was added to the residual oil at room temperature. After stirred for 2 h, the mixture was diluted with EtOAc and extracted with EtOAc. The organic layer was washed with water, aqueous HCl (6 M), water, and brine and was then dried over Na₂SO₄. After filtration, the solvents were removed under reduced pressure. The crude material was purified by flash column chromatography (SiO₂, Et₂O/hexane, 0:100–2:98) and reprecipitation or recrystallization to give the corresponding chiral bisphosphine as an orange or red solid.

4.4.3.3 2-[(1*S*)-(Adamantan-1-yl)(methyl)phosphanyl]-3-(di-*tert*-butylphosphanyl)quinoxaline [(*S*)-Quinox-Ad*t*Bu₂].

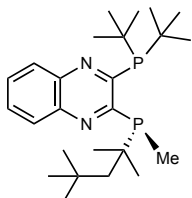


(*S*)-Quinox-Ad*t*Bu₂ was prepared from the corresponding chiral phosphine–borane complex (**AP2**, >99% ee, 0.50 mmol, 97.1 mg)⁵⁵ and 2-phosphinyl-3-chloro quinoxaline (0.30 mmol, 92.6 mg)⁵⁶ according to the procedure described above. Recrystallization from hexane/MeOH (1:4) afforded red crystals (0.26 mmol, 119 mg, 87%).

¹H NMR (392 MHz, CDCl₃, δ): 1.17 (d, *J*_{P-H} = 11.2 Hz, 9H), 1.37 (d, *J*_{P-H} = 11.7 Hz, 9H), 1.38 (d, *J*_{P-H} = 7.2 Hz, 3H), 1.59–1.72 (br-m, 6H), 1.73–1.83 (br-m, 3H), 1.87–1.97 (br-m, 6H), 7.69–7.76 (m, 2H), 8.06–8.12 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 4.3 (dd, *J* = 8.5, 17.9 Hz, CH₃), 28.6 (d, *J* = 8.5 Hz, CH), 30.4 (dd, *J* = 2.4, 12.7 Hz, CH₃), 30.7 (d, *J* = 14.1 Hz, CH₃), 34.3 (dd, *J* = 5.4, 23.7 Hz, C), 35.0 (dd, *J* = 1.9, 15.5 Hz, C), 35.5 (dd, *J* = 1.9, 24.0 Hz, C), 37.0 (CH₂), 38.9 (d, *J* = 10.8 Hz, CH₂), 129.48 (CH), 129.50 (CH), 129.56 (CH), 129.64 (CH), 140.9 (C), 141.0 (C), 166.3 (t, *J* = 32.2 Hz, C), 166.7 (t, *J* = 31.0 Hz, C). ³¹P NMR (160 MHz, CDCl₃, δ): –16.8 (d, *J* = 107.5 Hz), 21.4 (d, *J*

= 107.5 Hz). HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{27}H_{41}N_2P_2$, 455.2740; found, 455.2737. $[\alpha]_D^{23} +151$ (c 1.0, EtOAc). mp 116 °C.

4.4.3.4 (S)-2-(Di-*tert*-butylphosphanyl)-3-[methyl(2,4,4-trimethylpentan-2-yl)phosphanyl]quinoxaline [(S)-Quinox-*t*Oct*t*Bu₂].

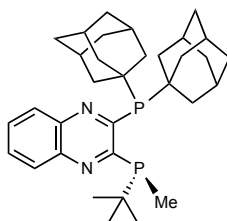


(S)-Quinox-*t*Oct*t*Bu₂

(S)-Quinox-*t*Oct*t*Bu₂ was prepared from the corresponding chiral phosphine–borane complex (CP3, >99% ee, 0.84 mmol, 146 mg)⁶ and 2-phosphinyl-3-chloro quinoxaline (0.60 mmol, 185 mg)⁵⁶ according to the procedure described above. Recrystallization from hexane/MeOH (1:4) afforded red crystals (0.49 mmol, 211 mg, 81%).

¹H NMR (392 MHz, CDCl₃, δ): 1.00 (s, 9H), 1.20 (d, J_{P-H} = 11.8 Hz, 9H), 1.30 (d, J_{P-H} = 5.4 Hz, 3H), 1.33 (d, J_{P-H} = 3.1 Hz, 3H), 1.35 (d, J_{P-H} = 11.7 Hz, 9H), 1.41 (d, J_{P-H} = 5.8 Hz, 3H), 1.52 (dd, J_{P-H} = 7.2, 14.4 Hz, 1H), 1.82 (dd, J_{P-H} = 9.0, 14.3 Hz, 1H), 7.69–7.75 (m, 2H), 8.05–8.10 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 6.5 (dd, J = 8.2, 20.4 Hz, CH₃), 25.0 (d, J = 12.2 Hz, CH₃), 25.6 (d, J = 10.8 Hz, CH₃), 30.5 (d, J = 10.8 Hz, CH₃), 30.6 (d, J = 13.6 Hz, CH₃), 33.6 (d, J = 11.3 Hz, C), 34.4 (dd, J = 4.7, 23.5 Hz, C), 35.2 (dd, J = 2.3, 23.5 Hz, C), 36.3 (dd, J = 3.5, 16.7 Hz, C), 51.1 (d, J = 17.4 Hz, CH₂), 129.35 (CH), 129.44 (CH), 129.5 (CH), 129.7 (CH), 140.8 (C), 140.9 (C), 166.5 (t, J = 30.8 Hz, C), 167.6 (dd, J = 31.0, 33.4 Hz, C). ³¹P NMR (160 MHz, CDCl₃, δ): –9.4 (d, J = 103.2 Hz), 21.3 (d, J = 103.2 Hz). HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{25}H_{43}N_2P_2$, 433.2896; found, 433.2893. $[\alpha]_D^{24} +84$ (c 0.52, EtOAc). mp 121 °C.

4.4.3.5 2-[(Diadamantan-1-yl)phosphanyl]-3-[(S)-*tert*-butyl(methyl)phosphanyl]quinoxaline [(S)-Quinox-*t*BuAd₂].

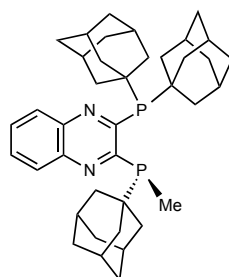


(S)-Quinox-*t*BuAd₂

(R)-Quinox-*t*BuAd₂ was prepared from the corresponding chiral phosphine–borane complex (CP1, >99% ee, 0.83 mmol, 97.3 mg)⁵⁴ and 2-phosphinyl-3-chloro quinoxaline (0.50 mmol, 233 mg)⁵⁶ according to the procedure described above. Recrystallization from hexane/MeOH (1:4) afforded red crystals (0.33 mmol, 174 mg, 65%).

^1H NMR (392 MHz, CDCl_3 , δ): 1.16 (d, $J_{\text{P-H}} = 12.1$ Hz, 9H), 1.42 (d, $J_{\text{P-H}} = 5.4$ Hz, 3H), 1.59–1.77 (br-m, 12H), 1.82–1.97 (br-m, 9H), 1.99–2.10 (br-m, 6H), 2.27–2.36 (br-m, 3H), 7.72 (dd, $J = 3.1, 6.7$ Hz, 1H), 7.74 (dd, $J = 2.9, 6.5$ Hz, 1H), 8.05–8.15 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 6.8 (dd, $J = 7.5, 18.8$ Hz, CH_3), 27.7 (d, $J = 14.1$ Hz, CH_3), 28.9 (d, $J = 7.5$ Hz, CH), 29.0 (d, $J = 7.5$ Hz, CH), 31.2 (dd, $J = 3.3, 14.6$ Hz, C), 36.9 (CH_2), 37.1 (CH_2), 39.4 (dd, $J = 4.7, 24.4$ Hz, C), 40.1 (dd, $J = 2.8, 24.4$ Hz, C), 41.5 (d, $J = 11.3$ Hz, CH_2), 41.6 (d, $J = 11.3$ Hz, CH_2), 129.4 (CH), 129.6 (CH), 129.7 (CH), 140.7 (C), 141.0 (C), 164.8 (t, $J = 30.5$ Hz, C), 167.9 (t, $J = 31.0$ Hz, C). ^{31}P NMR (160 MHz, CDCl_3 , δ): –14.9 (d, $J = 107.5$ Hz), 21.4 (d, $J = 103.2$ Hz). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{47}\text{N}_2\text{P}_2$, 533.3209; found, 533.3209. $[\alpha]_{\text{D}}^{24} +45$ (c 0.48, CHCl_3). mp 203 °C.

4.4.3.6 (*S*)-2-(Adamantan-1-yl(methyl)phosphanyl)-3-[(diadamantan-1-yl)phosphanyl]quinoxaline [(*S*)-Quinox-Ad₃].



(*S*)-Quinox-Ad₃

(*S*)-Quinox-Ad₃ was prepared from the corresponding chiral phosphine–borane complex (**CP2**, >99% ee, 0.83 mmol, 162 mg)⁵⁵ and 2-phosphinyl-3-chloro quinoxaline (0.50 mmol, 233 mg)⁴ according to the procedure described above. The product was obtained as an orange solid (0.45 mmol, 273 mg, 90%). Recrystallization from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (1:5) afforded red crystals to prepare crystals for single crystal XRD analysis.

^1H NMR (392 MHz, CDCl_3 , δ): 1.37 (d, $J_{\text{P-H}} = 5.4$ Hz, 3H), 1.57–2.10 (br-m, 42H), 2.30–2.39 (m, 3H), 7.73 (dd, $J = 3.1, 6.7$ Hz, 1H), 7.74 (dd, $J = 3.4, 6.5$ Hz, 1H), 8.07–8.15 (m, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 4.6 (dd, $J = 8.5, 17.9$ Hz, CH_3), 28.6 (d, $J = 8.5$ Hz, CH), 28.9 (d, $J = 8.5$ Hz, CH), 29.0 (d, $J = 8.5$ Hz, CH_3), 35.0 (dd, $J = 2.3, 15.5$ Hz, C), 36.9 (CH_2), 37.07 (CH_2), 37.14 (CH_2), 39.0 (d, $J = 10.3$ Hz, CH_2), 39.3 (dd, $J = 5.2, 24.9$ Hz, C), 40.4 (dd, $J = 1.9, 24.4$ Hz, C), 41.5 (d, $J = 11.3$ Hz, C), 41.6 (d, $J = 8.5$ Hz, CH_2), 129.4 (CH), 129.50 (CH), 129.52 (CH), 129.7 (CH), 140.6 (C), 140.9 (C). ^{31}P NMR (160 MHz, CDCl_3 , δ): –16.8 (d, $J = 103.2$ Hz), 21.5 (d, $J = 103.2$ Hz). HRMS-ESI (m/z): $[\text{M}+\text{H}]^+$ calcd for $\text{C}_{39}\text{H}_{53}\text{N}_2\text{P}_2$, 611.3679; found, 611.3681. $[\alpha]_{\text{D}}^{24} +125$ (c 0.52, CHCl_3). mp 268 °C.

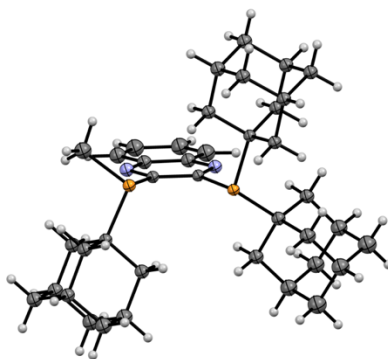
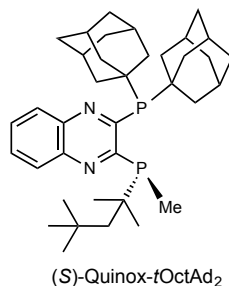


Fig. S4.2 ORTEP structure of (*S*)-Quinox-Ad₃. Thermal ellipsoids are drawn at the 50% probability level (CCDC 1817859).

Table S4.2 Summary of X-ray crystallographic data of (*S*)-Quinox-Ad₃.

CCDC Name	1817859
Empirical Formula	C ₃₉ H ₅₂ N ₂ P ₂
Formula Weight	610.80
Crystal System	monoclinic
Crystal Size / mm	0.368 × 0.367 × 0.091
<i>a</i> / Å	23.233(4)
<i>b</i> / Å	12.269(2)
<i>c</i> / Å	22.880(4)
β / °	91.775(7)
<i>V</i> / Å ³	6518.9(19)
Space Group	C ₂ (#5)
<i>Z</i> value	8
<i>D</i> _{calc} / g cm ⁻³	1.245
Temperature / K	123.15
$2\theta_{\max}$ / °	55.0
μ (Mo-K α) / cm ⁻¹	1.644
No. of Reflections	Total: 29639
Measured	Unique: 12918 (<i>R</i> _{int} = 0.0648)
No. of Observations (All reflections)	12918
Residuals: <i>R</i> ₁ (<i>I</i> > 2.00 σ (<i>I</i>))	0.0729
Residuals: <i>wR</i> ₂ (All reflections)	0.2362
Goodness of Fit Indicator (GOF)	0.898
Maximum Peak in Final Diff. Map / Å ³	1.37 e-
Minimum Peak in Final Diff. Map / Å ³	-0.58 e-
Flack Parameter	0.09(10)

4.4.3.7 2-[(Diadamantan-1-yl)phosphanyl]-3-[(*S*)-methyl(2,4,4-trimethylpentan-2-yl)phosphanyl]quinoxaline [(*S*)-Quinox-*t*OctAd₂].



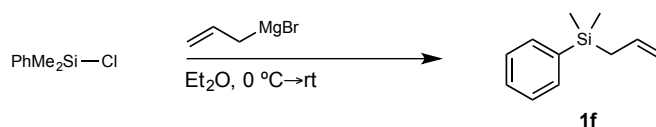
(*S*)-Quinox-*t*OctAd₂ was prepared from the corresponding chiral phosphine–borane complex (**CP3**, >99% ee, 0.83 mmol, 144 mg)⁶² and 2-phosphinyl-3-chloro quinoxaline (0.50 mmol, 233 mg)⁵⁶ according to the procedure described above. Recrystallization from MeOH afforded orange powder (0.36 mmol, 215 mg, 73%).

¹H NMR (392 MHz, CDCl₃, δ): 0.99 (s, 9H), 1.30 (d, *J*_{P–H} = 2.7 Hz, 3H), 1.33 (s, 3H), 1.40 (d, *J*_{P–H} = 5.8 Hz, 3H), 1.48 (dd, *J*_{P–H} = 7.4, 14.4 Hz, 1H), 1.58–1.75 (m, 12H), 1.82–1.96 (br-m, 10H), 2.00–2.10 (br-m, 6H), 2.28–2.36 (br-m, 3H), 7.72 (dd, *J* = 3.4, 6.5 Hz, 1H), 7.74 (dd, *J* = 3.4, 6.5 Hz, 1H), 8.05–8.15 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 6.7 (dd, *J* = 7.5, 20.7 Hz, CH₃), 25.1 (d, *J* = 14.1 Hz, CH₃), 25.4 (d, *J* = 9.4 Hz, CH₃), 28.9 (d, *J* = 4.7 Hz, CH), 29.0 (d, *J* = 5.6 Hz, CH), 32.3 (CH₃), 33.7 (d, *J* = 11.3 Hz, C), 36.5 (dd, *J* = 2.8, 16.9 Hz, C), 36.9 (CH₂), 37.1 (CH₂), 39.4 (dd, *J* = 4.7, 24.4 Hz, C), 40.1 (dd, *J* = 2.4, 24.9 Hz, CH₂), 41.5 (d, *J* = 11.3 Hz, CH₂), 41.6 (d, *J* = 9.4 Hz, CH₂), 51.2 (d, *J* = 17.9 Hz, CH₂), 129.4 (CH), 129.6 (CH), 129.7 (CH), 140.6 (C), 140.9 (C), 165.0 (t, *J* = 30.1 Hz, C), 168.1 (t, *J* = 32.4 Hz, C). ³¹P NMR (160 MHz, CDCl₃, δ): –9.5 (d, *J* = 98.9 Hz), 21.6 (d, *J* = 103.2 Hz). HRMS-ESI (*m/z*): [M+H]⁺ calcd for C₃₇H₅₅N₂P₂, 589.3835; found, 589.3837. [α]_D²³ +126 (c 0.51, EtOAc). mp 214 °C.

4.4.4 Substrate preparation

1f and **1h** were prepared by the reaction between allylmagnesium bromide and the corresponding electrophile. **1l** was synthesized from 10-bromo-1-decene through azidation of bromide. **1k**, **1m** and **1n** were synthesized according to our previous publication.⁴⁴ Other terminal alkene substrates were purchased from suppliers. The purchased starting materials were used without further purification.

4.4.4.1 Preparation of allyldimethyl(phenyl)silane (**1f**).⁶⁷

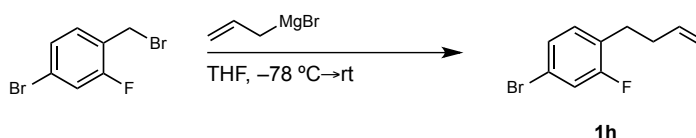


1g was prepared from 4-penten-1-ol according to the standard silylation procedure. In a vacuum dried round bottomed flask, dimethylphenylsilyl chloride (6.0 mmol, 1.0 mL) was added dropwise to

a solution of allylmagnesium bromide in Et₂O (0.7 M, 6.0 mmol, 8.6 mL) at 0 °C under nitrogen atmosphere. After stirring for 2 h at room temperature, the reaction mixture was quenched by addition of saturated aqueous NH₄Cl solution and extracted with Et₂O three times. The combined organic layer was dried over MgSO₄. After filtration, the solvent was removed under reduced pressure. The crude material was purified by column chromatography (SiO₂, hexane) to obtain the corresponding allylsilane (798 mg, 4.5 mmol, 75%) as a colorless oil.

¹H NMR (392 MHz, CDCl₃, δ): 0.28 (s, 6H), 1.76 (d, *J* = 8.1 Hz, 2H), 4.83–4.89 (m, 2H), 5.72–5.83 (m, 1H), 7.33–7.39 (m, 3H), 7.49–7.54 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): –3.5 (CH₃), 23.7 (CH₂), 113.4 (CH₂), 127.7 (CH), 129.0 (CH), 133.6 (CH), 134.6 (CH), 138.6 (C). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₁H₁₆Si, 176.1021; found, 176.1022.

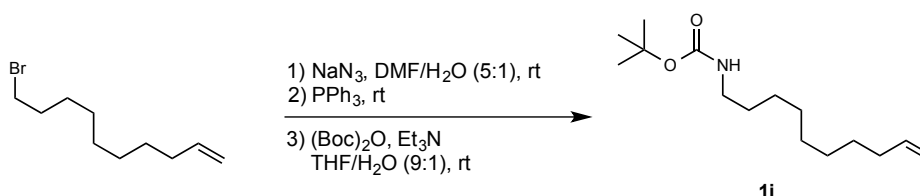
4.4.4.2 Preparation of 4-bromo-1-(but-3-en-1-yl)-2-fluorobenzene (1h).



In a vacuum dried round bottomed flask, a solution of allylmagnesium in Et₂O (0.7 M, 5.5 mmol, 7.9 mL) was added over 10 min to a solution of the corresponding benzyl bromide (5.0 mmol, 1.34 mg) in THF (12.5 mL) at –78 °C under nitrogen atmosphere. After stirring for 1 h at –78 °C, the mixture was then warmed to room temperature and stirring for 1 h. The reaction mixture was quenched by addition of water and extracted with Et₂O three times. The combined organic layer was dried over MgSO₄. After filtration, the solvent was removed under reduced pressure. The crude material was purified by column chromatography (SiO₂, hexane) to obtain the corresponding terminal alkene (927 mg, 4.0 mmol, 81%) as a colorless oil.

¹H NMR (392 MHz, CDCl₃, δ): 2.34 (dt, *J* = 7.0, 15.0 Hz, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 4.97–5.05 (m, 2H), 5.82 (ddt, *J* = 6.6, 10.3, 17.1 Hz, 1H), 7.05 (t, *J* = 8.1 Hz, 1H), 7.17–7.21 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 28.1 (CH₂), 33.8 (CH₂), 115.5 (CH₂), 118.8 (d, *J* = 26.3 Hz, CH), 119.5 (d, *J* = 9.4 Hz, C), 127.1 (d, *J* = 2.8 Hz, CH), 127.7 (d, *J* = 16.0 Hz, C), 131.7 (d, *J* = 5.6 Hz, CH), 160.9 (d, *J* = 249.0 Hz, C). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₀H₁₀BrF, 227.9950; found, 227.9949.

4.4.4.3 Preparation of *tert*-butyl dec-9-en-1-ylcarbamate (1i).⁶⁸



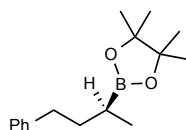
In a vacuum dried round bottomed flask, NaN₃ (11.7 mmol, 759 mg) was added portionwise to a solution of 10-bromo-1-decene (4.7 mmol, 1.0 mL) in DMF/H₂O (9:1, 18.6 mL) at room temperature under nitrogen atmosphere. After stirring for 19 h, the reaction mixture was diluted with brine and

extracted with Et₂O three times. The organic layer was dried over MgSO₄. After filtration, the solvents were removed under reduced pressure. In a vacuum dried round bottomed flask, the crude azide was dissolved to THF/H₂O (5:1, 16.4 mL). Then PPh₃ (5.6 mmol, 1.47 g) was added portionwise to the solution at room temperature under nitrogen atmosphere. After stirred for 17 h, triethylamine (18.8 mmol, 2.62 mL) and Boc₂O (10.3 mmol, 2.26 mL) were subsequently added to the mixture. After 11 h, the solvents were removed from the reaction mixture under reduced pressure. The residue was diluted with brine and extracted with Et₂O three times. The combined organic layer was dried over MgSO₄. After filtration, the solvent was removed under reduced pressure. The crude material was purified by column chromatography (SiO₂, EtOAc/hexane, 0:100–20:80) to obtained the corresponding Boc-protected amine **1i** (2.4 mmol, 617 mg) as a colorless oil.

¹H NMR (392 MHz, CDCl₃, δ): 1.23–1.52 (m, 21H), 2.04 (dt, *J* = 6.7, 14.8 Hz, 2H), 3.02–3.15 (m, 2H), 4.49 (br-s, *NH*, 1H), 4.91–5.02 (m, 2H), 5.81 (ddt, *J* = 6.7, 10.3, 17.1 Hz, 1 H). ¹³C NMR (99 MHz, CDCl₃, δ): 26.7 (CH₂), 28.3 (CH₃), 28.8 (CH₂), 29.0 (CH₂), 29.2 (CH₂), 29.3 (CH₂), 30.0 (CH₂), 33.7 (CH₂), 40.5 (CH₂), 78.8 (C), 114.1 (CH₂), 139.1 (CH), 155.9 (C). HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₁₅H₂₉NO₂Na, 278.2091; found, 278.2093..

4.4.5 Borylation Product Characterization

4.4.5.1 (*S*)-4,4,5,5-Tetramethyl-2-(4-phenylbutan-2-yl)-1,3,2-dioxaborolane [(*S*)-**3a**].^{51,52}

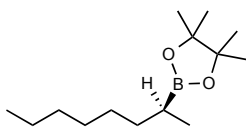


(*S*)-**3a**

According to the general borylation procedure, the reaction was conducted with 3 mol % [Cu(MeCN)₄]BF₄/(*S*)-Quinox-*t*OctAd₂ and 66.1 mg (0.50 mmol) of **1a**. The product (*S*)-**3a** was obtained in 94% yield (122 mg, 0.47 mmol, colorless oil) with 99% ee, **3/4** = 92:8. The regioselectivity was determined by GC analysis using the crude material. The absolute configuration of (*S*)-**3a** was confirmed using the optical rotation value of the previous reports.^{51,52}

¹H NMR (392 MHz, CDCl₃, δ): 0.99–1.13 (m, 4H), 1.25 (s, 12H), 1.54–1.67 (m, 1H), 1.74–1.83 (m, 1H), 2.56–2.68 (m, 2H), 7.13–7.22 (m, 3H), 7.23–7.30 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 15.4 (CH₃), 16.7 (br, B–CH), 24.7 (CH₃), 24.8 (CH₃), 35.3 (CH₂), 82.8 (C), 125.5 (CH), 128.1 (CH), 128.4 (CH), 143.0 (C). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₆H₂₅BO₂, 260.1951; found, 260.1947. [α]_D²⁴ +5.2 (c 1.1, CHCl₃, 99% ee). The ee value was determined by HPLC analysis of the corresponding alcohol after NaBO₃•4H₂O oxidation of (*S*)-**3a** in comparison of the racemic sample. Daicel CHIRALPAK® OZ-3, 2-PrOH/hexane = 2/98, 0.25 mL/min, 40 °C, *S* isomer: *t*_R = 38.5 min., *R* isomer: *t*_R = 43.8 min.

4.4.5.2 (S)-4,4,5,5-Tetramethyl-2-(octan-2-yl)-1,3,2-dioxaborolane [(S)-3b].⁶⁹

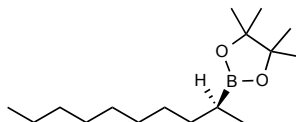


(S)-3b

According to the general borylation procedure, the reaction was conducted with 3 mol % $[\text{Cu}(\text{MeCN})_4]\text{BF}_4/(\text{S})\text{-Quinox-}t\text{OctAd}_2$ and 56.1 mg (0.50 mmol) of **1b**. The product (S)-**3b** was obtained in 76% yield (91.5 mg, 0.38 mmol, colorless oil) with 98% ee, **3/4** = 88:12. The regioselectivity was determined by GC analysis using the crude material. The regioisomer **4b** was removed by flash column chromatography (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{hexane}$, 0:100–32:68).

^1H NMR (392 MHz, CDCl_3 , δ): 0.87 (t, J = 7.0 Hz, 3H), 0.92–1.07 (m, 4H), 1.20–1.35 (m, 9H), 1.24 (s, 12H), 1.37–1.49 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 14.1 (CH_3), 15.5 (CH_3), 16.8 (br, B–CH), 22.6 (CH_2), 24.69 (CH_3), 24.73 (CH_3), 28.9 (CH_2), 29.5 (CH_2), 31.9 (CH_2), 33.2 (CH_2), 82.7 (C). HRMS–EI (m/z): $[\text{M}]^+$ calcd for $\text{C}_{14}\text{H}_{29}\text{BO}_2$, 240.2263; found, 240.2267. $[\alpha]_{\text{D}}^{23}$ +4.8 (c 1.0, CHCl_3 , 98% ee). The ee value was determined by HPLC analysis of the corresponding ester after $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ oxidation and esterification with *p*-bromobenzoyl chloride of (S)-**3b** in comparison of the racemic sample. Daicel CHIRALPAK® OZ-3, 2-PrOH/hexane = 0.1/99.9, 0.50 mL/min, 40 °C, *R* isomer: t_{R} = 20.3 min., *S* isomer: t_{R} = 21.7 min.

4.4.5.3 (S)-2-(Decan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(S)-3c].⁵¹



(S)-3c

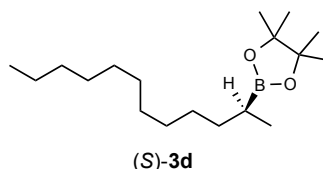
According to the general borylation procedure, the reaction was conducted with 3 mol % $[\text{Cu}(\text{MeCN})_4]\text{BF}_4/(\text{S})\text{-Quinox-}t\text{OctAd}_2$ and 70.1 mg (0.50 mmol) of **1c**. The product (S)-**3c** was obtained in 61% yield (81.6 mg, 0.31 mmol, colorless oil) with 99% ee, **3/4** = 89:11. The regioselectivity was determined by GC analysis using the crude material. The regioisomer **4c** was removed by flash column chromatography (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{hexane}$, 0:100–32:68).

Experiment in 5.0 mmol scale: According to the general borylation procedure, the reaction was conducted with 701.4 mg (5.0 mmol) of **1c**. The product (S)-**3c** was obtained in 71% yield (946 mg, 3.5 mmol, colorless oil) with 98% ee, **3/4** = 88:12. The regioselectivity was determined by GC analysis using the crude material. The regioisomer **4c** was removed by flash column chromatography (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{hexane}$, 0:100–32:68). The absolute configuration of (S)-**3c** was confirmed using the value of optical rotation of the previous report.⁵¹

^1H NMR (392 MHz, CDCl_3 , δ): 0.87 (t, J = 7.0 Hz, 3H), 0.92–1.07 (m, 4H), 1.19–1.35 (m, 13H), 1.24 (s, 12H), 1.36–1.49 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 14.1 (CH_3), 15.5 (CH_3), 16.9 (br, B–CH), 22.7 (CH_2), 24.68 (CH_3), 24.72 (CH_3), 29.0 (CH_2), 29.3 (CH_2), 29.6 (CH_2), 29.8 (CH_2), 31.9

(CH₂), 33.2 (CH₂), 82.7 (C). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₆H₃₃O₂B, 268.2577; found, 268.2581. [α]_D²² +7.7 (c 1.0, CHCl₃, 99% ee). The ee value was determined by HPLC analysis of the corresponding ester after NaBO₃•4H₂O oxidation and esterification with *p*-nitrobenzoyl chloride of (*S*)-**3c** in comparison of the racemic sample. Daicel CHIRALPAK® IC-3, 2-PrOH/hexane = 0.5/99.5, 0.50 mL/min, 40 °C, *R* isomer: *t*_R = 33.1 min., *S* isomer: *t*_R = 35.7 min.

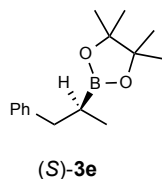
4.4.5.4 (*S*)-2-(Dodecan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*)-**3d**].⁵²



According to the general borylation procedure, the reaction was conducted with 3 mol % [Cu(MeCN)₄]BF₄/(*S*)-Quinox-*t*OctAd₂ and 84.2 mg (0.500 mmol) of **1d**. The product (*S*)-**3d** was obtained in 57% yield (113 mg, 0.27 mmol, colorless oil) with 97% ee, **3/4** = 88:12. The regioselectivity was determined by GC analysis using the crude material. The regioisomer **4d** was removed by flash column chromatography (SiO₂, CH₂Cl₂/hexane, 0:100–32:68). The absolute configuration of (*S*)-**3d** was confirmed using the value of optical rotation of the previous report.⁵²

¹H NMR (392 MHz, CDCl₃, δ): 0.88 (t, *J* = 6.7 Hz, 3H), 0.92–1.07 (m, 4H), 1.20–1.35 (m, 17H), 1.24 (s, 12H), 1.36–1.49 (m, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 14.1 (CH₃), 15.5 (CH₃), 17.0 (br, B–CH), 22.7 (CH₂), 24.70 (CH₃), 24.73 (CH₃), 29.0 (CH₂), 29.4 (CH₂), 29.6 (CH₂), 29.9 (CH₂), 31.9 (CH₂), 33.2 (CH₂), 82.7 (C). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₈H₃₇BO₂, 296.2890; found, 296.2889. [α]_D²³ +3.0 (c 1.0, CHCl₃, 97% ee). The ee value was determined by HPLC analysis of the corresponding ester after NaBO₃•4H₂O oxidation and esterification with *p*-bromobenzoyl chloride of (*S*)-**3d** in comparison of the racemic sample. Daicel CHIRALPAK® OZ-3, 2-PrOH/hexane = 0.1/99.9, 0.50 mL/min, 40 °C, *R* isomer: *t*_R = 18.6 min., *S* isomer: *t*_R = 20.0 min.

4.4.5.5 (*S*)-4,4,5,5-Tetramethyl-2-(1-phenylpropan-2-yl)-1,3,2-dioxaborolane [(*S*)-**3e**].^{70,71}

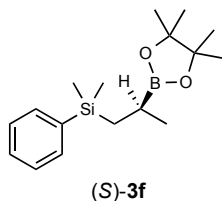


According to the general borylation procedure, the reaction was conducted with 5 mol % [Cu(MeCN)₄]BF₄/(*S*)-Quinox-*t*OctAd₂ and 59.1 mg (0.500 mmol) of **1e**. The product (*S*)-**3e** was obtained in 88% yield (109 mg, 0.44 mmol, colorless oil) with 99% ee, **3/4** = 85:15. The regioselectivity was determined by GC analysis using the crude material.

(*S*)-**3e** (*branched*)⁷⁰: ¹H NMR (392 MHz, CDCl₃, δ): 0.96 (d, *J* = 7.6 Hz, 3H), 1.18 (s, 6H), 1.19 (s, 6H), 1.32–1.42 (m, 1H), 2.54 (dd, *J* = 8.5, 13.5 Hz, 1H), 2.81 (dd, *J* = 7.4, 13.7 Hz, 1H), 7.13–7.28 (m, 5H). ¹³C NMR (99 MHz, CDCl₃, δ): 15.1 (CH₃), 24.7 (CH₃), 38.9 (CH₂), 82.9 (C), 125.5 (CH),

128.0 (CH), 128.9 (CH), 142.3 (C). **4e** (*linear*)⁷¹: ¹H NMR (392 MHz, CDCl₃, δ): 0.83 (t, *J* = 7.9 Hz, 2H), 1.24 (s, 12H), 1.73 (dt, *J* = 7.9, 15.7 Hz, 2H), 2.61 (t, *J* = 7.9 Hz, 2H), 7.13–7.28 (m, 5H). ¹³C NMR (99 MHz, CDCl₃, δ): 24.8 (CH₃), 26.1 (CH₂), 38.6 (CH₂), 82.9 (C), 125.5 (CH), 128.1 (CH), 128.5 (CH), 142.7 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS–EI (*m/z*): [M]⁺ calcd for C₁₅H₂₃BO₂, 246.1794; found, 246.1794. [α]_D²⁶ +3.7 (c 1.0, CHCl₃, 99% ee). The ee value was determined by HPLC analysis of the corresponding alcohol after NaBO₃•4H₂O oxidation of (*S*)-**3e** in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/hexane = 5/95, 0.50 mL/min, 40 °C, *S* isomer: *t*_R = 12.8 min., *R* isomer: *t*_R = 13.9 min.

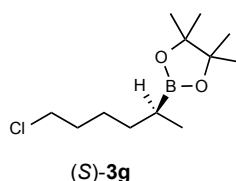
4.4.5.6 (*S*)-Dimethyl(phenyl)[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl]silane [(*S*)-**3f**].⁷²



According to the general borylation procedure, the reaction was conducted with 5 mol % [Cu(MeCN)₄]BF₄/(*S*)-Quinox-*t*OctAd₂ and 88.2 mg (0.500 mmol) of **1f** at –20 °C. The product (*S*)-**3f** was obtained in 60% yield (91.6 mg, 0.30 mmol, colorless oil) with 98% ee, **3/4** = 93:7. The regioselectivity was determined by GC analysis using the crude material. The absolute configuration of (*S*)-**3f** was confirmed using the optical rotation value of the previous report.⁷²

¹H NMR (392 MHz, CDCl₃, δ): 0.27 (s, 6H), 0.66–0.71 (m, 1H), 0.99 (d, *J* = 7.2 Hz, 3H), 1.03–1.16 (m, 2H), 1.20 (s, 12H), 7.31–7.35 (m, 3H), 7.51–7.53 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): –2.30 (CH₃), –2.25 (CH₃), 11.9 (br, B–CH), 18.8 (CH₂), 19.5 (CH), 24.69 (CH₃), 24.73 (CH₃), 82.8 (C), 127.6 (CH), 128.6 (CH), 133.6 (CH), 140.1 (C). HRMS–ESI (*m/z*): [M+Na]⁺ calcd for C₁₇H₂₉O₂BSiNa, 327.1922; found, 327.1926. [α]_D²⁶ +5.0 (c 1.0, CHCl₃, 98% ee). The ee value was determined by HPLC analysis of the corresponding alcohol after NaBO₃•4H₂O oxidation of (*S*)-**3f** in comparison of the racemic sample. Daicel CHIRALPAK® OZ-3, 2-PrOH/hexane = 0.5/99.5, 0.50 mL/min, 40 °C, *R* isomer: *t*_R = 35.4 min., *S* isomer: *t*_R = 36.5 min.

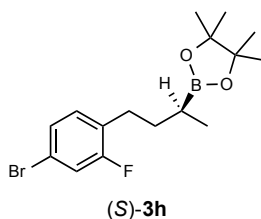
4.4.5.7 (*S*)-2-(6-Chlorohexan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*)-**3g**].^{51,73}



According to the general borylation procedure, the reaction was conducted with 5 mol % [Cu(MeCN)₄]BF₄/(*S*)-Quinox-*t*OctAd₂ and 59.3 mg (0.50 mmol) of **1g**. The product (*S*)-**3g** was obtained in 89% yield (110 mg, 0.45 mmol, colorless oil) with 98% ee, **3/4** = 86:14. The regioselectivity was determined by GC analysis using the crude material. The absolute configuration of (*S*)-**3g** was confirmed using the optical rotation value of the previous report.⁵¹

(*S*)-**3g** (*branched*)¹¹: ¹H NMR (392 MHz, CDCl₃, δ): 0.96–1.08 (m, 4H), 1.20–1.36 (m, 1H), 1.24 (s, 12 H), 1.39–1.52 (m, 3H), 1.76 (dt, *J* = 7.1 Hz, 14.2 Hz, 2H), 3.53 (t, *J* = 7.0 Hz, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 15.4 (CH₃), 16.9 (br, B–CH), 24.67 (CH₃), 24.72 (CH₃), 26.1 (CH₂), 32.3 (CH₂), 32.8 (CH₂), 45.1 (CH₂), 82.8 (C). **4g** (*linear*)¹⁷: ¹H NMR (392 MHz, CDCl₃, δ): 0.78 (t, *J* = 7.2 Hz, 2H), 1.20–1.36 (m, 2H), 1.25 (s, 12 H), 1.39–1.52 (m, 4H), 1.76 (dt, *J* = 7.1 Hz, 14.2 Hz, 2H), 3.52 (t, *J* = 6.7 Hz, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 16.9 (br, B–CH₂), 23.7 (CH₂), 24.8 (CH₃), 26.6 (CH₂), 31.5 (CH₂), 32.5 (CH₂), 45.1 (CH₂), 82.8 (C). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₂H₂₄BClO₂, 246.1560; found, 246.1562. [α]_D²² +4.6 (c 1.0, CHCl₃, 98% ee). The ee value was determined by HPLC analysis of the corresponding ester after NaBO₃•4H₂O oxidation and esterification with benzoyl chloride of (*S*)-**3g** in comparison of the racemic sample. Daicel CHIRALPAK® AD-3, 2-PrOH/hexane = 1/99, 0.50 mL/min, 40 °C, *R* isomer: *t*_R = 13.1 min., *S* isomer: *t*_R = 14.7 min.

4.4.5.8 (*S*)-2-[4-(4-Bromo-2-fluorophenyl)butan-2-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*)-**3h**].

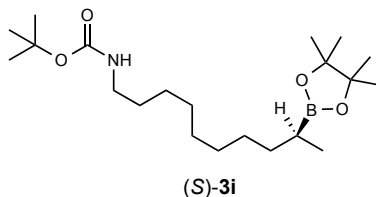


According to the general borylation procedure, the reaction was conducted with 3 mol % [Cu(MeCN)₄]BF₄/(*S*)-Quinox-*t*OctAd₂ and 115 mg (0.50 mmol) of **1h**. The product (*S*)-**3h** was obtained in 73% yield (131 mg, 0.37 mmol, colorless oil) with 99% ee, **3/4** = 84:16. The regioisomer **4h** was removed by flash column chromatography (SiO₂, Et₂O/hexane, 0:100–4:96). The regioselectivity was determined by GC analysis using the crude material.

¹H NMR (392 MHz, CDCl₃, δ): 1.01–1.09 (m, 4H), 1.25 (s, 12H), 1.49–1.58 (m, 1H), 1.69–1.78 (m, 1H), 2.54–2.66 (m, 2H), 7.06 (t, *J* = 8.1 Hz, 1H), 7.15–7.19 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 15.3 (CH₃), 16.7 (br, B–CH), 24.67 (CH₃), 24.73 (CH₃), 27.8 (CH₂), 33.5 (CH₂), 82.9 (C), 118.7 (d, *J* = 25.4 Hz, CH), 119.1 (d, *J* = 9.4 Hz, C), 127.0 (d, *J* = 3.8 Hz, CH), 128.9 (d, *J* = 16.0 Hz, C),

131.7 (d, $J = 5.6$ Hz, CH), 160.8 (d, $J = 249.0$ Hz, C). HRMS–EI (m/z): $[M]^+$ calcd for $C_{16}H_{23}BBrFO_2$, 356.0962; found, 356.0961. $[\alpha]_D^{26} + 8.2$ (c 1.0, $CHCl_3$, 99% ee). The ee value was determined by HPLC analysis of the corresponding alcohol after $NaBO_3 \cdot 4H_2O$ oxidation of (*S*)-**3h** in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/hexane = 1/99, 0.50 mL/min, 40 °C, *S* isomer: $t_R = 42.6$ min., *R* isomer: $t_R = 44.6$ min.

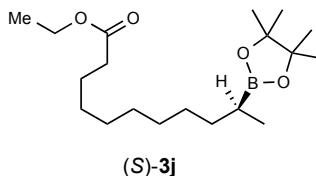
4.4.5.9 *tert*-Butyl (*S*)-(9-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)decyl)carbamate [(*S*)-**3i**].



According to the general borylation procedure, the reaction was conducted with 5 mol % $[Cu(MeCN)_4]BF_4/(S)$ -Quinox-*t*OctAd₂ and 128 mg (0.50 mmol) of **1i** at –10 °C. The product (*S*)-**3i** was obtained in 93% yield (178.5 mg, 0.47 mmol, colorless oil) with 97% ee, **3/4** = 87:13. The regioselectivity was determined by GC analysis using the crude material.

1H NMR (392 MHz, $CDCl_3$, δ): 0.92–1.07 (m, 4H), 1.19–1.36 (m, 12H), 1.24 (s, 12H), 1.38–1.52 (m, 11H), 3.02–3.15 (m, 2H), 4.49 (br-s, NH, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 15.5 (CH_3), 17.0 (br, B–CH), 24.66 (CH_3), 24.69 (CH_3), 26.8 (CH_2), 28.4 (CH_3), 28.9 (CH_2), 29.2 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 30.0 (CH_2), 33.1 (CH_2), 40.6 (CH_2), 78.9 (C), 82.7 (C), 155.9 (C). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{42}BO_4NNa$, 406.3103; found, 406.3101. $[\alpha]_D^{22} + 3.50$ (c 1.0, $CHCl_3$, 97% ee). The ee value was determined by HPLC analysis of the corresponding ester after $NaBO_3 \cdot 4H_2O$ oxidation and esterification with *p*-nitrobenzoyl chloride of (*S*)-**3i** in comparison of the racemic sample. Daicel CHIRALPAK® AD-3, 2-PrOH/hexane = 1/99, 0.50 mL/min, 40 °C, *S* isomer: $t_R = 48.3$ min., *R* isomer: $t_R = 51.5$ min.

4.4.5.10 Ethyl (*S*)-10-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)undecanoate [(*S*)-**3j**].

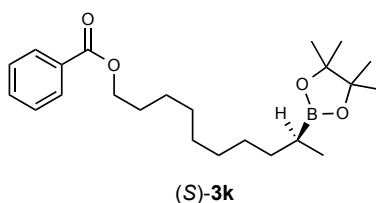


According to the general borylation procedure, the reaction was conducted with 5 mol % $[Cu(MeCN)_4]BF_4/(S)$ -Quinox-*t*OctAd₂ and 106 mg (0.50 mmol) of **1j**. The product (*S*)-**3j** was obtained in 91% yield (155 mg, 0.46 mmol, colorless oil) with 98% ee, **3/4** = 90:10. The regioselectivity was determined by GC analysis using the crude material.

1H NMR (392 MHz, $CDCl_3$, δ): 0.95–1.09 (m, 4H), 1.24 (s, 12H), 1.24–1.43 (m, 15H), 1.57–1.63 (m, 2H), 2.28 (t, $J = 7.6$ Hz, 2H), 4.12 (q, $J = 7.2$ Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 14.2 (CH_3),

15.5 (CH₃), 17.0 (br, B–CH), 24.6 (CH₃), 24.7 (CH₃), 24.9 (CH₂), 28.9 (CH₂), 29.1 (CH₂), 29.2 (CH₂), 29.4 (CH₂), 29.7 (CH₂), 33.2 (CH₂), 34.3 (CH₂), 60.1 (CH₂), 82.7 (C), 173.9 (C). HRMS–EI (*m/z*): [M]⁺ calcd for C₁₉H₃₇BO₄, 340.2788; found, 340.2788. [α]_D²² +6.8 (c 1.0, CHCl₃, 98% ee). The ee value was determined by HPLC analysis of the corresponding ester after NaBO₃•4H₂O oxidation and esterification with *p*-nitrobenzoyl chloride of (*S*)-**3j** in comparison of the racemic sample. Daicel CHIRALPAK® OJ-3, 2-PrOH/hexane = 2/98, 0.50 mL/min, 40 °C, *S* isomer: *t*_R = 26.7 min., *R* isomer: *t*_R = 46.0 min.

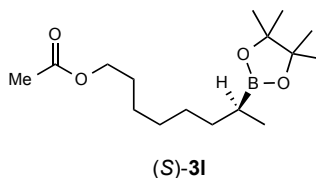
4.4.5.11 (*S*)-9-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)decyl benzoate [(*S*)-**3k**].⁴⁴



According to the general borylation procedure, the reaction was conducted with 5 mol % [Cu(MeCN)₄]BF₄/(*S*)-Quinox-*t*OctAd₂ and 130 mg (0.50 mmol) of **1k**. The product (*S*)-**3k** was obtained in 85% yield (166 mg, 0.43 mmol, colorless oil) with 96% ee, **3/4** = 90:10. The regioselectivity was determined by GC analysis using the crude material.

¹H NMR (392 MHz, CDCl₃, δ): 0.92–1.07 (m, 4H), 1.23 (s, 12H), 1.19–1.50 (m, 12H), 1.76 (dt, *J* = 7.1 Hz, 14.4 Hz, 2H), 4.31 (t, *J* = 6.7 Hz, 2H), 7.41–7.48 (m, 2H), 7.52–7.58 (m, 1H), 8.02–8.08 (m, 2H). ¹³C NMR (99 MHz, CDCl₃, δ): 15.5 (CH₃), 17.0 (br, B–CH), 24.66 (CH₃), 24.70 (CH₃), 26.0 (CH₂), 28.7 (CH₂), 28.9 (CH₂), 29.2 (CH₂), 29.4 (CH₂), 29.7 (CH₂), 33.2 (CH₂), 65.1 (CH₂), 82.7 (C), 128.3 (CH), 129.5 (CH), 130.5 (C), 132.7 (CH), 166.6 (C). HRMS–EI (*m/z*): [M]⁺ calcd for, C₂₃H₃₇BO₄, 388.2789; found, 388.2804. [α]_D²⁷ +2.4 (c 1.0, CHCl₃, 96% ee). The ee value was determined by HPLC analysis of the corresponding ester after NaBO₃•4H₂O oxidation and esterification with *p*-nitrobenzoyl chloride of (*S*)-**3k** in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/hexane = 1/99, 0.50 mL/min, 40 °C, *R* isomer: *t*_R = 43.4 min., *S* isomer: *t*_R = 46.8 min.

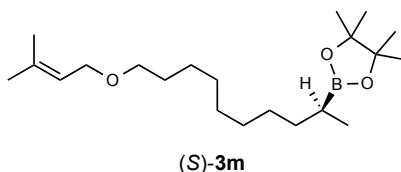
4.4.5.12 (*S*)-7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)octyl acetate [(*S*)-**3l**].



According to the general borylation procedure, the reaction was conducted with 5 mol % [Cu(MeCN)₄]BF₄/(*S*)-Quinox-*t*OctAd₂ and 85.1 mg (0.50 mmol) of **1l**. The product (*S*)-**3l** was obtained in 80% yield (120 mg, 0.40 mmol, colorless oil) with 96% ee, **3/4** = 89:11. The regioselectivity was determined by GC analysis using the crude material.

^1H NMR (392 MHz, CDCl_3 , δ): 0.93–1.07 (m, 4H), 1.20–1.49 (m, 8H), 1.24 (s, 12H), 1.55–1.66 (m, 2H), 2.04 (s, 3H), 4.04 (t, $J = 6.7$ Hz, 2H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 15.4 (CH_3), 17.0 (br-s, B–CH), 20.9 (CH_3), 24.6 (CH_3), 24.7 (CH_3), 25.8 (CH_2), 28.5 (CH_2), 28.7 (CH_2), 29.4 (CH_2), 33.0 (CH_2), 64.6 (CH_2), 82.7 (C), 171.1 (C). HRMS–ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{31}\text{BO}_4\text{Na}$, 321.2208; found, 321.2208. $[\alpha]_{\text{D}}^{27} +4.0$ (c 1.0, CHCl_3 , 96% ee). The ee value was determined by HPLC analysis of the corresponding ester after $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ oxidation and esterification with *p*-nitrobenzoyl chloride of (*S*)-**3l** in comparison of the racemic sample. Daicel CHIRALPAK® AD-3, 2-PrOH/hexane = 2/98, 0.50 mL/min, 40 °C, *R* isomer: $t_{\text{R}} = 43.8$ min., *S* isomer: $t_{\text{R}} = 45.6$ min.

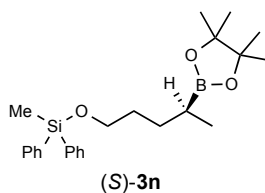
4.4.5.13 (*S*)-4,4,5,5-Tetramethyl-2-(10-((3-methylbut-2-en-1-yl)oxy)decan-2-yl)-1,3,2-dioxaborolane [(*S*)-**3m**].⁴⁴



According to the general borylation procedure, the reaction was conducted with 5 mol % $[\text{Cu}(\text{MeCN})_4]\text{BF}_4/(\text{S})\text{-Quinox-}t\text{OctAd}_2$ and 112 mg (0.50 mmol) of **1m**. The product (*S*)-**3m** was obtained in 71% yield (125 mg, 0.35 mmol, colorless oil) with 95% ee, **3/4** = 88:12. The regioselectivity was determined by GC analysis using the crude material.

^1H NMR (392 MHz, CDCl_3 , δ): 0.92–1.07 (m, 4H), 1.24 (s, 12H), 1.20–1.47 (m, 12H), 1.52–1.62 (m, 2H), 1.67 (s, 3H), 1.74 (s, 3H), 3.39 (t, $J = 6.7$ Hz, 2H), 3.93 (d, $J = 7.2$ Hz, 2H), 5.33–5.38 (m, 1H). ^{13}C NMR (99 MHz, CDCl_3 , δ): 15.5 (CH_3), 17.0 (br, B–CH), 17.9 (CH_3), 24.6 (CH_3), 24.7 (CH_3), 25.7 (CH_3), 26.1 (CH_2), 28.9 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 33.2 (CH_2), 67.1 (CH_2), 70.3 (CH_2), 82.7 (C), 121.3 (CH), 136.5 (C). HRMS–EI (m/z): $[\text{M}]^+$ calcd for, $\text{C}_{21}\text{H}_{41}\text{BO}_3$, 352.3153; found, 352.3158. $[\alpha]_{\text{D}}^{27} +4.0$ (c 1.0, CHCl_3 , 95% ee). The ee value was determined by HPLC analysis of the corresponding ester after $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ oxidation and esterification with *p*-bromobenzoyl chloride of (*S*)-**3m** in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/hexane = 0.5/99.5, 0.50 mL/min, 40 °C, *R* isomer: $t_{\text{R}} = 14.7$ min., *S* isomer: $t_{\text{R}} = 29.1$ min.

4.4.5.14 (*S*)-Methyldiphenyl{[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl]oxy}silane [(*S*)-**3n**].⁴⁴

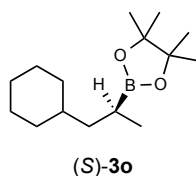


According to the general borylation procedure, the reaction was conducted with 5 mol % $[\text{Cu}(\text{MeCN})_4]\text{BF}_4/(\text{S})\text{-Quinox-}t\text{OctAd}_2$ and 141 mg (0.50 mmol) of **1n**. The product (*S*)-**3n** was

obtained in 54% yield (111 mg, 0.27 mmol, colorless oil) with 95% ee, **3/4** = 90:10. The regioselectivity was determined by GC analysis using the crude material.

¹H NMR (392 MHz, CDCl₃, δ): 0.62 (s, 3H), 0.94–1.05 (m, 4H), 1.22 (s, 12H), 1.26–1.50 (m, 2H), 1.54–1.64 (m, 2H), 3.68 (t, *J* = 6.3 Hz, 2H), 7.34–7.42 (m, 6H), 7.57–7.60 (m, 4H). ¹³C NMR (99 MHz, CDCl₃, δ): –3.0 (CH₃), 15.5 (CH₃), 16.8 (br, B–CH), 24.68 (CH₃), 24.70 (CH₃), 29.2 (CH₂), 31.9 (CH₂), 63.9 (CH₂), 82.7 (C), 127.7 (CH), 129.6 (CH), 134.3 (CH), 136.3 (C). HRMS–EI (*m/z*): [*M*]⁺ calcd for C₂₄H₃₅BSiO₃, 410.2453; found, 410.2444. [*α*]_D²² + 4.0 (c 1.0, CHCl₃, 95% ee). The ee value was determined by HPLC analysis of the corresponding alcohol after NaBO₃•4H₂O oxidation of (*S*)-**3n** in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/hexane = 3/97, 0.50 mL/min, 40 °C, *R* isomer: *t*_R = 16.4 min., *S* isomer: *t*_R = 17.3 min.

4.4.5.15 (*S*)-2-(1-Cyclohexylpropan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*S*)-**3o**].^{44,74}

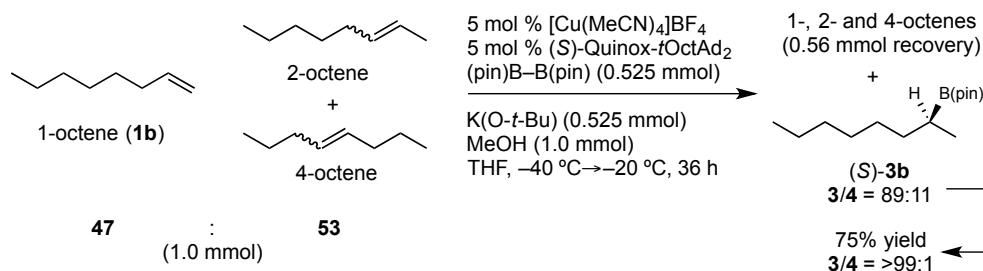


According to the general borylation procedure, the reaction was conducted with 5 mol % [Cu(MeCN)₄]BF₄/(*S*)-Quinox-*t*OctAd₂ and 62.1 mg (0.50 mmol) of **1o**. The product (*S*)-**3o** was obtained in 67% yield (84.7 mg, 0.34 mmol, colorless oil) with 95% ee, **3/4** = 83:17. The regioselectivity was determined by GC analysis using the crude material.

(*S*)-**3o** (*branched*)⁴⁴: ¹H NMR (392 MHz, CDCl₃, δ): 0.79–0.94 (m, 4H), 1.06–1.44 (m, 19H), 1.58–1.70 (m, 6H). ¹³C NMR (99 MHz, CDCl₃, δ): 13.9 (br, B–CH), 15.7 (CH₃), 24.7 (CH₃), 26.4 (CH₂), 26.5 (CH₂), 26.7 (CH₂), 33.1 (CH₂), 33.6 (CH₂), 36.5 (CH), 40.7 (CH₂), 82.7 (C). **4o** (*linear*)⁷⁴: ¹H NMR (392 MHz, CDCl₃, δ): 0.74 (t, *J* = 6.7 Hz, 2H), 0.79–0.94 (m, 2H), 1.06–1.44 (m, 19H), 1.58–1.70 (m, 6H). ¹³C NMR (99 MHz, CDCl₃, δ): 13.9 (br, B–CH), 21.3 (CH₂), 24.8 (CH₃), 26.4 (CH₂), 26.7 (CH₂), 33.4 (CH₂), 37.4 (CH), 40.4 (CH₂), 82.8 (C). HRMS–EI (*m/z*): [*M*]⁺ calcd for, C₁₅H₂₉BO₂, 252.2263; found, 252.2268. [*α*]_D²³ + 2.9 (c 1.0, CHCl₃, 95% ee). The ee value was determined by HPLC analysis of the corresponding ester after NaBO₃•4H₂O oxidation and esterification with *p*-nitrobenzoyl chloride of (*S*)-**3o** in comparison of the racemic sample. Daicel CHIRALPAK® OZ-3, 2-PrOH/hexane = 0.5/99.5, 0.50 mL/min, 40 °C, *R* isomer: *t*_R = 25.8 min., *S* isomer: *t*_R = 27.6 min.

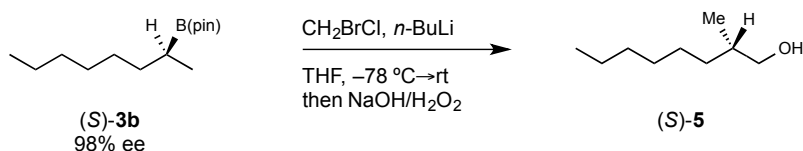
4.4.6 Application of Enantioselective Markovnikov Hydroboration

4.4.6.1 1-Octene selective asymmetric Markovnikov hydroboration.



$[\text{Cu}(\text{MeCN})_4]\text{BF}_4$ (7.9 mg, 0.025 mmol), bis(pinacolato)diboron (**2**) (133 mg, 0.53 mmol) and (*S*)-Quinox-*t*OctAd₂ (14.7 mg, 0.025 mmol) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a TeflonTM-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dry THF (1.48 mL) and K(O-*t*-Bu)/THF (1.00 M, 0.53 mL, 0.53 mmol) were added in the vial through the rubber septum using a syringe. After stirring for 30 min at $-40\text{ }^\circ\text{C}$, the mixture of octenes [112 mg, 1.0 mmol, 47% 1-octene (**1b**)] and methanol (0.040 mL, 1.0 mmol) were added to the mixture at $-40\text{ }^\circ\text{C}$. After stirring for 1 h, the mixture was warmed to $-20\text{ }^\circ\text{C}$ and stirred for 35 h. The reaction mixture was then passed through a short silica gel (Φ : 10 mm, height of the silica-gel column: 30 mm) eluting with Et₂O. The crude material was purified by flash column chromatography (SiO₂, CH₂Cl₂/hexane, 0:100–32:68) to give the corresponding alkylboronate (*S*)-**3c** (91.8 mg, 0.38 mmol, 75% yield based on an amount of 1-octene in the mixture).

4.4.6.2 Synthesis of (*S*)-2-methyloctan-1-ol [(*S*)-**5**].⁷⁵



In an oven- dried reaction vial, (*S*)-**3b** (48.0 mg, 0.2 mmol) and bromochloromethane (51.8 mg, 0.4 mmol) were dissolved in dry THF (1.5 mL) under nitrogen atmosphere. After the mixture was cooled to $-78\text{ }^\circ\text{C}$, a solution of *n*-BuLi in hexane (1.55 M, 194 μL , 0.3 mmol) was added dropwise. The mixture was stirred at $-78\text{ }^\circ\text{C}$ for 30 min, and then stirring at room temperature for 2 hours. The reaction mixture was quenched by addition of water and extracted three times with Et₂O. The combined organic layer was dried over MgSO₄. After filtration, the resulting crude material was submitted to the subsequent reaction without further purification. In a reaction vial, the crude material of above reaction was dissolved in the mixture of THF (1.0 mL) and aqueous NaOH solution (3.0 M, 1.0 mL). Aqueous H₂O₂ solution (30%, 0.5 mL) was then added at $0\text{ }^\circ\text{C}$. After stirring for 1 hours, the reaction mixture was quenched by saturated Na₂S₂O₃ solution at $0\text{ }^\circ\text{C}$ and extracted with Et₂O. The organic layer was dried over MgSO₄. After filtration, the crude mixture was purified by flash column chromatography (SiO₂, Et₂O/hexane, 0:100–32:68) to afford the corresponding alcohol (25.7 mg, 0.18

mmol, 89%, 2 steps) as a colorless oil.

¹H NMR (392 MHz, CDCl₃, δ): 0.88 (t, J = 6.7 Hz, 3H), 0.92 (d, J = 6.3 Hz, 3H), 1.06–1.14 (m, OH, 1H), 1.21–1.48 (m, 10H), 1.55–1.67 (m, 1H), 3.42 (dd, J = 6.5, 10.8 Hz, 1H), 3.51 (dd, J = 5.8, 10.3 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 14.0 (CH₃), 16.5 (CH₃), 22.6 (CH₂), 26.9 (CH₂), 29.6 (CH₂), 31.8 (CH₂), 33.1 (CH₂), 35.7 (CH), 68.3 (CH₂). HRMS-ESI (m/z): [M+Na]⁺ calcd for C₉H₂₀O₁Na, 167.1412; found, 167.1412. [α]_D²³ –14 (c 1.0, CHCl₃, 98% ee). The ee value was determined by HPLC analysis of the corresponding ester after esterification of (*S*)-**5** in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/hexane = 0.1/99.9, 0.50 mL/min, 40 °C, *R* isomer: t_R = 17.4 min., *S* isomer: t_R = 19.3 min. The absolute configuration of (*S*)-**5** was confirmed by the optical rotation value of the previous report.⁷⁵

4.4.7 Computational Study

4.4.7.1 Calculation method.

All calculations were performed with Gaussian 09 (revision C.01) program package.⁷⁶ Geometry optimizations and transition state (TS) calculations were carried out at ω B97XD level of theory⁵⁸ with SDD basis set for Cu and 6-311G(d,p) basis set for the other atoms in the gas phase. Frequency calculations were conducted at the same level of theory on the optimized geometries to check the all the stationary points as either minima or transition states. The intrinsic reaction coordinate (IRC) was calculated for the transition states to confirm that the structures were indeed connected by two relevant minimas. Molecular structures were drawn using the Mercury 3.5 program.

4.4.7.2 Calculation method.

According to the previous work for copper(I)-catalyzed hydroboration with diboron reagent, the reaction proceeds through the borylcupration from the π -complex (**II**) to give the alkylcopper(I) intermediate (**III**) followed by the protonation of **III** with alcohol to give the borylation products (**3** and **4**) and the copper alkoxide (**IV**) (Fig. S4.3). The transition state of the borylcupration steps (**TS**) are the highest stationary point in each routs and are the rate- and stereoselectivity determining step.^{44–47,50,52,77} We thus calculated the π -complex (**II**), the transition state structures (**TS**) and the alkylcopper(I) intermediate (**III**) for the eight reaction pathways with (*S*)-Quinox-*t*Bu₃ and (*S*)-Quinox-Ad₃ respectively. The predicted stereoselectivities for the ligands were calculated from the activation energy values of **TSs** by Supplementary Equations (1) and (2) (Fig. S4.4, S4.5, Fig. 4.9 and Fig. 4.13).

$$ee_{pre}(\%) = \frac{\sum e^{-\frac{\Delta G_S}{RT}} - \sum e^{-\frac{\Delta G_R}{RT}}}{\sum e^{-\frac{\Delta G_S}{RT}} + \sum e^{-\frac{\Delta G_R}{RT}}} \times 100 \quad (1)$$

$$3/4_{pre} = \frac{\sum e^{-\frac{\Delta G_S}{RT}} + \sum e^{-\frac{\Delta G_R}{RT}}}{\sum e^{-\frac{\Delta G_S}{RT}} + \sum e^{-\frac{\Delta G_R}{RT}} + \sum e^{-\frac{\Delta G_L}{RT}}} \quad (2)$$

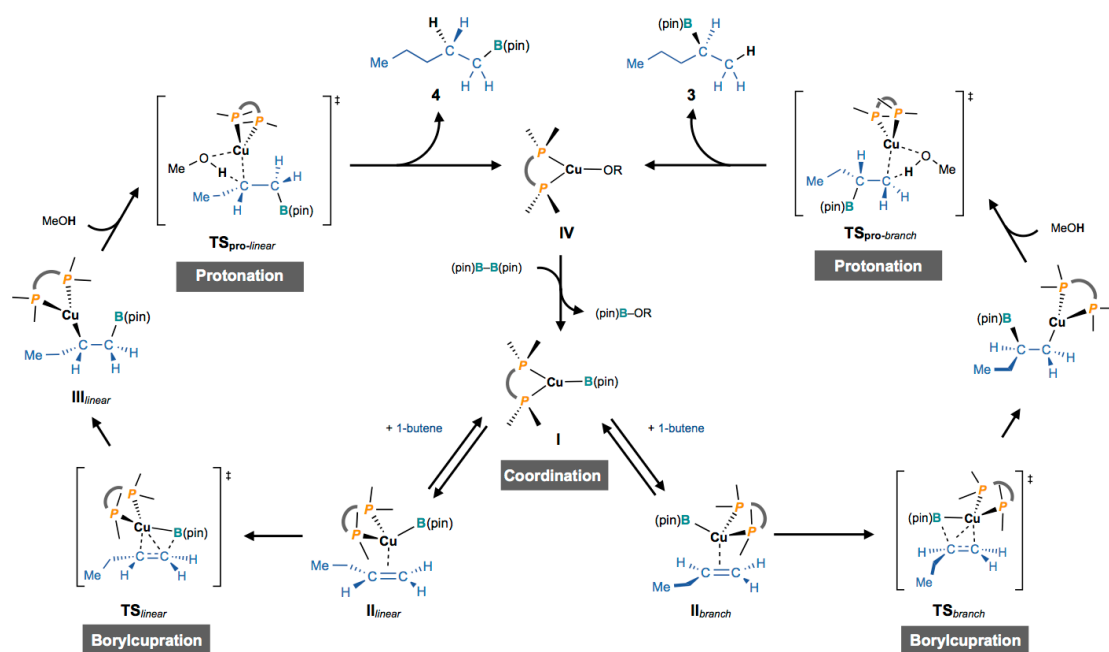


Fig. S4.3 Proposed reaction pathways for the branched product **3** and the linear product **4**.

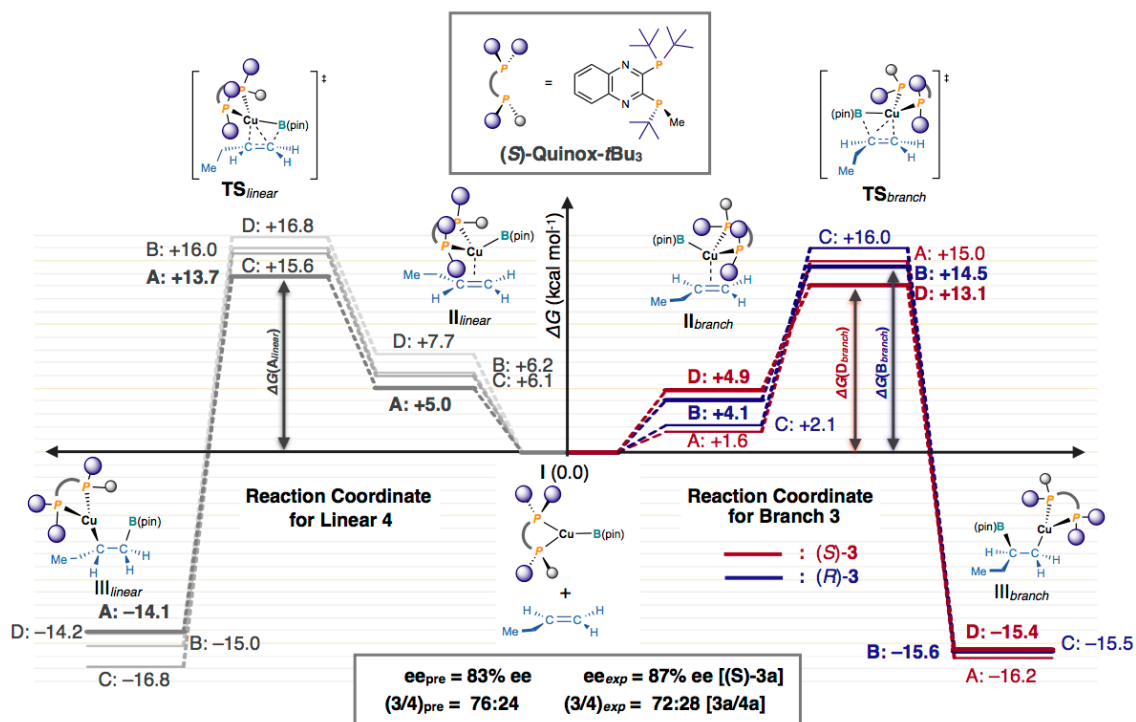


Fig. S4.4 Energy level diagram of borylcupration step with (S)-Quinox-*t*Bu₃.

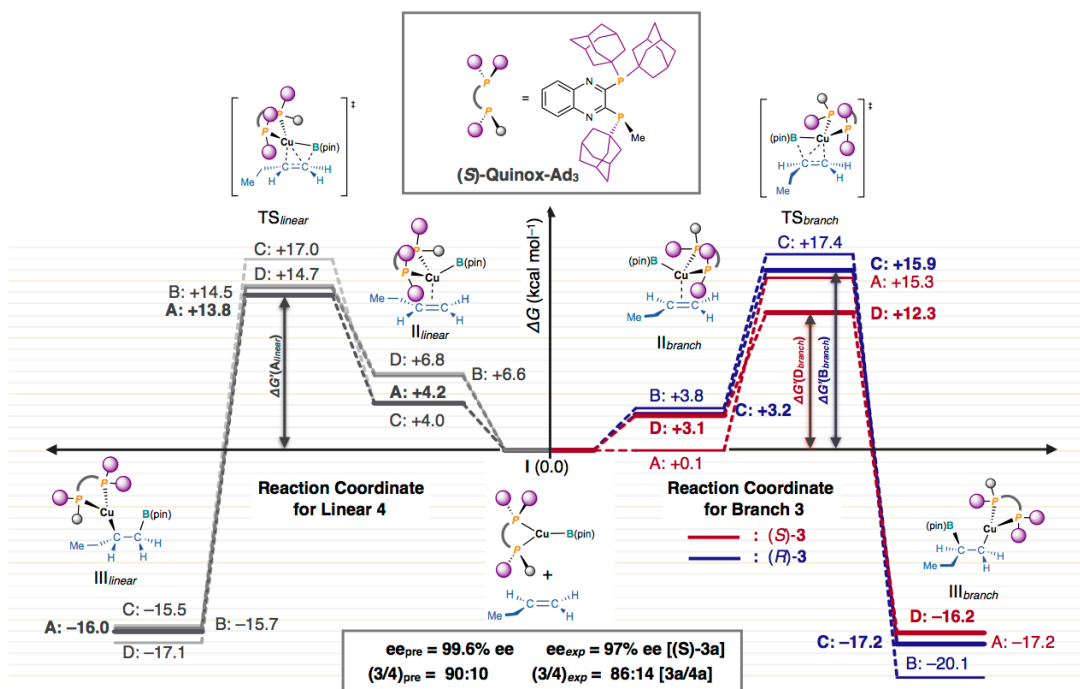
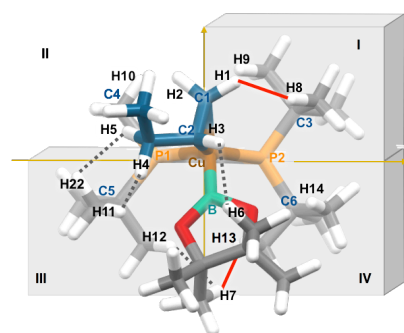


Fig. S4.5 Energy level diagram of borylcupration step with (S)-Quinox-Ad₃.

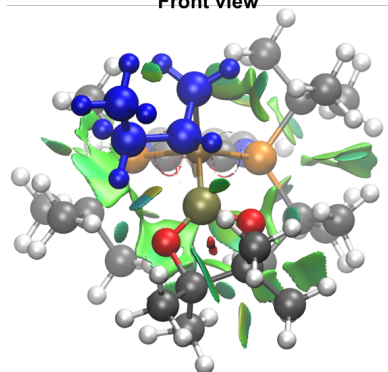
4.4.7.3 Analysis of optimized transition state structures and NCI Plots.

The transition state (TS) structures of the borylcupration of 1-butene were obtained by the DFT calculation study. We then conducted the analysis of these structures focused on the steric congestion and strain to understand the origin of the regio- and enantioselectivity of the enantioselective Markovnikov hydroboration of aliphatic terminal alkenes. Furthermore, non-covalent interactions (NCI) analysis which is the visualization method of noncovalent interactions^{78,79} were greatly helpful for searching steric congestion area in the TS structures.

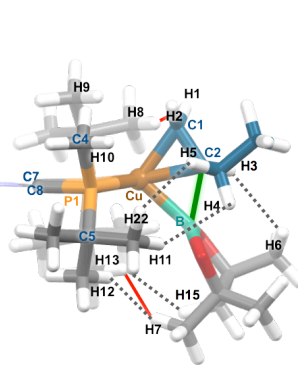
TS-A_{branch} (+1.9)



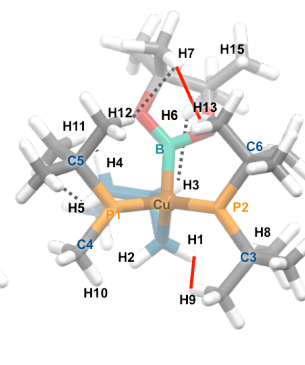
Front view



NCI plot



Side view



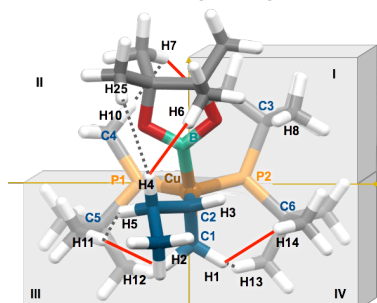
Back view

atom distance: **H1-H8 = 2.08** H7-H12 = 2.51 bond length: **P1-Cu = 2.26**
H3-H6 = 2.58 **H7-H13 = 2.04** **P2-Cu = 2.26**
H4-H11 = 2.59 H13-H15 = 2.66 **C1-Cu = 2.01**
H5-H11 = 2.68 **C3-C4 = 5.51** **C2-Cu = 2.06**
Cu-B = 2.09
C2-B = 1.94

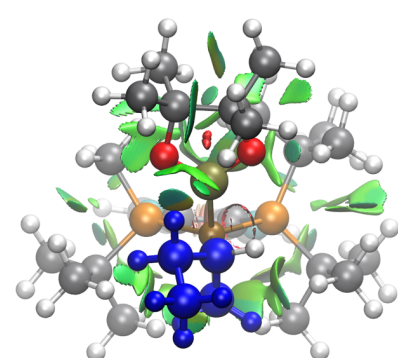
bond angle: **B-C2-C1 = 126.90°** **C3-P2-C6 = 111.42°** **C4-P1-C5 = 104.06°**
C6-P2-C7 = 102.76° **C5-P1-C8 = 105.12°**
C7-P2-C3 = 102.89° **C8-P1-C4 = 99.87°**

dihedral angle: **B-Cu-C1-C2 = -14.68°**

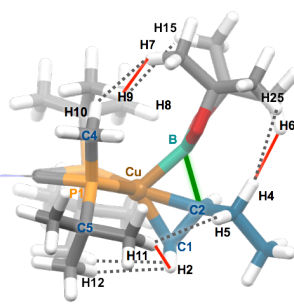
TS-B_{branch} (+1.4)



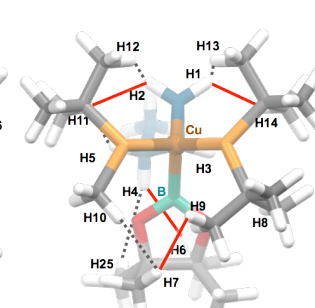
Front view



NCI plot



Side view



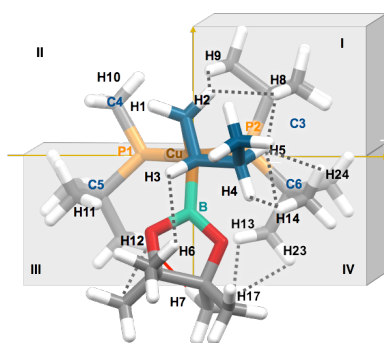
Back view

atom distance: H1-H13 = 2.46 H5-H11 = 2.34 bond length: **P1-Cu = 2.24**
H1-H14 = 2.11 **H7-H9 = 2.09** **P2-Cu = 2.28**
H2-H11 = 2.26 H7-H10 = 2.51 **C1-Cu = 2.00**
H2-H12 = 2.56 H9-H15 = 2.62 **C2-Cu = 2.06**
H4-H6 = 2.29 **C3-C4 = 4.95** **Cu-B = 2.06**
H4-H25 = 2.65 **C5-C6 = 5.91** **C2-B = 2.01**

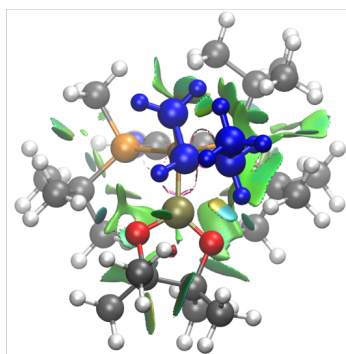
bond angle: **B-C2-C1 = 127.22°** **C3-P2-C6 = 112.01°** **C4-P1-C5 = 104.71°**
C6-P2-C7 = 104.86° **C5-P1-C8 = 104.48°**
C7-P2-C3 = 100.46° **C8-P1-C4 = 100.89°**

dihedral angle: **B-Cu-C1-C2 = -3.08°**

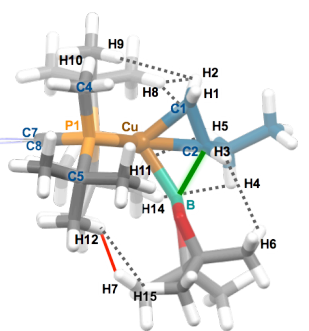
TS-C_{branch} (+2.9)



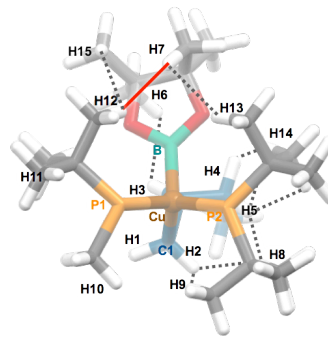
Front view



NCI plot



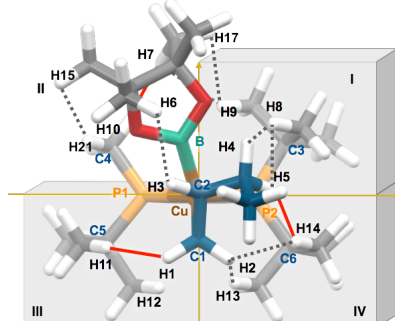
Side view



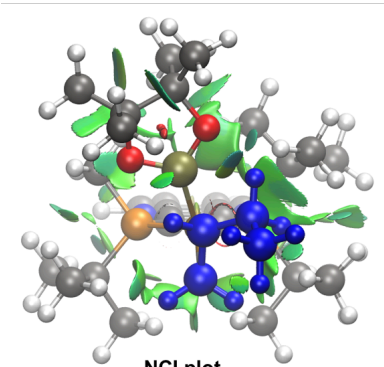
Back view

atom distance:	H2-H8 = 2.42	H7-H12 = 2.17	bond length:	P1-Cu = 2.25
	H2-H9 = 2.56	H7-H13 = 2.38		P2-Cu = 2.28
	H3-H6 = 2.53	H12-H15 = 2.53		C1-Cu = 2.00
	H4-H14 = 2.56	H13-H17 = 2.56		C2-Cu = 2.07
	H5-H8 = 2.32	C3-C4 = 4.88		Cu-B = 2.11
	H5-H14 = 2.58	C5-C6 = 6.00		C2-B = 1.90
	H5-H24 = 2.66			
bond angle:	B-C2-C1 = 127.30°	C3-P2-C6 = 112.40°		C4-P1-C5 = 103.69°
		C6-P2-C7 = 103.92°		C5-P1-C8 = 105.40°
		C7-P2-C3 = 101.02°		C8-P1-C4 = 99.81°
dihedral angle:	B-Cu-C1-C2 = 14.54°			

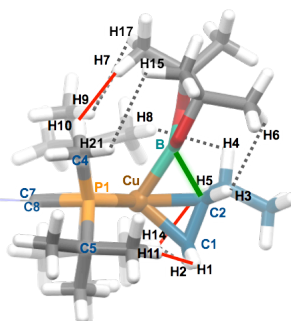
TS-D_{branch} (+0.0)



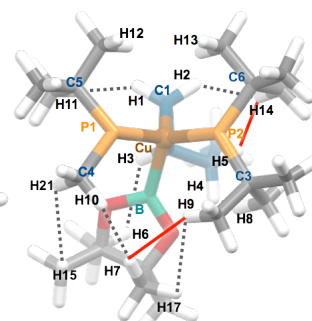
Front view



NCI plot



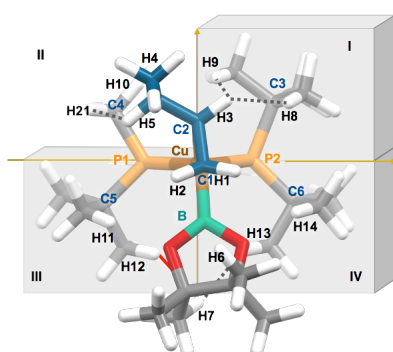
Side view



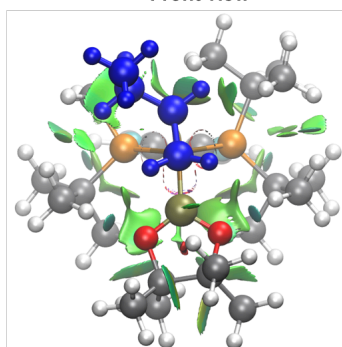
Back view

atom distance:	H1-H11 = 2.24	H7-H9 = 2.42	bond length:	P1-Cu = 2.23
	H2-H13 = 2.47	H7-H10 = 2.24		P2-Cu = 2.28
	H2-H14 = 2.38	H9-H17 = 2.64		C1-Cu = 2.01
	H3-H6 = 2.49	H15-H21 = 2.67		C2-Cu = 2.05
	H4-H8 = 2.60	C3-C4 = 5.32		Cu-B = 2.07
	H5-H8 = 2.60	C5-C6 = 5.59		C2-B = 1.98
	H5-H14 = 2.25			
bond angle:	B-C2-C1 = 125.46°	C3-P2-C6 = 112.89°		C4-P1-C5 = 104.59°
		C6-P2-C7 = 102.86°		C5-P1-C8 = 105.56°
		C7-P2-C3 = 102.27°		C8-P1-C4 = 99.55°
dihedral angle:	B-Cu-C1-C2 = -17.33°			

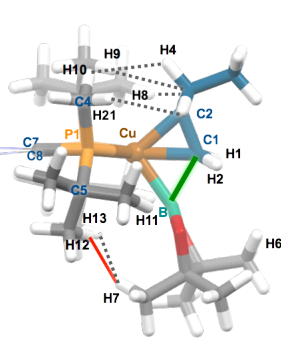
TS-A_{linear} (+0.6)



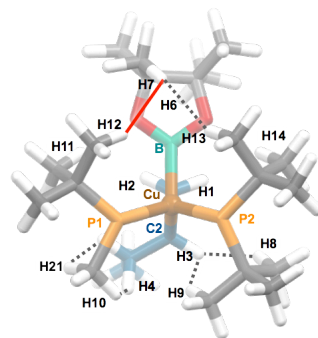
Front view



NCI plot



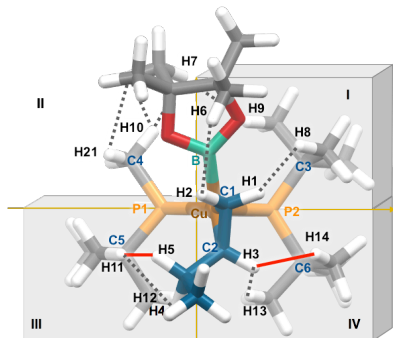
Side view



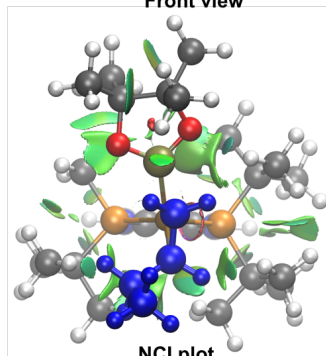
Back view

atom distance:	H3-H8 = 2.34	H7-H13 = 2.37	bond length:	P1-Cu = 2.25
	H3-H9 = 2.54	C3-C4 = 4.91		P2-Cu = 2.27
	H4-H10 = 2.59	C5-C6 = 5.96		C1-Cu = 2.04
	H5-H21 = 2.63			C2-Cu = 2.01
	H7-H12 = 2.28			Cu-B = 2.12
				C1-B = 1.88
bond angle:	B-C1-C2 = 132.48°	C3-P2-C6 = 112.75°		C4-P1-C5 = 103.93°
		C6-P2-C7 = 104.38°		C5-P1-C8 = 104.37°
		C7-P2-C3 = 100.52°		C8-P1-C4 = 100.27°
dihedral angle:	B-Cu-C2-C1 = 3.55°			

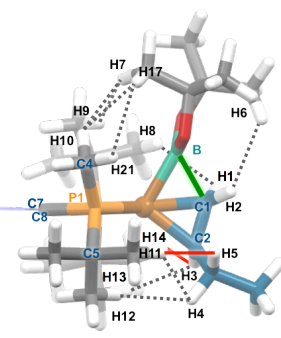
TS-B_{linear} (+2.9)



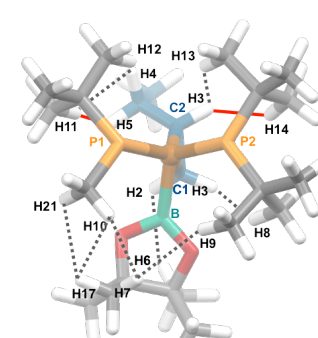
Front view



NCI plot



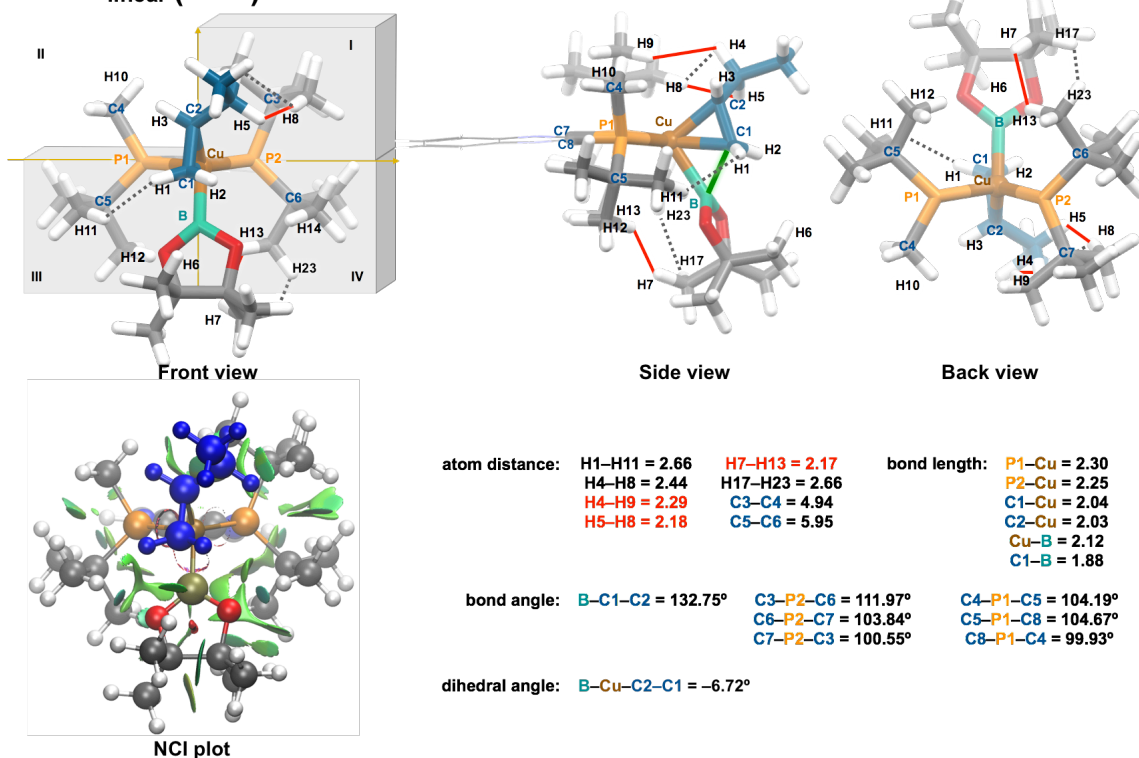
Side view



Back view

atom distance:	H1-H8 = 2.69	H7-H9 = 2.61	bond length:	P1-Cu = 2.23
	H2-H6 = 2.54	H7-H10 = 2.36		P2-Cu = 2.30
	H3-H13 = 2.35	H10-H21 = 2.56		C1-Cu = 2.02
	H3-H14 = 2.25	H17-H21 = 2.57		C2-Cu = 2.03
	H4-H11 = 2.51	C3-C4 = 5.42		Cu-B = 2.08
	H4-H12 = 2.37	C5-C6 = 5.54		C1-B = 1.96
	H5-H11 = 2.25			
bond angle:	B-C1-C2 = 130.09°	C3-P2-C6 = 112.10°		C4-P1-C5 = 104.27°
		C6-P2-C7 = 102.78°		C5-P1-C8 = 105.25°
		C7-P2-C3 = 102.59°		C8-P1-C4 = 99.37°
dihedral angle:	B-Cu-C2-C1 = -12.24°			

TS-C_{linear} (+2.5)



TS-D_{linear} (+3.6)

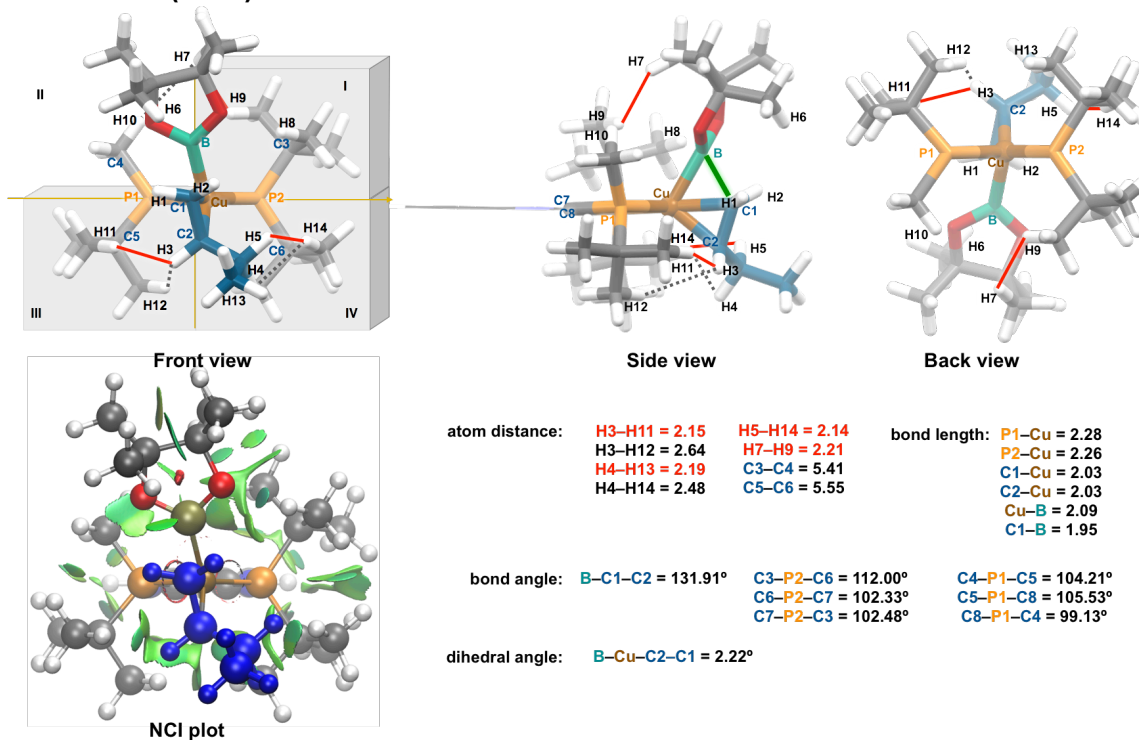
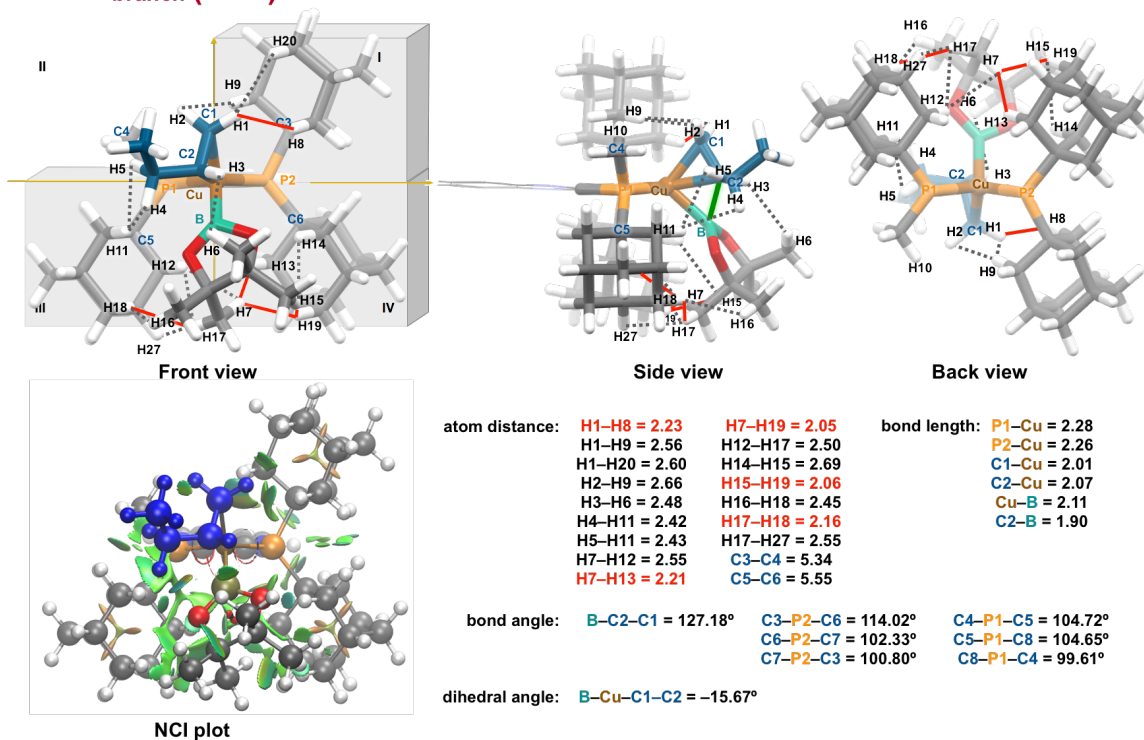
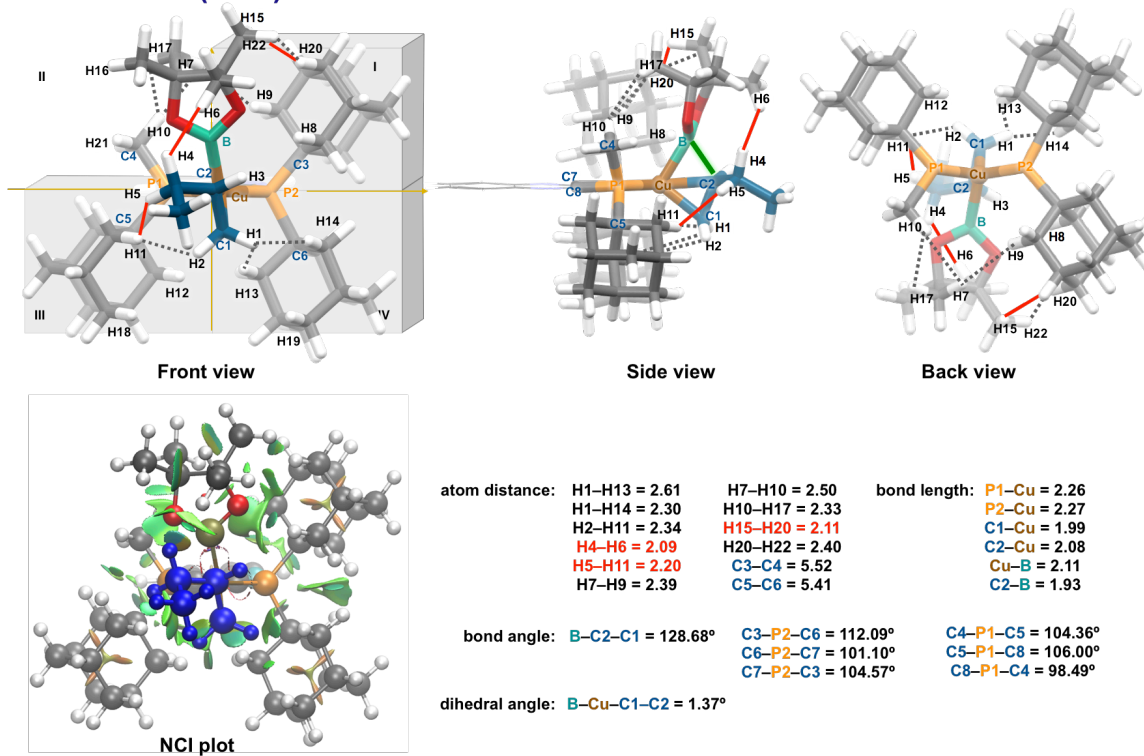


Fig. S4.6 Transition state structures with (*S*)-Quinox-*t*Bu₃. In the back views, the quinoxaline backbone was omitted for clarity (H-H distance < 2.3 Å: red line; 2.3 Å < H-H distance < 2.7 Å: gray dotted line).

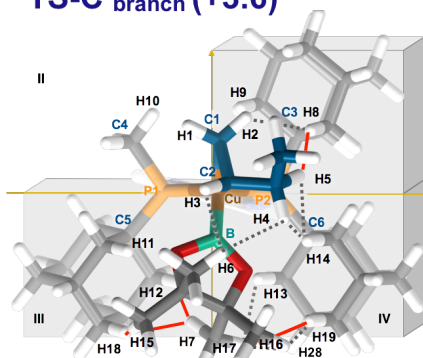
TS-A' branch (+3.0)



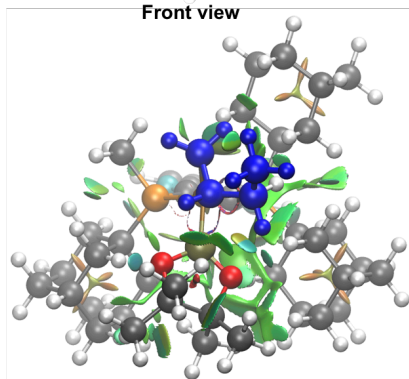
TS-B' branch (+5.1)



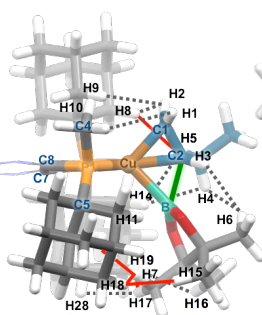
TS-C' branch (+3.6)



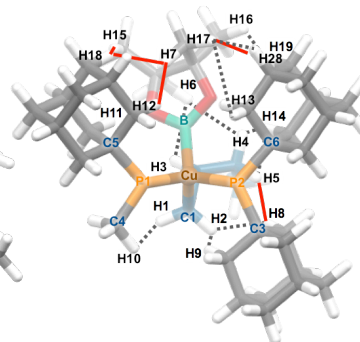
Front view



NCI plot



Side view



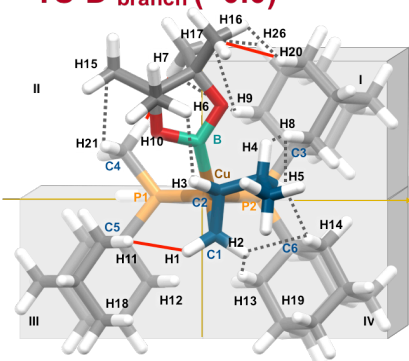
Back view

atom distance: H2-H8 = 2.34 H7-H18 = 2.17 bond length: P1-Cu = 2.24
H2-H9 = 2.36 H13-H17 = 2.53 P2-Cu = 2.30
H3-H6 = 2.48 H15-H18 = 2.02 C1-Cu = 2.00
H4-H6 = 2.61 H16-H19 = 2.31 C2-Cu = 2.07
H4-H14 = 2.51 H17-H19 = 2.15 Cu-B = 2.12
H5-H8 = 2.16 H17-H28 = 2.63 C2-B = 1.88
H5-H14 = 2.39 C3-C4 = 5.13
H7-H12 = 2.13 C5-C6 = 5.72

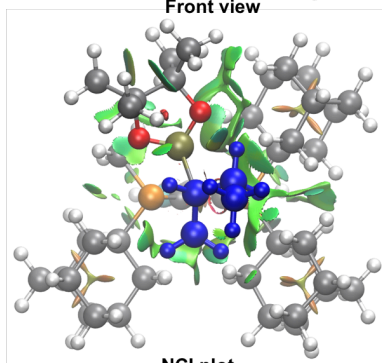
bond angle: B-C2-C1 = 127.51° C3-P2-C6 = 113.50° C4-P1-C5 = 104.53°
C6-P2-C7 = 104.97° C5-P1-C8 = 101.32°
C7-P2-C3 = 98.99° C8-P1-C4 = 101.18°

dihedral angle: B-Cu-C1-C2 = 15.39°

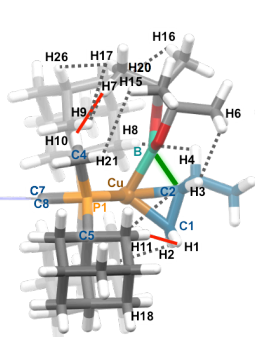
TS-D' branch (+0.0)



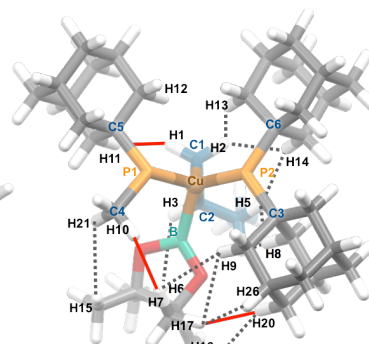
Front view



NCI plot



Side view



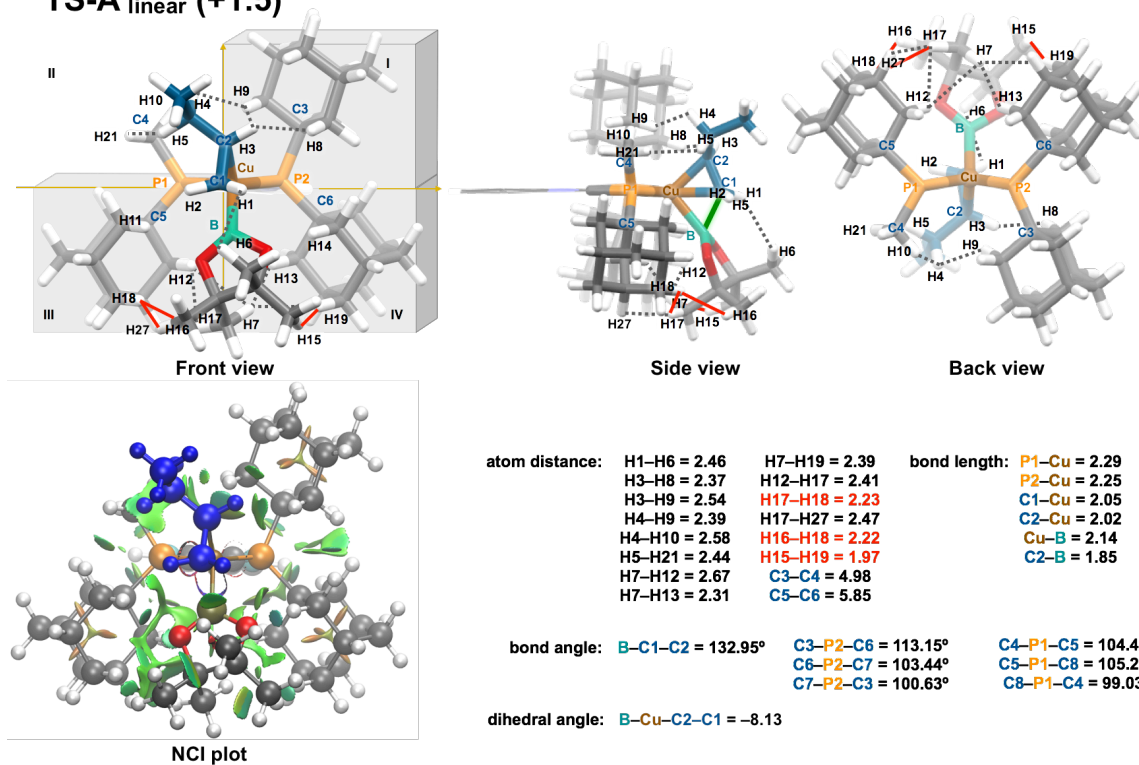
Back view

atom distance: H1-H11 = 2.27 H7-H9 = 2.53 bond length: P1-Cu = 2.23
H2-H13 = 2.40 H9-H17 = 2.52 P2-Cu = 2.28
H2-H14 = 2.52 H15-H21 = 2.68 C1-Cu = 2.01
H3-H6 = 2.48 H16-H20 = 2.52 C2-Cu = 2.05
H4-H8 = 2.43 H17-H20 = 2.19 Cu-B = 2.07
H5-H8 = 2.41 H17-H26 = 2.50 C2-B = 1.98
H5-H14 = 2.36 C3-C4 = 5.44
H7-H10 = 2.18 C5-C6 = 5.46

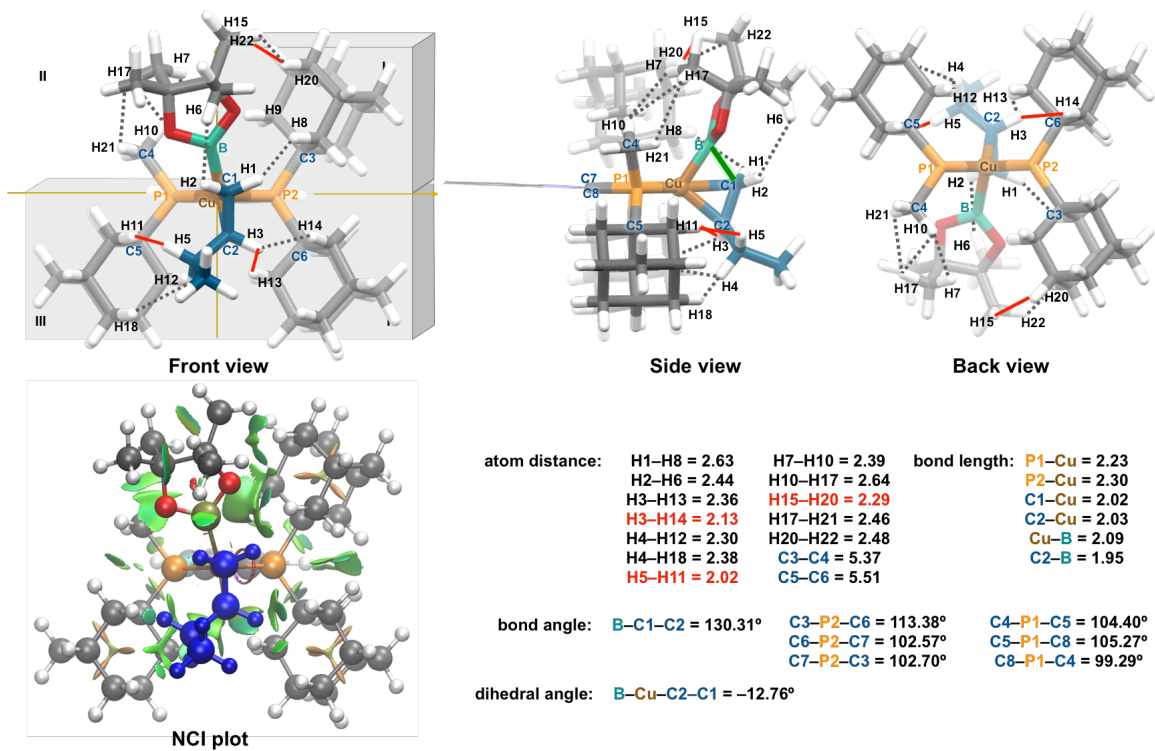
bond angle: B-C2-C1 = 125.50° C3-P2-C6 = 112.73° C4-P1-C5 = 104.68°
C6-P2-C7 = 102.48° C5-P1-C8 = 105.71°
C7-P2-C3 = 103.08° C8-P1-C4 = 99.69°

dihedral angle: B-Cu-C1-C2 = -17.36°

TS-A' linear (+1.5)



TS-B' linear (+2.2)



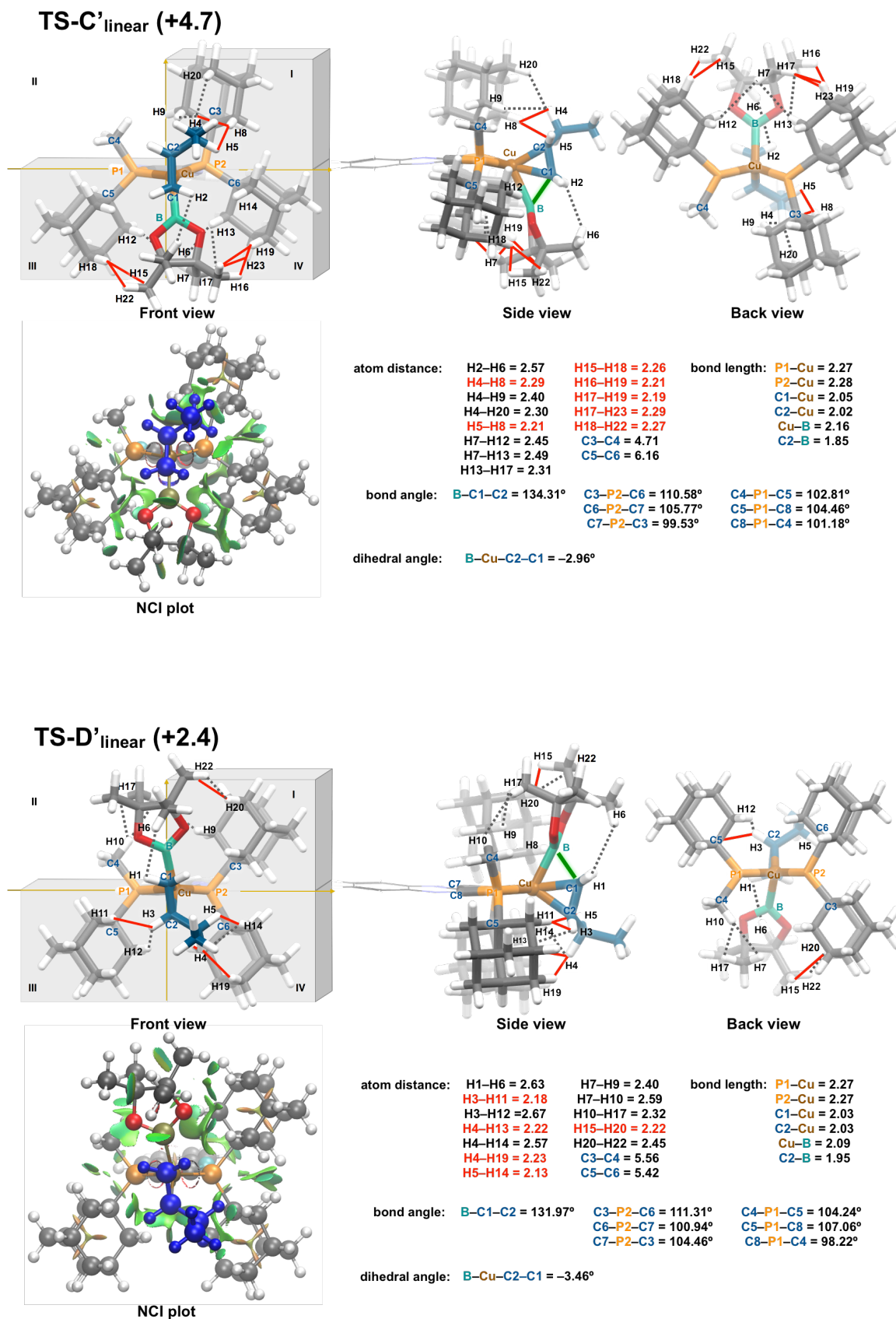


Fig. S4.7 Transition state structures with (*S*)-Quinox-Ad₃. In the back views, the quinoxaline backbone was omitted for clarity (H-H distance < 2.3 Å: red line; 2.3 Å < H-H distance < 2.7 Å: gray dotted line).

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List of Publications

Chapter 1

Copper(I)-Catalyzed carbon–halogen bond-selective boryl substitution of alkyl halides bearing terminal alkene moieties

Iwamoto, H.; Kubota, K.; Yamamoto, E.; Ito, H.
Chem. Commun. **2015**, 51, 9655–9658.

Chapter 2

Copper(I)-Catalyzed Stereo- and Chemoselective Borylative Radical Cyclization of Alkyl Halides Bearing an Alkene Moiety

Iwamoto, H.; Akiyama, S.; Hayama, K.; Ito, H.
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Copper(I)-Catalyzed Regio- and Stereoselective Intramolecular Alkylboration of Propargyl Ethers and Amines

Iwamoto, H.; Ozawa, Y.; Kubota, K.; Ito, H.
J. Org. Chem. **2017**, 82, 10563–10573.

Chapter 3

Highly Selective Markovnikov Hydroboration of Alkyl-Substituted Terminal Alkenes with a Phosphine–Copper(I) Catalyst

Iwamoto, H.; Kubota, K.; Ito, H.
Chem. Commun. **2016**, 52, 5916–5919.

Chapter 4

Computational design of high-performance ligand for enantioselective Markovnikov hydroboration of aliphatic terminal alkenes

Iwamoto, H.; Imamoto, T.; Ito, H.
Nat. Commun. **2018**, 9, Article Number: 2290.

Other of Publications

1. Silicon-Tethered Strategy for Copper(I)-Catalyzed Stereo- and Regioselective Alkylboration of Alkynes

Kubota, K.; Iwamoto, H.; Yamamoto, E.; Ito, H.

Org. Lett. **2015**, *17*, 620.

2. Enantioselective Borylative Dearomatization of Indoles through Copper(I) Catalysis

Kubota, K.; Hayama, K.; Iwamoto, H.; Ito, H.

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3. Copper(I)-Catalyzed Diastereoselective Dearomative Carboborylation of Indoles

Hayama, K.; Kubota, K.; Iwamoto, H.; Ito, H.

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4. Copper(I)-Catalysed Regio- and Diastereoselective Intramolecular alkylboration of Terminal Allenes via Allylcopper(I) Isomerization

Ozawa, Y.; Iwamoto, H.; Ito, H.

Chem. Commun. **2018**, *54*, 4991–4994.

5. Catalytic asymmetric propargyl- and allylboration of hydrazonoesters: a metal-free approach to sterically encumbered chiral α -amino acid derivatives

Jonker, S. J. T.; Colin, D.; Schulz, G.; Iwamoto, H.; Eriksson, L.; Szabó, K. J.

Chem. Commun. **2018**, *54*, 12852–12855.

6. Formal nucleophilic borylation and borylative cyclization of organic halides

Kubota, K.; Iwamoto, H.; Ito, H.

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