Synthesis of Functionalized Organoboron Compounds through Copper(I) Catalysis

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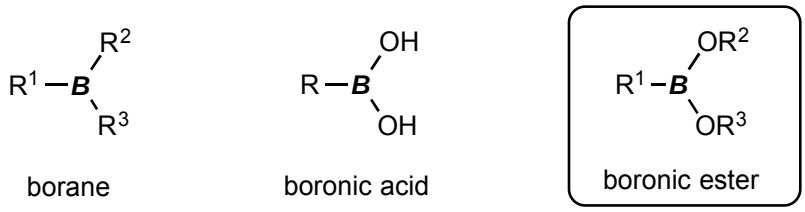
Table of Contents

General Introduction

Structurally, organoborons are trivalent boron-containing organic molecules with six valence electrons and a consequent deficiency of two electrons at the boron center, which possess a vacant p orbital and show a Lewis acidic character. Therefore, triakylboranes or trihaloboranes are generally highly reactive and air-sensitive reagents. Boronate esters, the main precursors for boronic acid derivatives, are most often used in organic chemistry as well as other broad scientific fields, which possess one organic group and two oxygenated substituents to lower the Lewis acidity of a boron atom through the hyperconjugation between a lone pair of oxygen and a vacant p orbital of boron center (Figure 1). Their unique properties as mild organic Lewis acids and their mitigated reactivity, coupled with their stability and ease of handling, makes boronic acid derivatives a very attractive class of nucleophilic organometallic reagents. Furthermore, considering their low toxicity, boronic acid derivatives can be regarded as the environmentally friendly "green" organic molecules.

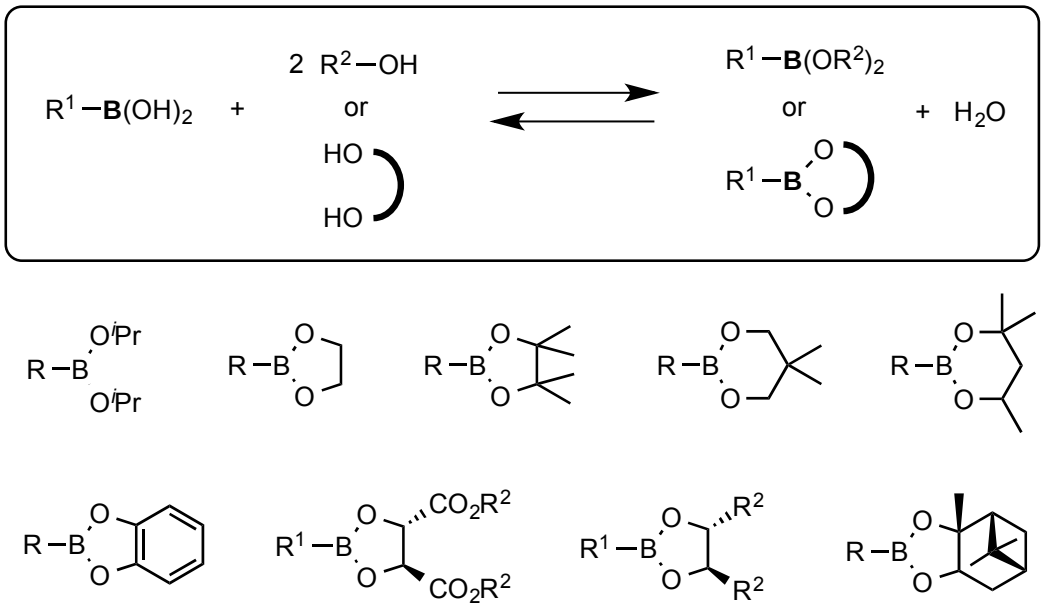
Figure 1. Oxygenated Organoboron Compounds



Boronate esters are readily prepared by simple dehydration of boronic acids with alcohols. By losing the hydrogen bond in the hydroxyl groups, boronate esters are less polar and easier to handle and purification than boronic acids. They also serve as protecting groups to control and ture their reactivity of boron-carbon bonds. Thus, there are many types of boronic esters including chiral auxiliaries have been synthesized for organic synthetic

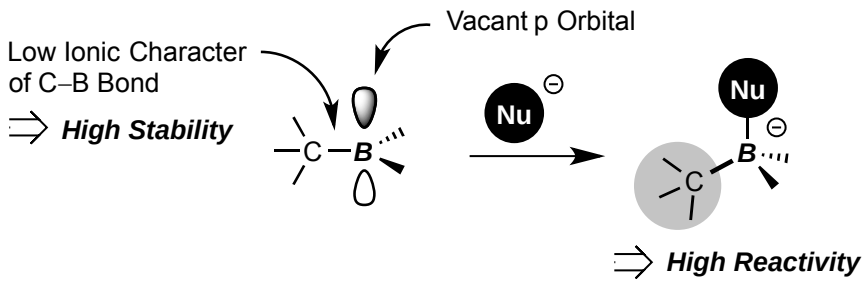
applications (Figure 2).

Figure 2. Common Boronic Esters in Organic Synthesis



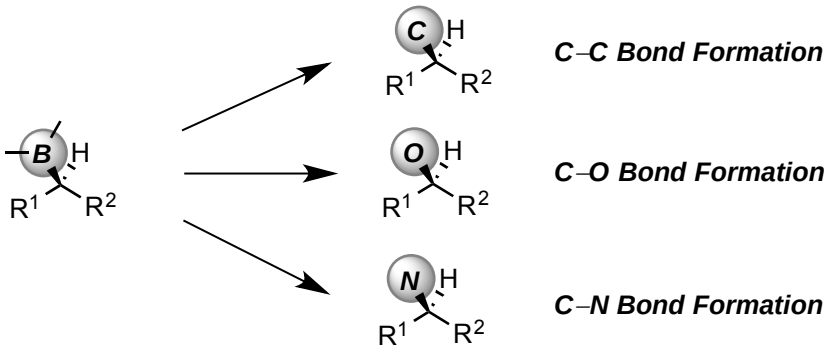
As for the reactivity of organoboron compounds, they have quite milder nucleophilicity compared to other organometallics such as organolithium, organomagnesium, and organozinc reagents because the ionic character of a carbon-boron bond is relatively lower than those of the reagents. Thus, organoboronate esters have significant advantages because they can be easily purified prior to utilization and have reasonable shelf stability under normal atmospheric conditions. When an appropriate activation procedure is employed, organoboron compounds are also sufficiently reactive for the use in synthetic chemistry, especially as reagents for transition-metal-catalyzed cross-coupling reactions with various electrophiles (Figure 1).[2] The attribution of the 2010 Chemistry Nobel Prize for palladium-catalyzed cross-coupling reactions, shared by Professor Akira Suzuki, cements the importance of organoborons in C–C bond forming processes (Figure 3).

Figure 3. Fundamental Property of Organoboron Reagents



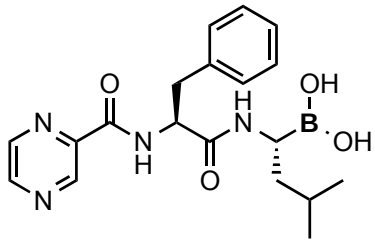
Moreover, enantioenriched chiral alkylboronate esters have been recognized as important chiral building blocks in organic synthesis because they undergo stereospecific transformations of the stereogenic C–B bonds to form C–O, C–N, or C–C bonds (Figure 4).[3]

Figure 4. Stereospecific Transformations of Enantioenriched Alkylboronate Esters

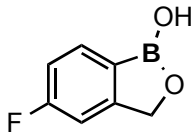


In addition to their great synthetic utility, organoboron compounds have been used in other scientific fields, such as medicinal chemistry.[1] For examples, chiral boronic acid Bortezomib has been widely used as malignant lymphoma therapeutics. Furthermore, Tavaborole has been known to show an antimycotic property (Figure 5).

Figure 5. Boron-Containing Pharmaceutical Drugs



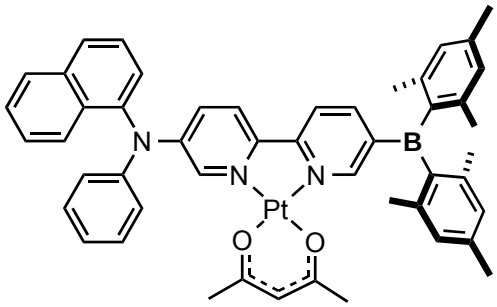
Bortezomib
Malignant lymphoma therapeutics



Tavaborole
Antimycotic therapeutics

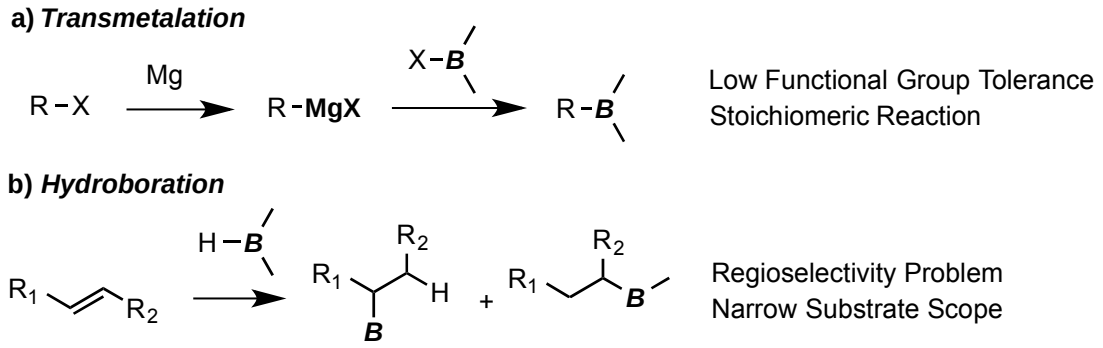
Recently, a triarylboryl group has been utilized in material chemistry because the optical properties can be controlled by π-accepter character of a boryl group. For examples, the platinum complex bearing the boron-contaning ligand has been reported to be a potential organic electroluminescence element (Figure 6).[4]

Figure 6. Selected Example for Boron-Containing Organic EL



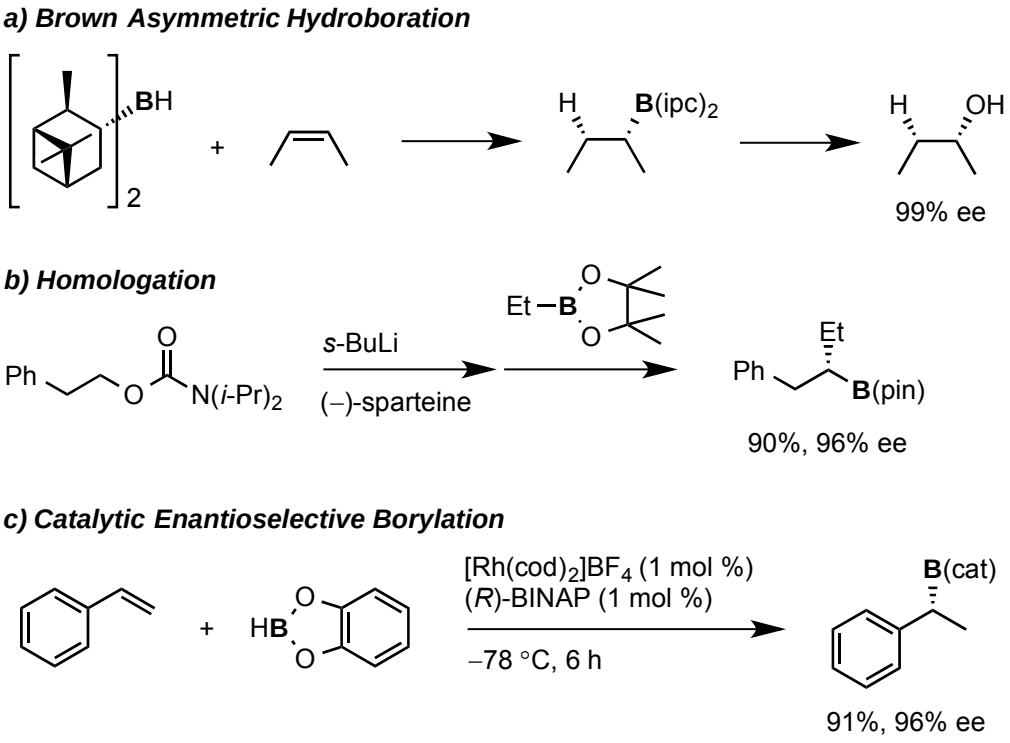
Organoboronates are most often prepared through the transmetalation between organomagnesium or organolithium reagents and electrophilic boron precursors (Sheme 1a). However, these methods suffer from poor functional group tolerance. Hydroboration of alkenes is one of the most efficient and straightforward protocols to access alkylboronic esters. This method has also significant limitation, such as regioselectivity issue in the case of hydroboration of internal alkenes (Scheme 1b).

Scheme 1. Conventional Synthetic Routes to Organoboronate Esters



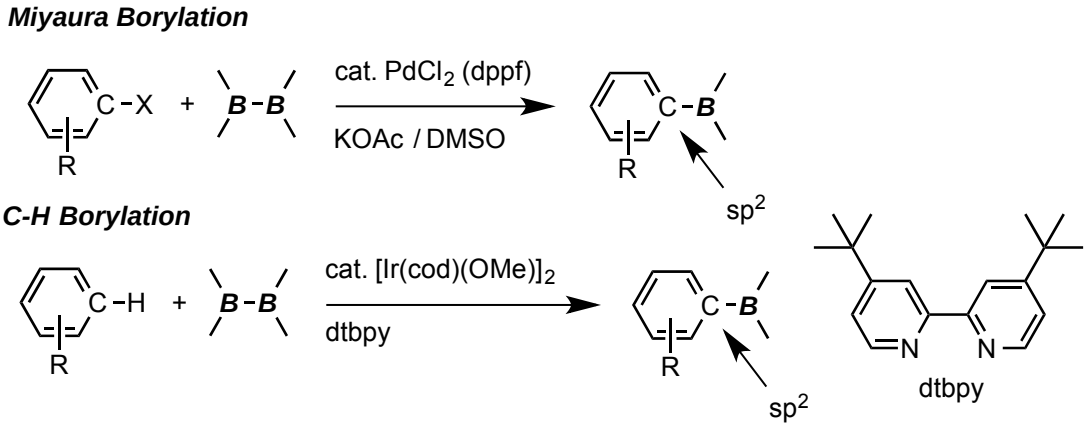
Conventional synthetic approaches toward optically active organoboronates are shown in Scheme 2. Brown's asymmetric hydroboration using (+)-diisopinocamphenylborane (Ipc_2BH) is one of the most practical and scalable protocols to access chiral boron compounds with high enantiometric purity (Scheme 2a). Homologation methodology using organo lithium compound and (–)-sparteine with boron electrophile also produces the chiral boronate with high enantiometric excess (Scheme 2b). However, these reactions require stoichiometric amount of chiral auxiliary. Considering this drawback, catalytic asymmetric borylation reaction is a highly desirable method for the construction of a stereogenic C–B bond. In 1989, Prof. Hayashi and Prof. Ito reported the first transition-metal-catalyzed enantioselective hydroboration of styrenes to afford the corresponding chiral boronate with an excellent enantioselectivity (Scheme 2c).[5] Despite the great utility of this catalytic approach, the development of the method has been less explored for other prochiral alkenes.

Scheme 2. Selected Studies on the Synthesis of Chiral Organoboron Compounds



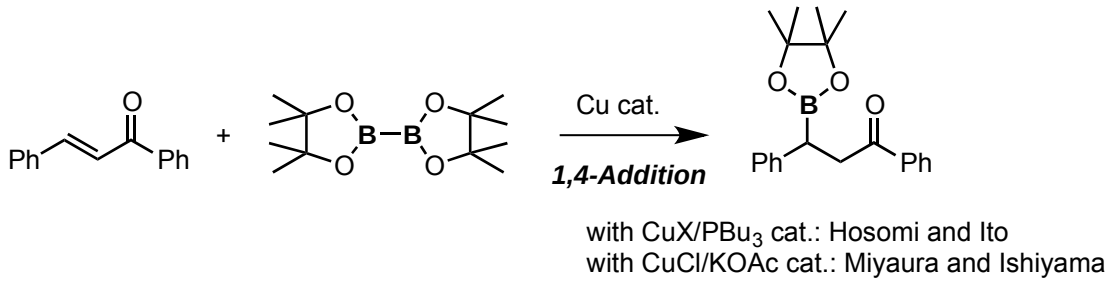
Transition-metal-catalyzed borylation reactions have emerged as an alternative and powerful tool for the production of various organoboronate esters, which have been the subject of extensive research during the past several years.[1b] Significant efforts have been focused on the investigation of catalytic borylation of C(sp^2)–X and C(sp^2)–H bonds of alkenes or arenes for the synthesis of alkenyl- or arylboronates (Scheme 3).[6] However, transition-metal-catalyzed highly useful and practical borylations for alkylboron synthesis are not well explored.

Scheme 3. Examples of Transition-Metal-Catalyzed Borylation for the Construction of C(sp^2)−B Bond: Miyaura-Ishiyama-Hartwig Borylation



In 2000, the borylation reactions of α,β-carbonyl compounds using copper(I)/diboron catalytic system, which provided the corresponding 1,4-boryl addition products, were developed by Hosomi and Ito, and Miyaura and Ishiyama groups independently (Scheme 4).[7,8] These reactions are the first examples of activation of a B–B bond with a copper(I) salt to generate nucleophilic borylcopper(I) species.

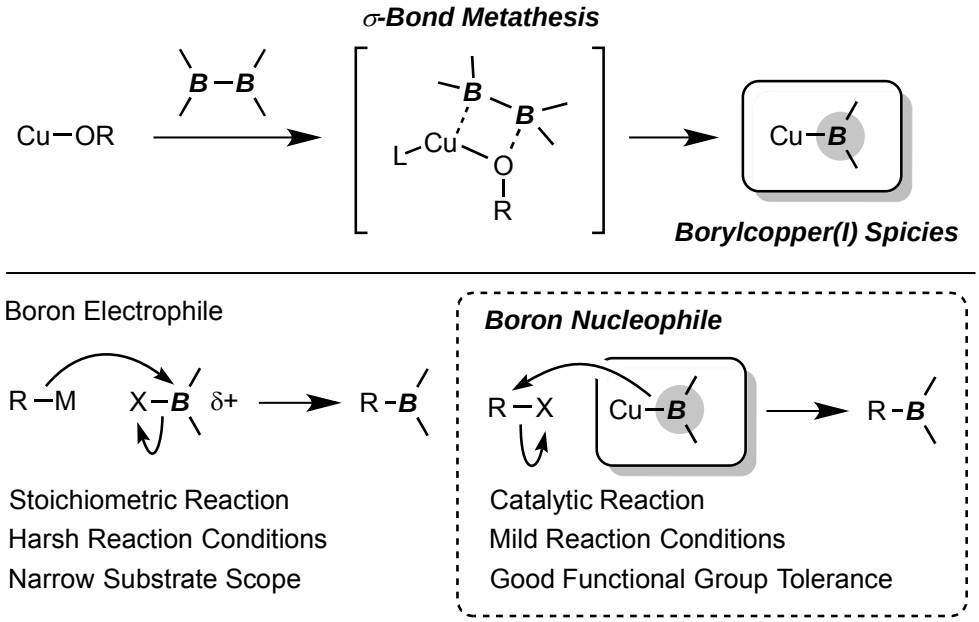
Scheme 4. Copper(I)-Catalyzed Borylation of Conjugated Enone



These reactions have various advantages over classical procedures for the synthesis of alkylboronate esters (Scheme 5). In the presence of a copper(I) salt and diboron, σ-bond metathesis occurs to generate nucleophilic borylcopper(I) intermediates. Unlike conventional stoichiometric "boron electrophilic reaction" methods, this reaction does not require stoichiometric amounts of highly reactive carbon nucleophiles such as Grignard reagents or organolithium compounds. Moreover, this reaction can be applied to

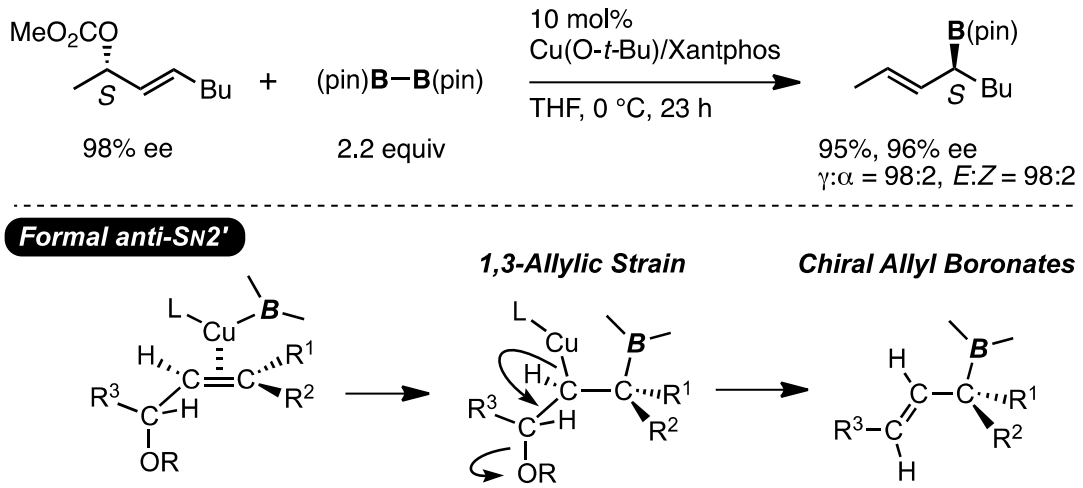
catalytic enantioselective borylation reaction by introducing appropriate chiral ligands.

Scheme 5. Generation and Reactivity of Borylcopper(I) Intermediate



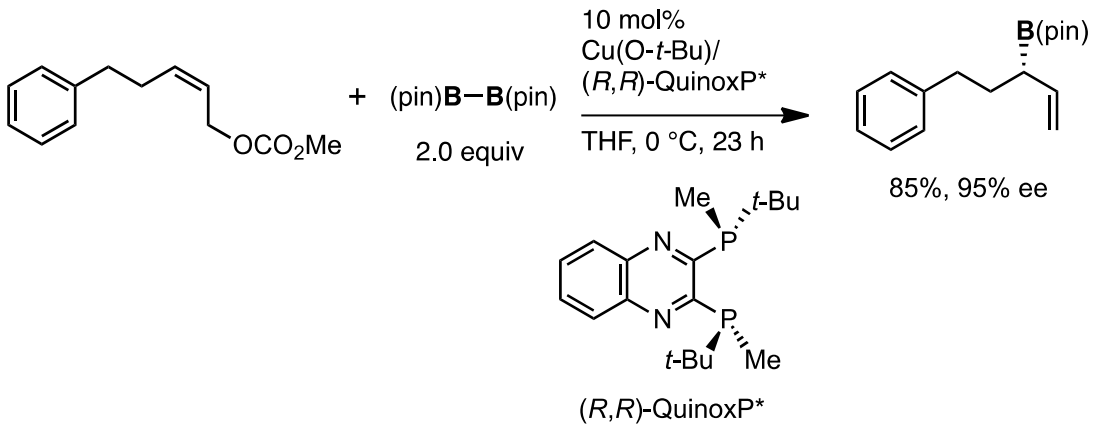
Since then, Ito, Sawamura, and co-workers reported several asymmetric or non-asymmetric borylations using copper(I)/diboron catalytic systems.[9,10] In the presence of a copper(I) catalyst and diboron, allylic carbonates were converted into the corresponding allyboronate esters with almost complete chirality-transfer and γ-selectivity (Scheme 6).[9a] The observed stereochemical outcome can be explained by the S_N2'-attack of borylcopper(I) spicies to an allylic carbonates in a comformation that avoids an allylic 1,3-strain.

Scheme 6. Stereospecific Borylation of Allylic Carbonates



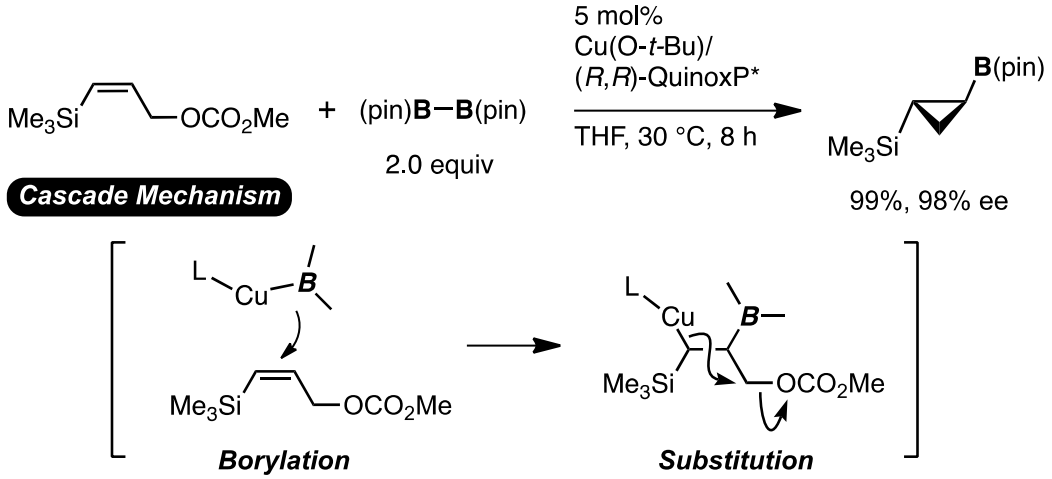
Enantioselective borylation reactions were also performed with an chiral bisphosphine ligand QuinoxP*.[9b] The reaction of prochiral (*Z*)-allylic carbonate with diboron in the presence of copper(I)/(*R,R*)-QuinoxP* catalyst afforded the corresponding optically active allylboronates with excellent enantioselectivity (Scheme 7).

Scheme 7. Copper(I)-Catalyzed Enantioselective Boryl Substitution of Allylic Carbonates



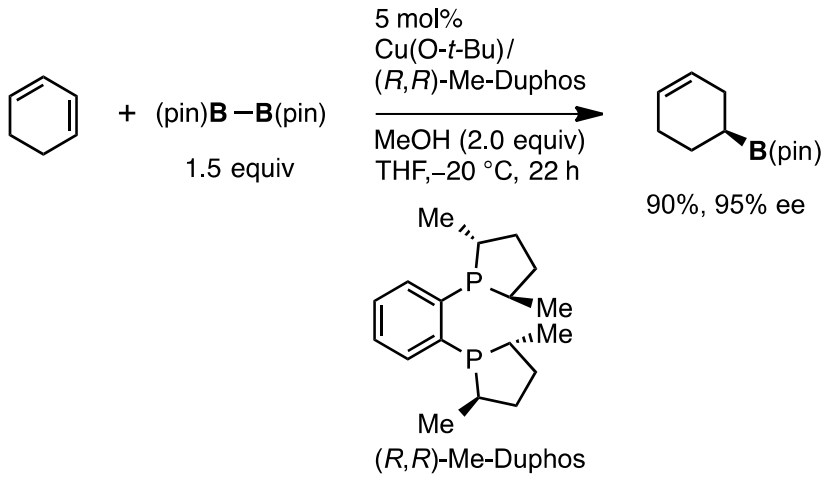
In the reaction of 3-silylated allylic carbonates with copper(I)/(*R,R*)-QuinoxP* catalyst, the optically active boron-silicon bifunctional cyclopropane derivatives were obtained exclusively instead of allylboron compounds (Scheme 8).[9c]

Scheme 8. Asymmetric Borylative Cyclization of Silyl Substituted Alkenes



Regio- and enantioselective protoborylation of conjugated 1,3-diene using chiral copper(I) catalysis has also been devolped.[9e] The reaction of cyclohexadiene in the presence of Cu(O-*t*-Bu)/(*R,R*)-Me-Duphos and MeOH as a proton source proceeded to give the chiral homoallylic boronate with excellent regio- and enantioselectivity (Scheme 9).

Scheme 9. Regio- and Enantioselective Borylation of Conjugated 1,3-Diene

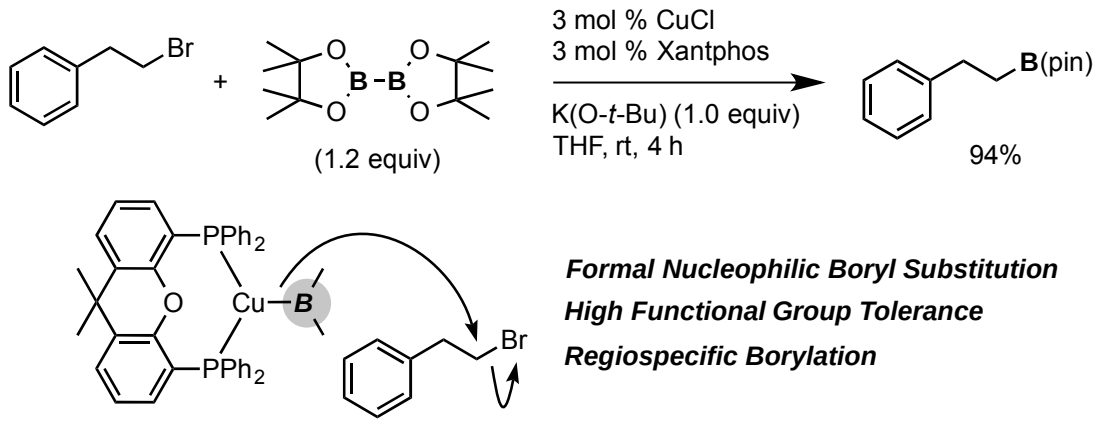


The author also focuses on the reactivity of nucleophilic borylcopper(I) complex and pursues the development of novel catalytic borylation reactions based on above results. This thesis describes several new types of reactions

for alkylboron synthesis: direact boryl substitution of unactivated alkyl halides (Chapter 1), borylative *exo*-cyclization of alkenyl halides containing unactivated C–C double bond (Chapter 2), regio- and enantioselective protoborylation of alkenylsilanes by using copper(I)/BenzP* complex catalysis (Chapter 3), enantioselective nucleophilic borylation of aldehydes by using copper(I)/DTBM-SEGPHOS complex catalysis (Chapter 4) and enantioselective synthesis of chiral borylpiperidines through regio- and enantioselective protoborylation of 1,2-dihydropyridines by using copper(I)/QuinoxP* or SEGPHOS complex catalysis (Chapter 5).

Chapter 1 describes the copper(I)/Xantphos-catalyzed boryl substitution of unactivated alkyl halides (Scheme 9).[11,12] This reaction is the first practical procedure for direct boryl substitution of unactivated alkyl halides. This reaction offers a direct umpolung pathway for the conventional carbon nucleophile methods, and has high functional group compatibility and interesting stereochemical-controlling properties. This novel protocol will be a powerful synthetic method for a broad range of alkylboronates, including those that could not be synthesized by previous methods.

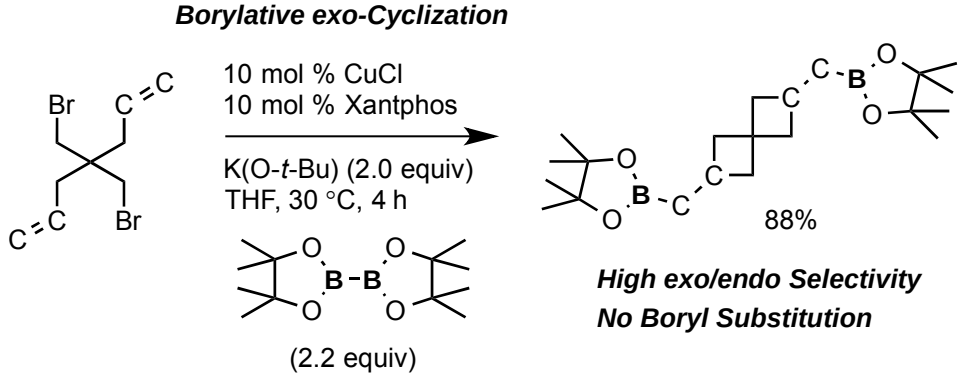
Scheme 9. Copper(I)-Catalyzed Boryl Substitution of Unactivated Alkyl Halides



Chapter 2 describes the copper(I)/Xantphos-catalyzed borylative *exo*-cyalization of alkenyl halides (Scheme 10).[13] This reaction based on the

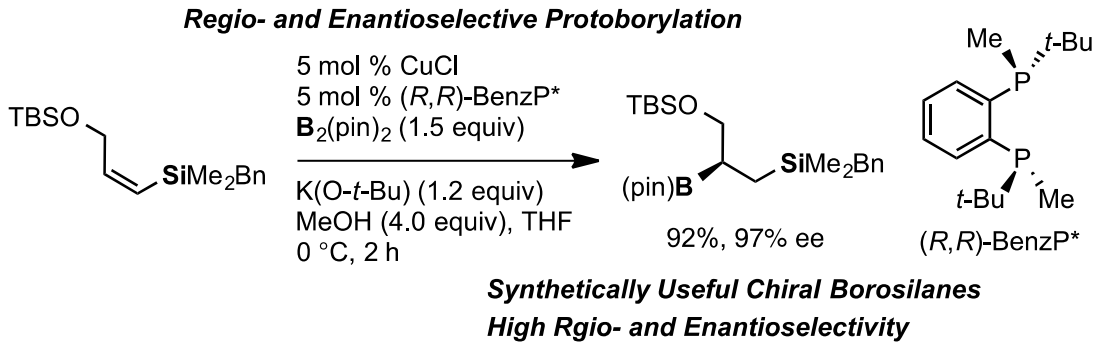
unprecedented regioselective borylation reaction of unactivated alkenes using copper(I) catalyst. The reaction includes the regioselective addition of a borylcopper(I) intermediate to unactivated terminal alkenes, followed by the intramolecular substitution of the resulting alkylcopper(I) moiety for the halide leaving groups. To understand the reaction mechanism and the reactivity of borylcopper(I) complexes toward alkenes, density functional thory (DFT) calculations have also been conducted. This reaction provides a new method for the synthesis of alkylboronates containing strained cycloalkyl structures from simple starting materials.

Scheme 10. Copper(I)-Catalyzed Borylative *exo*-Cyclization of Alkenyl Halides



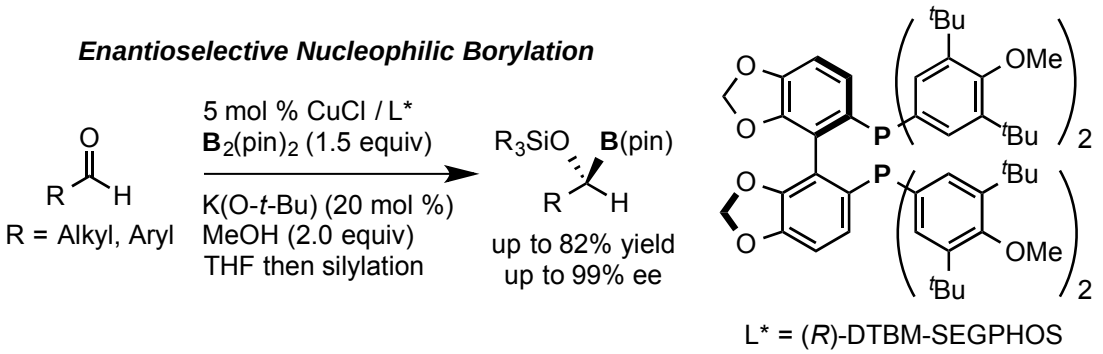
Chapter 3 describes the highly regio- and enantioselective protoborylation of alkenylsilanes catalyzed by an electron-donating chiral copper(I)/BenzP* complex (Scheme 11).[14,15] This is the first example of asymmetric β-borylation of (*Z*)-alkenylsilane substrates to provide enantiomerically enriched vicinal borosilanes, which can be derivatized through stepwise, stereospecific transformations of the boron and silicon functionalities. The reaction of various alkenylsilanes bearing functional groups, such as silyl ether, cyano and ester proceeded in high yields with excellent enantioselectivities. The synthetic utility of this protocol was demonstrated by the stepwise and stereoselective transformation of the products into enantioenriched 1,2-diol and 1,2-aminoalcohol derivatives.

Scheme 11. Regio- and Enantioselective Borylation of (Z)-Alkenylsilanes



Chapter 4 describes the the first example for enantioselective borylation of a C=O double bond (Scheme 12).[16] A series of aldehydes reacted with a diboron compound in the presence of a copper(I)/DTBM-SEGPHOS complex catalyst using MeOH as a proton source to give the corresponding opticaly active α-alkoxyorganoboronate esters with excellent enantioselectivies.

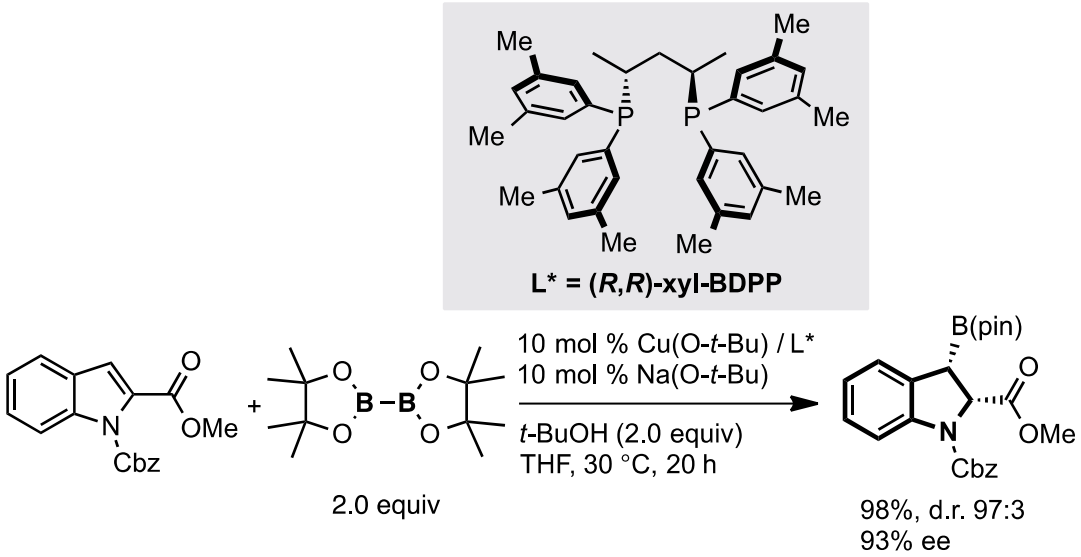
Scheme 12. Enantioselective Nucleophilic Borylation of Aldehydes



Chapter 5 describes density functional theory calculations were performed to validate the proposed reaction mechanism for the enantioselective nucleophilic borylation of a polarized C=O double bond in the presence of diphosphine/borylcopper(I) complexes.[17] Consequently, the author successfully elucidated the origin for the regioselectivity and the mechanism for the enantioselectivity of the reaction. The author also obtained theoretical explanations for the fact that the presence of a proton

source gave a higher reactivity and a better enantioselectivity in the borylation reaction of aldehydes with a copper(I)/(*R*)-DTBM-SEGPHOS complex catalyst.

Chapter 6 describes the first enantioselective borylative dearomatization of indoles by copper(I) catalysis (Scheme 13).[18] This reaction involves the unprecedented regio- and enantioselective addition of active borylcopper(I) species to indole-2-carboxylates, followed by the diastereoselective protonation of the resulting copper(I) enolate to give the corresponding chiral indolines bearing consecutive centers.

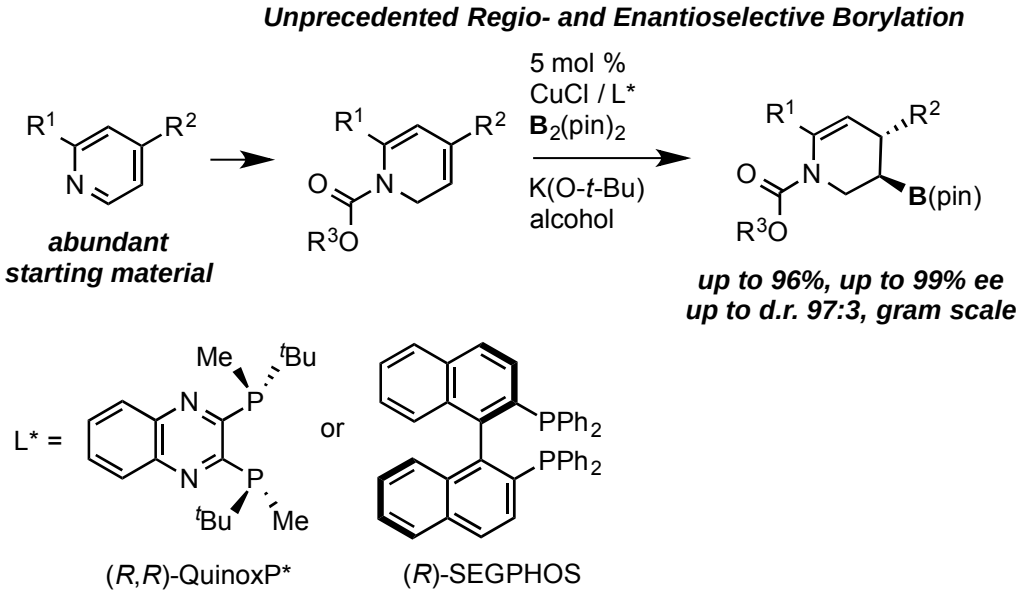


Scheme 13. Enantioselective Borylative Dearomatization of Indoles

Chapter 7 describes a novel approach to chiral 3-borylpiperidines via the copper(I)-catalyzed regio- and enantioselective protoborylation of 1,2-dihydropyridines derived from dearomative reduction of pyridine derivatives (Scheme 14).[19] This reaction involved the unprecedented regio- and enantioselective borylcupration of nitrogen containing cyclic conjugated diene and subsequent protonation of resulting allylcopper(I) intermediate. This dearomatization/enantioselective borylation sequence of readily available aromatic compound pyridines provided a simple, mild and rapid

route to a variety of chiral piperidines, which are very important components in various bioactive molecules and pharmaceutical drugs.

Scheme 14. Dearomatization/Enantioselective Borylation Stepwise Strategy for Chiral Piperidine Synthesis



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Chapter 1.

Copper(I)-Catalyzed Direct Boryl Substitution of Unactivated Alkyl Halides

Abstract

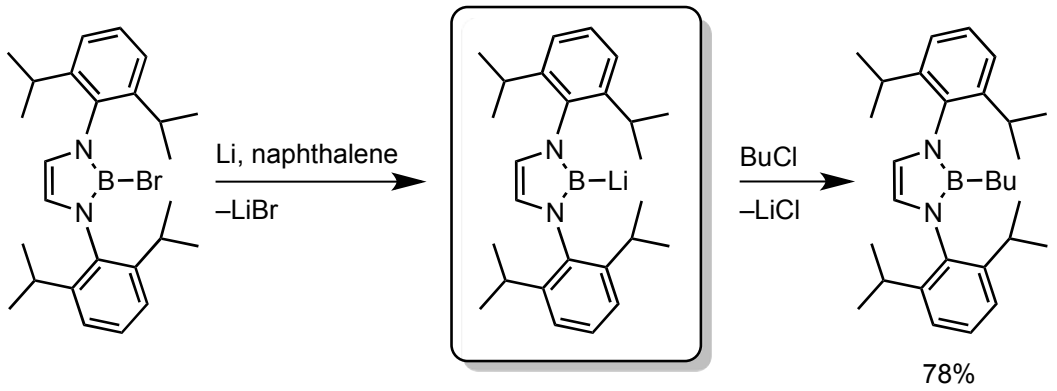
Borylation of Alkyl Halides with diboron proceeded in the presence of a copper(I)/Xantphos catalyst and a stoichiometric amount of K(O-*t*-Bu) base. The boryl substitution proceeded with normal and secondary alkyl chlorides, bromides, and iodides, but alkyl sulfonates did not react. Menthyl halides afforded the corresponding borylation product with excellent diastereoselectivity, whereas (*R*)-2-bromo-5-phenylpentane gave a racemic product. Reaction with cyclopropylmethyl bromide resulted in ring-opening products, suggesting the reaction involves a radical pathway.

Introduction

Organoboron compounds are indispensable synthetic reagents in organic synthesis; much effort has therefore been devoted to the development of efficient synthesis of organoborons.[1–8] Although many excellent procedures have been reported, boryl substitution of alkyl halides is still challenging. In conventional procedures for organoboron synthesis, alkyl halides are the starting materials for the organometallic nucleophiles, such as Grignard or organolithium reagents, which react with boron electrophiles. This procedure has significant limitations, especially in the presence of the functional groups often found in structurally complex molecules. Direct borylation of alkyl halides should be quite promising in this respect.

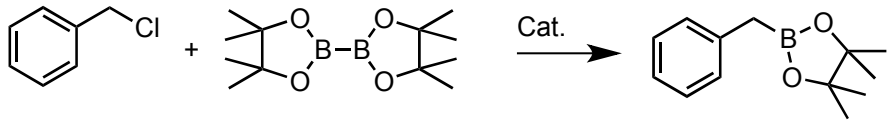
Yamashita and Nozaki recently created a boryllithium species by introducing significant steric hindrance around the boryl atom (Scheme 1).[3] Although this species has enough nucleophilicity to react with unactivated alkyl halides, this elaborate reaction is not suitable for many common organic syntheses.

Scheme 1. Synthesis of Boryllithium: Reactivity as a Boryl Anion



Miyaura and Marder also reported boryl substitutions of activated alkyl halides such as allyl and benzyl chlorides; however, there are no general borylation procedures for unactivated alkyl halides (Scheme 2).[1,5a,b,7]

Scheme 2. Transion-Metal-Catalyzed Boryl Substitution of Activated Alkyl Halides



with Pd cat./KOAc: Miyaura and Ishiyama (2002), 85%
with Cu cat./K(O-*t*-Bu): T. B. Marder (2009), 61%

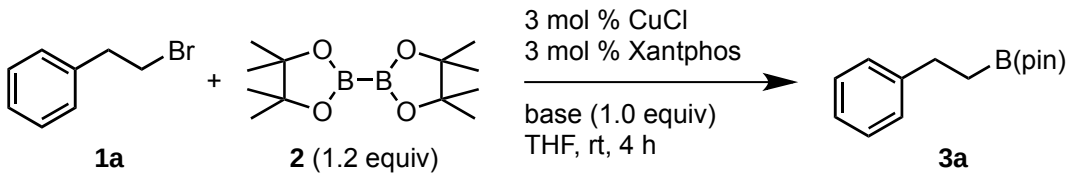
The author reports here the first practical method for boryl substitution that is applicable to a broad range of alkyl halides with various functional groups, offering a direct umpolung pathway for conventional reactions based on carbon nucleophiles generated from alkyl halides.

Results and Discussion

Recent advances in copper(I)-catalyzed reactions with diboron derivatives[4–8] enable introduction of boryl groups into various organic electrophiles such as α β-unsaturated carbonyl compounds,[4a,5] allylic esters,[4b,c,f,g,6] aryl halides,[7] allyl and benzyl halides,[5a,b,7] and other substrates.[4d,h,i,j,k,8] The author did not anticipate that unactivated alkyl halides could afford boron compounds by copper(I)-catalyzed borylation because previous studies found that alkyl sulfonates, which are good substrates for nucleophilic substitutions, were resistant to direct boryl substitution.[4h,9]

In the course of the study, the author accidentally found that an alkyl halide reacted with a diboron compound to produce the corresponding alkylboronate in the presence of a copper(I) catalyst, which is very similar to those our group previously reported.[4b,h] As shown in Table 1, entry 1, the reaction between 2-phenylethyl bromide **1a** and bis(pinacolato)diboron **2** proceeded smoothly in the presence of a CuCl/Xantphos catalyst (3 mol%) and a stoichiometric amount of K(O-*t*-Bu) base (1.0 equiv). The reaction was complete within 4 h at room temperature and produced the corresponding boronate **3a** in high yield (94%) without any side-product detection (Table 1, entry 1). This catalysis requires a K(O-*t*-Bu) base, a copper(I) salt, and a ligand, for the reaction to proceed (entries 2–4). Xantphos provided the best result among the phosphine ligands tested; the reactions with PPh_3, dppe dppp, dppb, and dppf were slow and incomplete, resulting in moderate yields of the product, even after long reaction times (entries 5–9). Use of a copper(I)/NHC (NHC: *N*-heterocyclic carbene) catalyst gave a much slower initial reaction rate (entry 10). When a catalytic or stoichiometric amount of Cu(O-*t*-Bu) was used instead of a CuCl/K(O-*t*-Bu) combination, only trace amounts of the product were observed (entries 11 and 12). CuI, CuCN, and $Cu(OAc)_2$ can be used, but longer reaction times were required (entries 13–15).[10] A lower catalyst loading of 1 mol % also gave an excellent result (96%, 4 h, entry 16).

Table 1. Studies of Reaction Conditions for Copper(I)-Catalyzed Boryl Substitution of Alkyl Halides 1a[a]



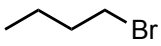
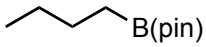
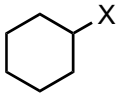
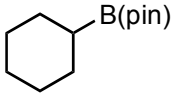
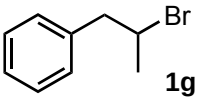
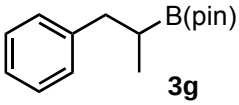
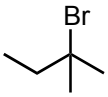
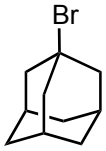
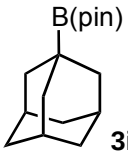
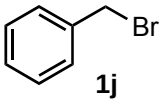
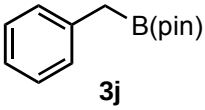
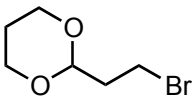
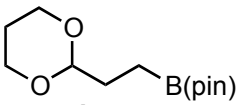
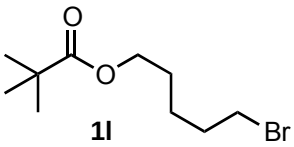
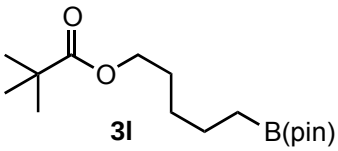
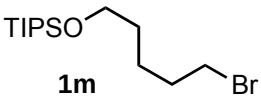
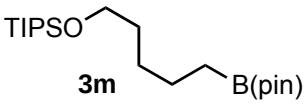
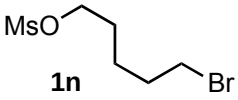
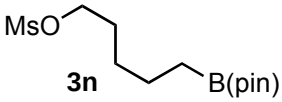
entry	CuX	ligand	base	yield (%)[b]
1	CuCl	Xantphos	K(O-*t*-Bu)	94
2	CuCl	Xantphos	none	0
3	none	Xantphos	K(O-*t*-Bu)	0
4	CuCl	none	K(O-*t*-Bu)	2
5	CuCl	PPh_3	K(O-*t*-Bu)	69
6	CuCl	dppe	K(O-*t*-Bu)	73
7	CuCl	dppp	K(O-*t*-Bu)	79
8	CuCl	dppb	K(O-*t*-Bu)	65
9	CuCl	dppf	K(O-*t*-Bu)	74
10	CuClIPr		K(O-*t*-Bu)	13
11	Cu(O-*t*-Bu) / 10 mol %	Xantphos / 10 mol %	none	3
12	Cu(O-*t*-Bu) / 100 mol %	Xantphos / 10 mol %	none	2
13	CuI	Xantphos	K(O-*t*-Bu)	70
14	CuCN	Xantphos	K(O-*t*-Bu)	47
15	$Cu(OAc)_2$	Xantphos	K(O-*t*-Bu)	88
16	CuCl / 1 mol %	Xantphos / 1 mol %	K(O-*t*-Bu)	96

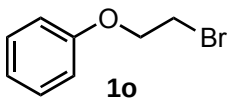
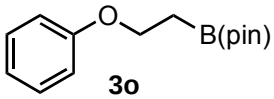
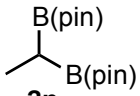
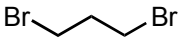
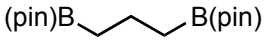
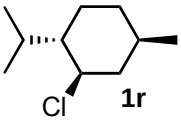
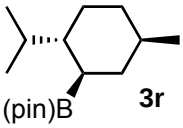
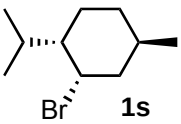
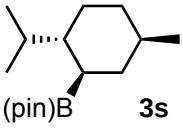
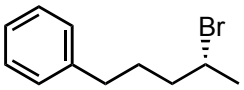
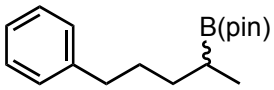
[a]Conditions: **1a** (0.5 mmol), CuX (0.015 mmol), ligand (0.015 mmol), K(O-*t*-Bu)/THF (1.0 M, 0.5 mL), **2** (0.6 mmol). [b]Yield was determined by GC analysis of crude mixture with an internal standard. [c]CuClIPr: chloro [1,3-bis(2,6-diisopropylphenyl)-imidazole-2-ylidene]copper(I).

This reaction was then evaluated for various alkyl halides, as summarized in Table 2. Unactivated primary and secondary alkyl halides were converted to the corresponding alkylboronates in good yield (entries 1–6). The effects of the leaving group were investigated with cyclohexyl substrates (entries 2–5). Reaction of cyclohexyl bromide **1d** gave the borylation product **3c** in the highest yield, with a short reaction time (91%, 5 h), among cyclohexyl chloride **1c** and bromide **1e** (72%, 18 h; 79%, 48 h, respectively). In contrast, cyclohexyl mesylate **1f** did not react (entry 5). This inreactivity is consistent

with our previous studies of related mesylate substrates.[4h] The reactions of tertiary alkyl halides **1h** and **1i** were quite sluggish (entries 7 and 8). An activated alkyl halide, benzyl bromide **1j**, also gave the desired product in moderate yield, accompanied by a small amount of a homo-coupling side-product (1,2-diphenylethane, 9%).[7] This reaction proceeded in the presence of various functional groups; acetal (**1k**), ester (**1l**), silyl ether (**1m**), and sulfonate (**1n)** were compatible under these reaction conditions (entries 9–14). Alkylboronates bearing a -alkoxy group were not accessible by Grignard or organolithium methods because the corresponding organometallic compounds with a -alkoxy group could not be easily prepared because they readily undergo -alkoxy elimination. This method enables direct conversion of alkyl halide **1o** to **3o** (entry 14). Reactions of 1,1- and 1,3-dibromo compounds proceeded smoothly to produce the corresponding bis-boryl products (entries 14 and 15). (1*R*,2*R*,4*R*)-Menthyl boronate **3r** was synthesized with excellent diastereoselectivity (>99:1) from both (1*S*,2*R*,5*R*)-menthyl chloride **1r** and (1*S*,2*S*,4*R*)-neomenthyl bromide **1s** (entries 16 and 17, 85% and 81%, respectively). The reaction of the optically active secondary alkyl halide (*R*)-**1t** afforded the racemic product **3t** (entry 19). These results indicate that the stereocenter originating from the chiral C(sp^3)–X bond undergoes rapid interconversion of configuration during the reaction. This may cause epimerization to a thermodynamically stable product (entries 17 and 18) and complete racemization (entry 19). This is quite different from the results of our previous studies on copper(I)-catalyzed substitution of acyclic allylic carbonates with diboron, where the *anti*-S_N2' reaction proceeded with high stereospecificity.[4b,11]

Table 2. Copper(I)-Catalyzed Boryl Substitution of Various Alkyl Halides

entry	substrate	product	time (h)	yield (%)[b]
1	 **1b**	 **3b**	4	85
				
2	**1c**, X = Cl	**3c**	18	72
3	**1d**, X = Br		5	91
4	**1e**, X = I		48	79
5	**1f**, X = OMs		18	0
6	 **1g**	 **3g**	5	90
7	 **1h**		44	0
8	 **1i**	 **3i**	48	17
9	 **1j**	 **3j**	5	51(59)
10	 **1k**	 **3k**	5	86
11	 **1l**	 **3l**	24	80
12	 **1m**	 **3m**	24	82
13	 **1n**	 **3n**	6	80

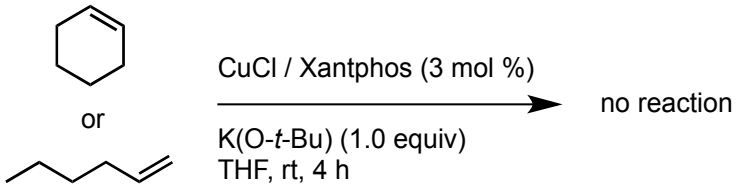
14	 **1o**	 **3o**	6	51(65)
15[d,e]	 **1p**	 **3p**	24	62
16[d,e]	 **1q**	 **3q**	30	68
17[f,e]	 **1r**	 **3r**	31	85
18[f,e]	 **1s**	 **3s**	30	81
19[c]	 (*R*)-**1t**, >99% ee	 (*rac*)-**3t**	24	93

[a]Conditions: **1a** (0.5 mmol), CuX (0.015 mmol), ligand (0.015 mmol), K(O-*t*-Bu)/THF (1.0 M, 0.5 mL), **2** (0.6 mmol), room temparature. [b]Isolated yield. Values in parenthese are the yields determined by ^{1}H NMR analysis of the crude reaction mixture. [c]5 mol % of catalyst and 1.2 equiv of K(O-*t*-Bu) were used. [d]Reaction was conducted at 40 °C with 15 mol % of catalyst and 2.2 equiv of **2**. [e]2.0 equiv of K(O-*t*-Bu) was used. [f]10 mol % of catalyst and 2.0 equiv of **2** were used.

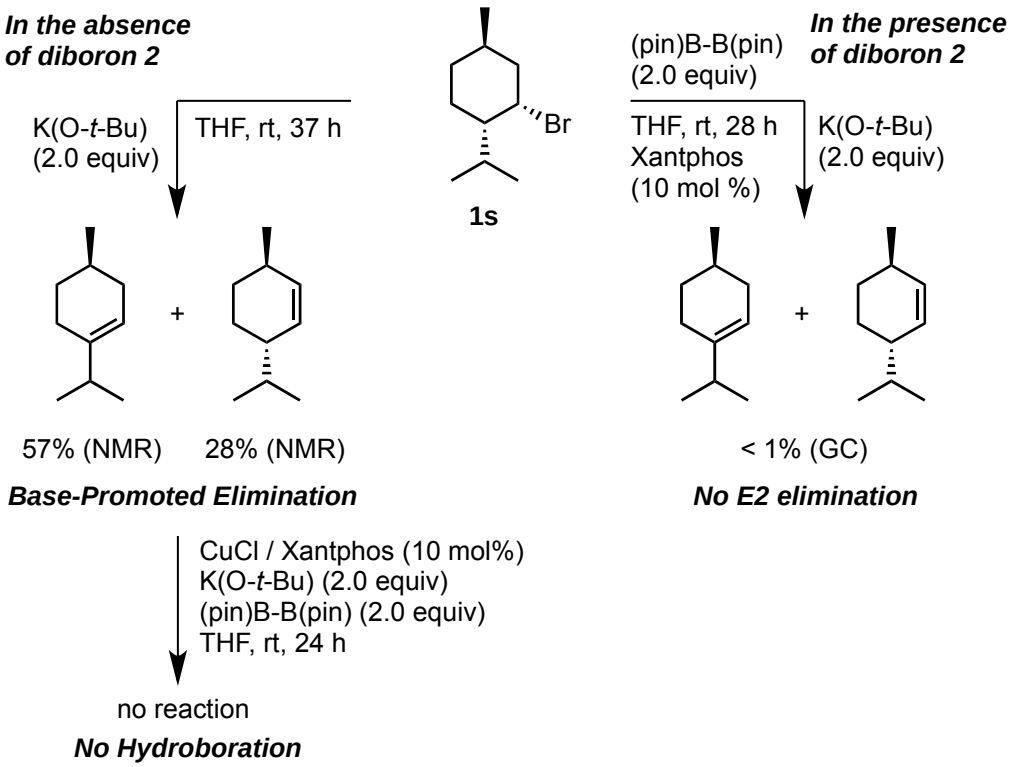
This reaction does not include base-promoted elimination/alkene hydroboration pathway. The following experiments exclude this mechanism. (1) Alkenes did not undergo hydroboration under the reaction conditions presented in Table 1 and 2 (Scheme 3 and 4). (2) Base-promoted elimination of alkylhalides proceeded quickly in the presence of *t*-BuOK; however, by addition of **2**, base-promoted elimination was completely inhibited (Scheme 4). Complexation of *t*-BuOK and Lewis acidic **2** would reduce the basicity of *t*-BuOK siginificantly. (3) Our boryl substitution of secondary alkyl halides was regiospecific (Table 2, entries 6, 17, 18, and 19). However, elimination products of secondary alkyl halides should give regio isomers in term of

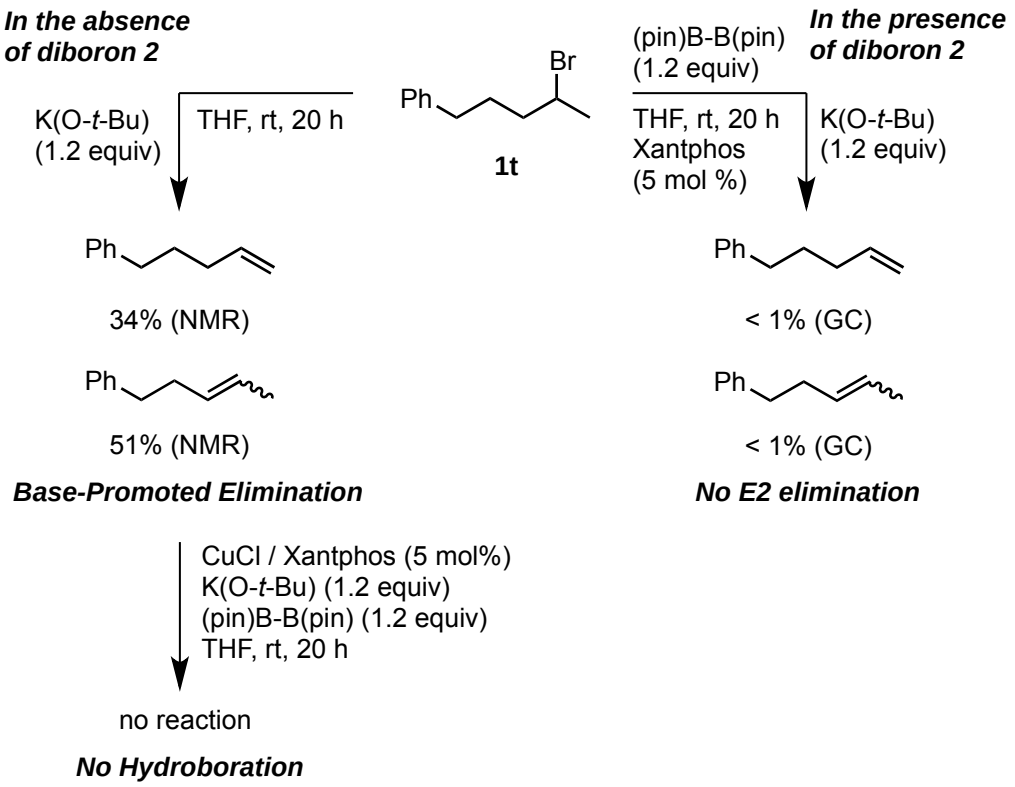
double bond (Scheme 4). It is difficult to assume product convergence in hydroboration of regio isomeric alkenes. In addition, the base-promoted elimination products from **1s** and **1t** did not underwent hydroboration under the conditions for our copper(I)-catalyzed boryl substitution of alkyl halides (Scheme 4).

Scheme 3. Attempts of Copper(I)-Catalyzed Hydroboration of Alkenes with Diboron **2**



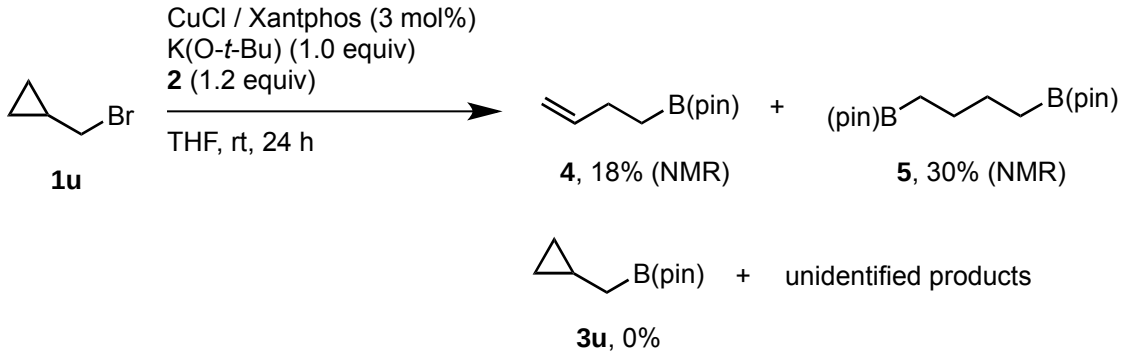
Scheme 4. Experiments for Exclusion of Elimination/Hydroboration Pathway of **1s** and **1t**





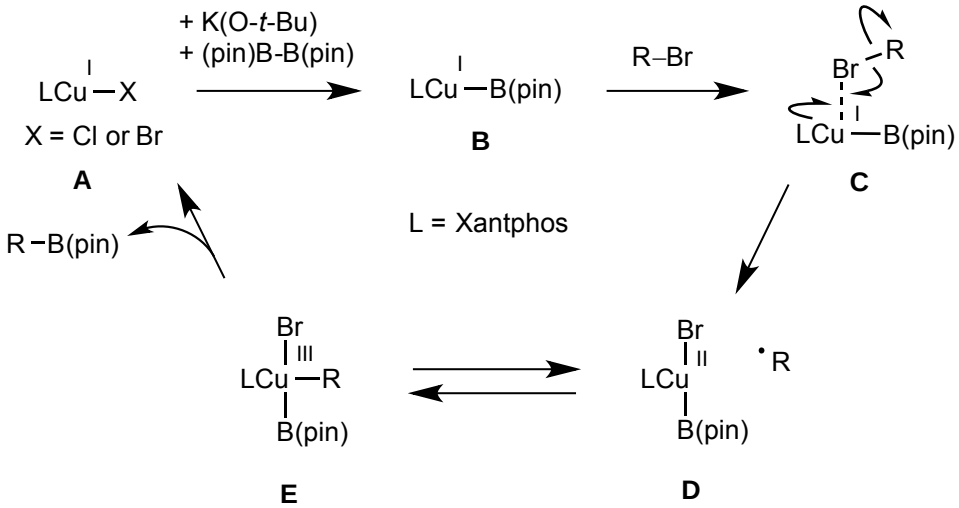
In order to probe the reaction mechanism further, the author also carried out the copper(I)-catalyzed borylation of cyclopropylmethyl bromide (**1u**), as illustrated in Scheme 5. 3-Butenylboronate **4** (18%) and bis-boryl product **5** (30%), which could be derived from **4** through further borylation of the terminal double bond, were found in the reaction mixture, but the simple boryl substitution product **3u** was not detected. The formation of the ring-opening products suggests that this reaction could include a radical pathway; this assumption is not inconsistent with the stereochemical outcomes observed in entries 17–19, Table 2.[12,13]

Scheme 5. Copper(I)/Xantphos-Catalyzed Borylation of Cyclopropylmethyl bromide (**1u**)



The proposed reaction mechanism of the current borylation reaction is shown in Scheme 6. First, copper(I) salt **A** reacts with K(O-*t*-Bu) base and a diboron compound to form active species **B**. The single electron transfer between a borylcopper(I) and alkylhalide occurs to generate copper(II) intermediate **D** and alkyl redical species. Further single electron transfer proceeds to give the copper(III) complex **E** and then subsequent reductive elimination provides the corresponding boryl substituted product and copper(I) halide **A**.

Scheme 6. Proposed Reaction Mechanism



Conclusion

In summary, the auther have developed a novel copper(I)-catalyzed reaction as the first practical procedure for boryl substitution of unactivated alkyl halides. This reaction offers a direct umpolung pathway for the conventional carbon nucleophile method, and has high functional group compatibility and interesting stereochemical-controlling properties. The author believes that this procedure will be a powerful synthetic method for a broad range of alkylboronates, including those that could not be synthesized by previous methods.

Experimental

General.

Materials were obtained from commercial suppliers and purified by the standard procedure unless otherwise noted. Solvents were purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried on MS 4A. NMR spectra were recorded on JEOL JNM-ECX400P spectrometer (1H: 400 MHz and 13C: 100 MHz). Tetramethylsilane (1H) and $CDCl_3$ (^{13}C) were employed as external standards, respectively. CuCl (ReagentPlus® grade, 224332-25G, ≥99%) and K(O-*t*-Bu)/THF (1.0 M, 328650-50ML) were purchased from Sigma-Aldrich Co. and used as received. Mesitylene or 1,1,2,2-tetrachloroethane was used as the internal standard for determining NMR yield. GLC analysis was conducted with Shimadzu GC-2014 or GC-2025 equipped with ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and a FID detector HPLC analyses with chiral stationary phase were carried out using Hitachi LaChrome Elite HPLC system with L-2400 UV detector. Recycle preparative gel permeation chromatography was conducted with JAI LC-9101 using CHCl3 as the eluent. Low- and High-resolution mass spectra were recorded at the Center for Instrumental Analysis, Hokkaido University.

Experimental.

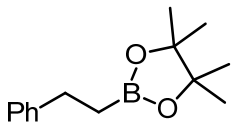
Starting Materials.

1f and **1n** were prepared from the corresponding alcohols and methanesulfonyl chloride by a standard procedure. **1l** and **1m** were synthesized from the 5-bromopentanol by standard esterification and silylation procedures. **1s** was synthesized by bromination of (–)-menthol with CBr_4/PPh_3 reagents.[15] Other alkyl halide substrates were purchased from commercial suppliers. The purchased starting materials were not subjected to further purification but dried over MS4A before use.

Representative Procedure for Borylation.

Cooper chloride (1.5 mg, 0.015 mmol) and bis(pinacolato)diboron (152.4 mg, 0.6 mmol), Xantphos (8.7 mg, 0.015 mmol) were placed in an oven-dried reaction vial. 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, evacuated and backfilled with nitrogen. THF (0.5 mmol) and K(O-*t*-Bu)/THF (1.0 M, 0.25 mL, 0.25 mmol) were added in the vial through the rubber septum. Then alkyl halide 1 (0.5 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short silica column eluting with ethyl acetate/hexane (10:90). The crude mixture was further purified by flash column chromatography (SiO2, ethyl acetate/hexane, 0.5:99.5–2.5:97.5). The flash column chromatography is completed within 10 min. to minimize decomposition of the product.

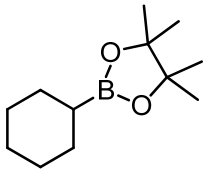
4,4,5,5-Tetramethyl-2-phenethyl-1,3,2-dioxaborolane (3a).[16]



3a

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.14 (t, *J* = 8.2 Hz, 2H), 1.22 (s, 12H), 2.75 (t, *J* = 8.4 Hz, 2H), 7.13–7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 13.0 (br, B–CH2), 24.7 (CH3), 29.9 (CH2), 83.0 (C), 125.4 (CH), 127.9 (CH), 128.1 (CH), 144.3 (C). HRMS–EI (*m*/*z*): $[M]^+$ calcd for C14H21BO2, 232.1636; found, 232.1635. Anal. Calcd for $C_{14}H_{21}BO_2$: C, 72.44; H, 9.12. Found: C, 72.68; H, 9.31.

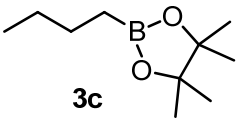
4,4,5,5-Tetramethyl-2-cyclohexyl-1,3,2-dioxaborolane (3b).[17]



3b

^{1}H NMR (400 MHz, $CDCl_3$, δ):0.94–1.05 (m, 1H), 1.24 (s, 12H), 1.25–1.39 (m, 4H), 1.59–1.67 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 22.0 (br, B–CH2), 24.7 (CH3), 26.7 (CH2), 27.1 (CH2), 27.9 (CH2), 82.6 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{23}BO_2$, 210.1791; found, 210.1802.

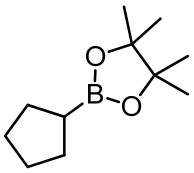
4,4,5,5-Tetramethyl-2-butyl-1,3,2-dioxaborolane (3c).[18]



3c

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.78 (t, *J* = 7.8 Hz, 2H), 0.88 (t, *J* = 7.3 Hz, 3H), 1.24 (s, 12H), 1.28–1.43 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 10.5 (br, B–CH2), 13.8 (CH3), 24.7 (CH3), 25.4 (CH2), 26.2 (CH2), 82.8 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_{21}BO_2$, 184.1635; found, 184.1644.

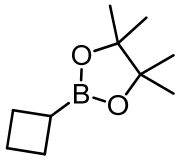
2-cyclopentyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3d).



3d

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.13-1.19 (m, 1H), 1.24 (s, 12H), 1.40-1.54 (m, 4H), 1.58-1.64 (m, 2H), 1.71-1.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 21.8 (br, B–CH), 24.6 (CH3), 26.8 (CH2), 28.4 (CH2), 82.7 (*C*). HRMS–EI (*m*/*z*): $[M-CH_3]^+$ calcd for $C_{10}H_{18}BO_2$, 181.13998; found, 181.13998.

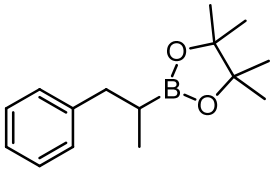
2-cyclobutyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3e).



3e

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.26 (s, 12H), 1.88-2.12 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 17.9 (br, B–CH), 22.6 (CH2), 23.8 (CH2), 24.7 (CH3), 82.8 (*C*). HRMS–EI (*m*/*z*): $[M-CH_3]^+$ calcd for $C_9H_{16}BO_2$, 167.12422; found, 167.12445.

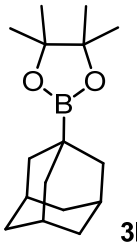
4,4,5,5-Tetramethyl-2-(2-phenylpopan-2-yl)-1,3,2-dioxaborolane (3f).[19]



3f

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.96 (d, *J* = 7.3 Hz, 3H), 1.19 (s, 12H), 1.37 (q, *J* = 7.8 Hz, 1H), 2.54 (dd, *J* = 8.7 and 13.7 Hz, 1H), 2.81 (dd, *J* = 7.8 and 13.7 Hz, 1H), 7.13–7.26 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 15.1 (CH3), 19.5 (br, B–CH), 24.6 (CH3), 38.9 (CH2), 82.9 (*C*), 125.5 (CH), 127.9 (CH), 128.8 (CH), 142.2 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{23}BO_2$, 246.1791; found, 246.1791.

2-Adamantyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3h).

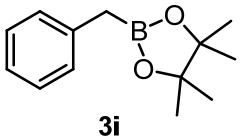


3h

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.21 (s, 12H), 1.73–1.77 (br, 12H), 1.82–1.87 (br, 3H). ^{13}C NMR (100 MHz, CDCl3, δ): 24.6 (CH3), 27.5 (CH), 37.5 (CH2), 37.9

(*C*H2), 82.6 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{27}BO_2$, 262.2104; found, 262.2109.

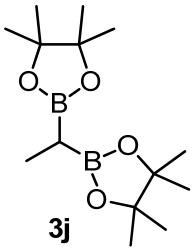
2-Benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3i).[20]



3i

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.23 (s, 12H), 2.29 (s, 2H), 7.09–7.25 (m, 5H). ^{13}C NMR (100 MHz, CDCl3, δ): 20.0 (br, B–*C*H2), 24.7 (*C*H3), 83.3 (*C*), 124.8 (*C*H), 128.2 (*C*H), 128.9 (*C*H), 138.6 (*C*). HRMS–EI (*m*/*z*): [M]+ calcd for $C_{13}H_{19}BO_2$, 218.1478; found, 218.1478.

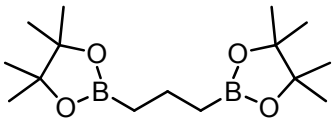
1,1-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethane (**3j**).[21]



3j

^{1}H NMR (400 MHz, CDCl3, δ): 0.73 (q, *J* = 7.4 Hz, 1H), 1.05 (d, *J* = 7.7 Hz, 3H), 1.227 (s, 12H), 1.234 (s, 12H). ^{13}C NMR (100 MHz, CDCl3, δ): 0.2 (br, B–*C*H2), 9.0 (*C*H3), 24.5 (*C*H3), 24.5 (*C*H3), 82.8 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{28}B_2NaO_4$, 305.2067; found, 305.2066.

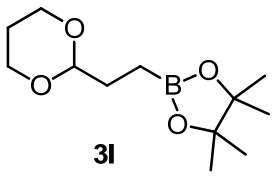
1,1-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propane (**3k**).



3k

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.81 (t, *J* = 8.1 Hz, 4H), 1.24 (s, 24H), 1.54 (quint, *J* = 8.1 Hz,
2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.0 (br, B–CH2), 18.5 (CH2), 24.7 (CH3), 82.7 (*C*). HRMS–EI (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{30}B_2NaO_4$, 319.2228; found, 319.2223.

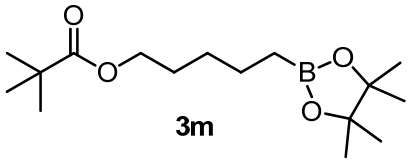
2-(2-(1,3-Dioxan-2-yl)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3l).



3l

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.83 (t, *J* = 7.9 Hz, 2H), 1.23 (s, 12H), 1.28–1.36 (m, 1H), 1.72 (dt, *J* = 7.7 and 5.1 Hz, 2H), 2.00–2.12 (m, 1H), 3.774 (m, 2H), 4.1 (m, 2H), 4.47 (t, *J* = 5.1 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3, δ): 5.3 (br, B–CH2), 24.6 (CH3), 25.7 (CH2), 29.3 (CH2), 66.6 (CH2), 82.7 (*C*), 102.9 (CH). HRMS–EI (*m*/*z*): $[M–H]^+$ calcd for C12H22BO4, 241.1611; found, 241.1619.
Anal. Calcd for $C_{12}H_{23}BO_4$: C, 59.53; H, 9.57. Found: C, 59.77; H, 9.67.

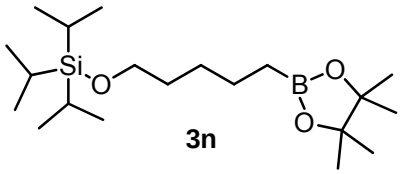
5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl pivalate (3m).



3m

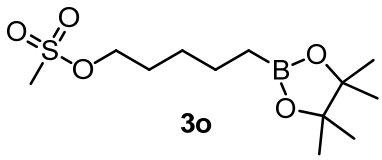
^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.79 (t, *J* = 7.7 Hz, 2H), 1.19 (s, 9H), 1.24 (s, 12H), 1.32–1.49 (m, 4H), 1.59–1.66 (m, 2H), 4.04 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 10.5 (br, B–CH2), 23.5 (CH2), 24.7 (CH3), 27.1 (CH3), 28.3 (CH2), 28.5 (CH2), 38.5 (*C*), 64.3 (CH2), 82.7 (*C*), 178.4 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{31}BNaO_4$, 321.2208; found, 321.2208.

4,4,5,5-Tetramethyl-5-tri(isopropyl)silyloxy-1,3,2-dioxaborolane (3n).



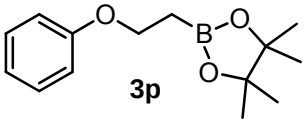
^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.78 (t, *J* = 7.9 Hz, 2H), 1.02–1.13 (m, 21H), 1.24 (s, 12H), 1.30–1.47 (m, 4H), 1.50–1.59 (m, 1H), 3.66 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 11.1 (br, B–CH2), 11.9 (CH), 18.0 (CH3), 23.9 (CH2), 24.7 (CH3), 28.6 (CH2), 32.9 (CH2), 63.5 (CH2), 82.8 (C). HRMS–EI (*m*/*z*): $[M–CH3]^+$ calcd for C19H40BO3Si, 355.2840; found, 355.2843. Anal. Calcd for $C_{20}H_{43}BO_3Si$: C, 64.84; H, 11.70. Found: C, 64.66; H, 11.88.

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl methanesulfonate (3o).



^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.79 (t, *J* = 7.5 Hz, 2H), 1.23 (s, 12H), 1.34–1.48 (m, 4H), 1.75 (quint, *J* = 7.1 Hz, 2H), 3.00 (s, 3H), 4.20 (t, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 10.9 (br, B–CH2), 23.3 (CH2), 24.7 (CH3), 27.8 (CH2), 28.7 (CH2), 37.2 (CH3), 70.1 (CH2), 82.8 (C). HRMS–EI (*m*/*z*): $[M+Na]^+$ calcd for C12H25BNaO5S, 315.1413; found, 315.1408. Anal. Calcd for $C_{12}H_{25}BO_5S$: C, 49.33; H, 8.62. Found: C, 49.35; H, 8.64.

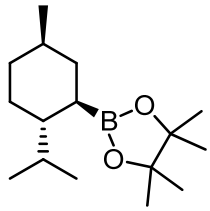
4,4,5,5-Tetramethyl-2-(2-phenoxyethyl)-1,3,2-dioxaborolane (3p).



^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.26 (s, 12H), 1.37 (t, *J* = 7.9 Hz, 2H), 4.11 (t, *J* = 8.0 Hz, 2H), 6.89–6.94 (m, 3H), 7.24–7.29 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$,

δ): 12.3 (br, B–CH2), 24.7 (CH3), 64.7 (CH2), 83.3 (*C*), 114.5 (CH), 120.3 (CH), 129.3 (CH), 159.0 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{21}BO_3$, 248.1584; found, 248.1579.

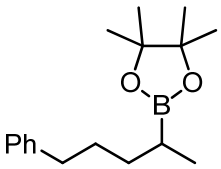
2-[(1*R*,2*R*,5*R*)-2-Isopropyl-5-methylcyclohexyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3r).



3r

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.72–1.00 (m, 4H), 0.77 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 1.21–1.32 (m, 14H), 1.56–1.72 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 16.4 (CH3), 21.6 (CH3), 22.7 (CH3), 24.6 (CH3), 24.7 (CH3), 25.8 (CH2), 28.0 (br, B-CH), 32.0 (CH), 33.4 (CH), 35.3 (CH2), 37.1 (CH2), 43.7 (CH), 82.6 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for C16H31BO2, 266.2417; found, 266.2415. Anal. Calcd for $C_{16}H_{31}BO_2$: C, 72.18; H, 11.74. Found: C, 72.31; H, 11.74. $[\alpha]_D^{20.5}$ –2.00 (deg cm3 g-1 dm-1) (*c* 0.0583 in CHCl3).

4,4,5,5-Tetramethyl-2-(5-phenylpentan-2-yl)-1,3,2-dioxaborolane (3t).

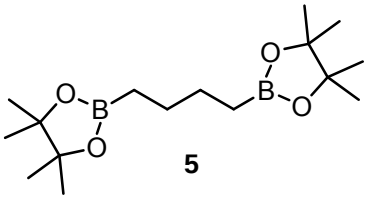


3t

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.96 (d, *J* = 7.0 Hz, 3H), 1.00–1.09 (m, 1H), 1.23 (s, 12H), 1.30–1.39 (m, 1H), 1.47–1.56 (m, 1H), 1.59–1.69 (m, 2H), 2.60 (t, *J* = 7.9 Hz, 2H), 7.14–7.18 (m, 3H), 7.25–7.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 15.4 (CH3), 16.8 (br, B–CH), 24.6 (CH3), 24.7 (CH3), 30.8 (CH2), 32.9 (CH2), 36.1 (CH2), 82.7 (*C*), 125.4 (CH), 128.1 (CH), 128.3 (CH), 142.8 (*C*).

HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{17}H_{27}BO_2$, 274.2104; found, 274.2104.

1,4-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butane (5)



5

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.77 (t, *J* = 7.3 Hz, 4H), 1.24 (s, 24H), 1.39–1.42 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 10.8 (br, B–CH2), 24.8 (CH3), 26.9 (CH2), 82.8 (*C*). $[M–CH_3]^+$ calcd for $C_{15}H_{29}B_2O_4$, 295.2252; found, 293.2250.

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Chapter 2.

Copper(I)-Catalyzed Intramolecular Borylative *exo*-Cyclization of Alkenyl Halides Containing Unactivated Double-Bond

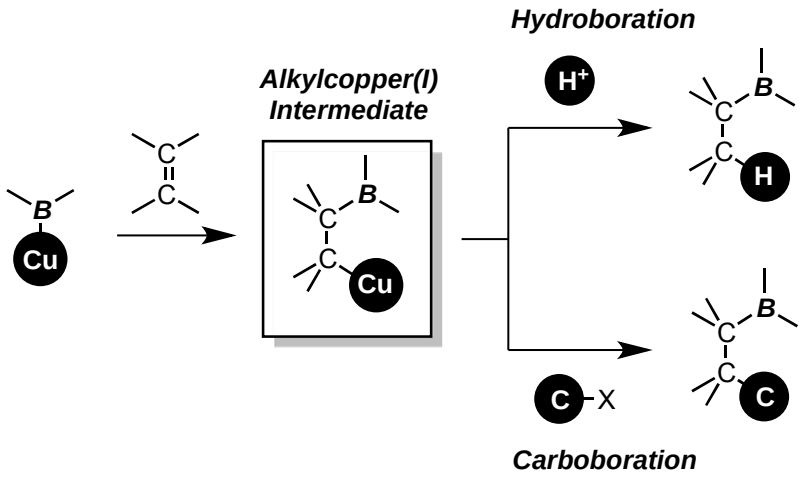
Abstract

A borylative *exo*-cyclization of alkenyl halides has been reported. The reaction includes the regioselective addition of a borylcopper(I) intermediate to unactivated terminal alkenes, followed by the intramolecular substitution of the resulting alkylcopper(I) moiety for the halide leaving groups. Experimental and theoretical investigations of the reaction mechanism have also been described. This reaction provides a new method for the synthesis of alkylboronates containing strained cycloalkyl structures from simple starting materials.

Introduction

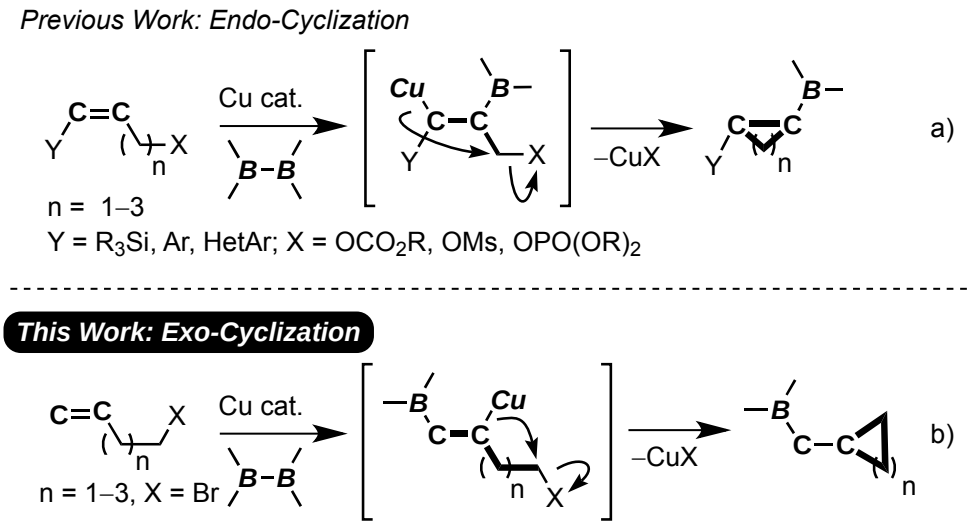
Organoboron compounds are very important synthetic reagents and their efficient preparation has attracted considerable levels of attention over the years.[1] The hydroboration of alkenes is an established method for alkylborane synthesis. When the hydroboration of a carbon-carbon double bond occurs with concomitant C–C bond formation, this can be highly beneficial for the efficient construction of various alkylboronates. Furthermore, the products of these reactions invariably possess more complex structures than those that could be obtained via conventional hydroboration chemistries or other classical methods involving carbon nucleophiles. In spite of these potential benefits, reactions based on this concept of 1,2-carboboration have been scarcely reported in the literature (Figure 1).[2–6]

Figure 1. Two Types of Borylation Reaction of C–C Double Bond by using Borylcopper(I) Spicies



Ito and Sawamura group previously reported copper(I)-catalyzed borylative cyclizations as an example of a borylation process involving a C–C bond formation (Scheme 1a).[7–9] These reactions included the regioselective addition of the borylcopper(I) to alkene, which was facilitated by an electronic directing group (Y). The subsequent intramolecular substitution afforded a variety of different cycloalkyl boronates as the *endo*-cyclization products. Herein, the author reports a new borylative cyclization reaction involving the unprecedented regioselective addition of a borylcopper(I) intermediate to an unactivated terminal double bond, followed by intermolecular cyclization to produce the *exo*-cyclization product (Scheme 1b).[9,10] The resulting products have interesting carbocyclic structure with a borylmethyl moiety. Derivatizations of the product using the boryl group, such as oxidation, amination, homologation and Suzuki-Miyaura coupling, were conducted to demonstrate the synthetic utility of this reaction. Experimental and theoretical investigations of the reaction mechanism have also been described.

Scheme 1. Copper(I)-Catalyzed Intramolecular Borylative Cyclization of Alkenes

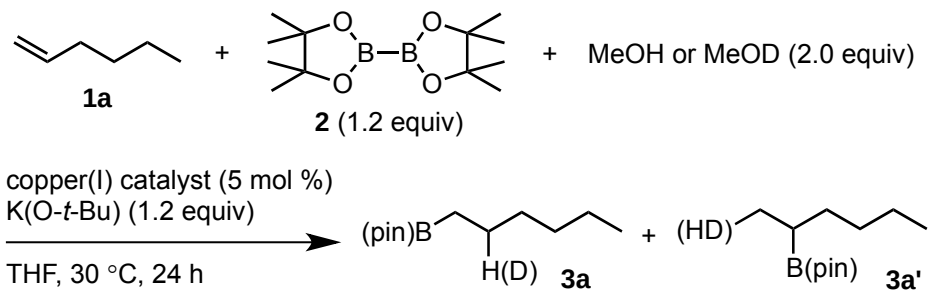


Results and Discussion

In all of the previous reports concerning the copper(I)-catalyzed borylation of carbon-carbon double bonds, electronically activated substrates have been used (i.e. substrates with a low LUMO level capable of effectively interacting with the borylcopper(I) HOMO).[7,8,11,12] For reported previous cyclization reactions, a silyl or an aryl group (Y) was required to promote the reaction and provide a high level of regioselectivity (Scheme 1a).[7] There have been no reports for the reaction between the borylcopper(I) intermediate and unactivated alkenes such as 1-hexene.[11,13] To design a new carboboration process, the author initially checked this preconceived reactivity profile (Table 1). Pleasingly, the reaction between 1-hexene (**1a**) with bis(pinacolato)diboron (**2**) in the presence of a Cu(O-*t*-Bu)/Xantphos catalyst system with MeOH as a proton source proceeded smoothly to afford the monoborylation product **3a** in excellent yield with good regioselectivity (**3a**, 81%; **3a′**, 7%) (Table 1, entry 1). The same reaction proceeded well with the more readily available CuCl/Xantphos/K(O-*t*-Bu) catalytic system (entry 2).

The use of MeOD instead of MeOH gave the 2-deuterated product that corresponded to the trapping product of the alkylcopper(I) intermediate (entry 3). In contrast, the use of PPh_3 or *N*-heterocyclic carbenes (NHC) in the same reaction instead of Xantphos gave poor results without detection of *β*-hydride elimination products (entries 4–6). Interestingly, the investigation of a reaction using the internal alkene, 2-hexene, resulted only in failure even when the Xantphos ligand was used (entry 7).

Table 1. Copper(I)-Catalyzed Monoborylation of Unactivated Alkenes



entry	copper(I) catalyst	**3a** (%)[b]	**3a'** (%)[b]
1[c]	Cu(O-*t*-Bu)/Xantphos	81	7
2	CuCl/Xantphos/K(O-*t*-Bu)	91	7
3[d]	CuCl/Xantphos/K(O-*t*-Bu)	92 (>95% D)	6
4	CuCl/PPh_3/K(O-*t*-Bu)	14	3
5[e]	CuCl/IPr/K(O-*t*-Bu)	1	7
6[e]	CuCl/IMes/K(O-*t*-Bu)	12	16
7[f]	CuCl/Xantphos/K(O-*t*-Bu)	trace	0

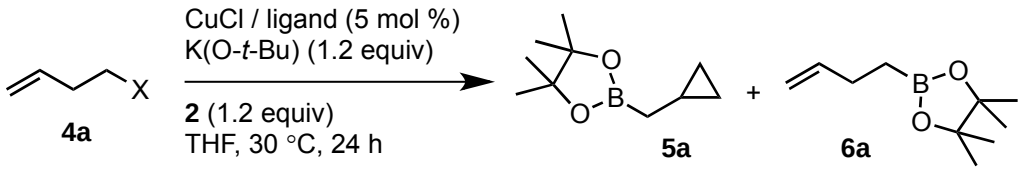
[a]Conditions: **1** (0.5 mmol), CuCl (0.025 mmol), ligand (0.025 mmol), K(O-*t*-Bu)/THF (0.6 M, 1.0 mL), **2** (0.6 mmol), MeOH (1.0 mmol). [b]Yield was determined by GC analysis of the crude mixture with an internal standard. [c]Cu(O-t-Bu) (0.025 mmol) was used. [d]MeOD (1.0 mmol) was used. [e]IPr: 1,3-bis(2,6-diisopropylphenyl)imidazolium. IMes: 1,3-bis(2,4,6-trimethylphenyl)imidazolium. [f]2-Hexene was used instead of 1-hexene.

With a new procedure in hand for the regioselective addition of borylcopper(I) to terminal double bonds, the author proceeded to investigate the *exo*-cyclization process (Table 2). The desired product **5a** was exclusively

produced from **4a** in excellent yield (entries 1 and 2) when chloride or bromide was used as the leaving group and the ligand was Xantphos. Although alkyl halides lacking a terminal double bond are good substrates for the copper(I)-catalyzed boryl substitution reaction, in this reaction, none of the simple boryl substitution product was detected.[9] Alkenyl iodide and tosylate were converted into an isomeric mixture of **5a** and **6a** (entries 3 and 4). The author next investigated the ligand effect (entries 5–13). In the absence of a ligand, the reaction did not proceed to completion (entry 5). In the presence of the monophosphine ligands, the reactions tended to produce the boryl substitution product **6a** rather than the cyclization product **5a** (entries 6–9). When the reaction was conducted in the presence of rigid diphosphine ligands (Xantphos, dppf), they showed a preference for the cyclization reaction (enties 1–4, 13). Use of a stoichiometric amount of Cu(O-*t*-Bu) instead of CuCl/K(O-*t*-Bu) resulted in almost no reaction (entry 14), indicating that K(O-*t*-Bu) is needed for the cyclization step.

The author also tested the construction of cyclobutane frameworks through the borylative *exo*-cyclization (Scheme 2). 5-Bromopentene (**4b**) was successfully converted into the cyclobutylmethylboronate **5b** in good yield (88%) with excellent chemoselectivity (**6b**, <1%). In a similar manner to the cyclopropanation case, the cyclization/substitution selectivity could be switched when $P(C_6F_5)_3$ was used as the ligand (**5b**/**6b** = 12:88).

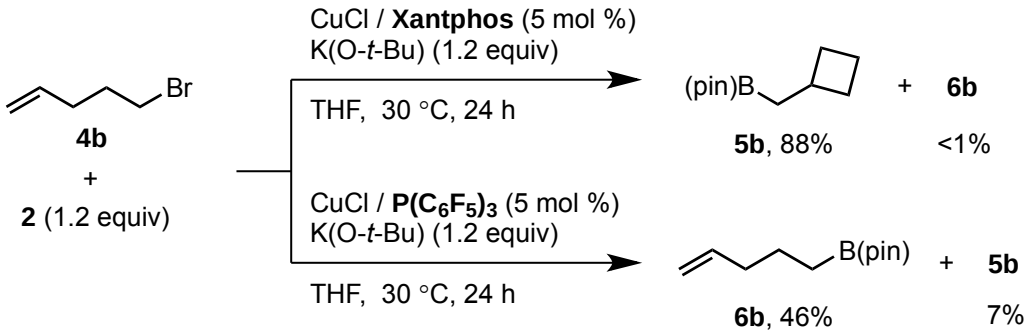
Table 2. Copper(I)-Catalyzed Borylative Cyclization and Substitution Reactions of Alkenyl Halides and Pseudo Halides **4a**[a]



entry	X	ligand	**5a** (%)[b]	**6a** (%)[b]
1	Cl	Xantphos	99	<1
2	Br	Xantphos	99	<1
3	I	Xantphos	38	42
4	OTs	Xantphos	65	27
5	Br	none	15	7
6	Br	PPh_3	15	35
7	Br	$P(C_6F_5)_3$	6	45
8	Br	$P(OPh)_3$	6	32
9	Br	PBu_3	11	31
10	Br	dppe	32	33
11	Br	dppp	47	24
12	Br	dppb	9	47
13	Br	dppf	87	4
14[c]	Br	Xantphos	<1	4

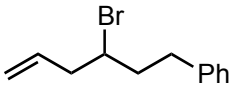
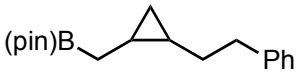
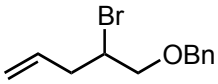
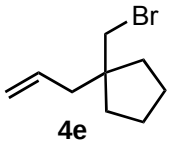
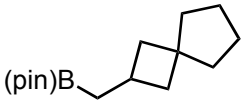
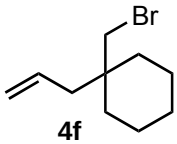
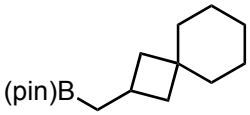
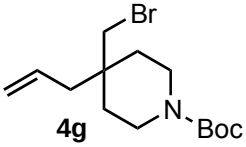
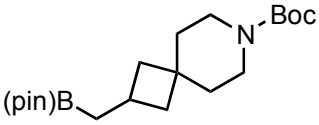
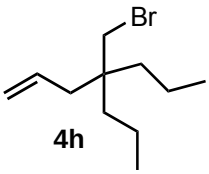
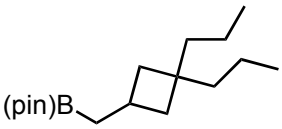
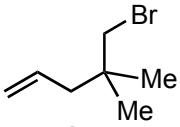
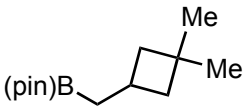
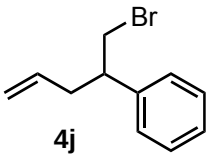
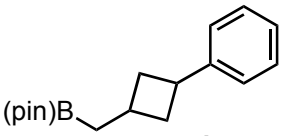
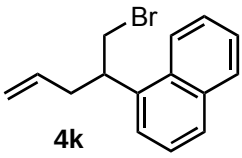
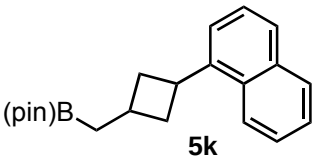
[a]Conditions: **4a** (0.5 mmol), CuCl (0.025 mmol), ligand (0.025 mmol), K(O-*t*-Bu)/THF (0.6 M, 1.0 mL), **2** (0.6 mmol). [b]Yield was determined by GC analysis of the crude mixture with an internal standard. [c]Cu(O-t-Bu) (0.025 mmol) was used instead of CuCl/K(O-*t*-Bu).

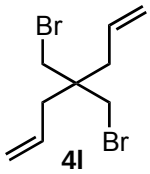
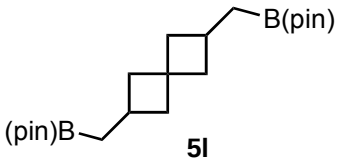
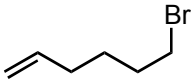
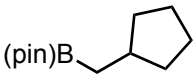
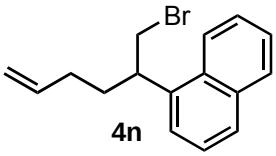
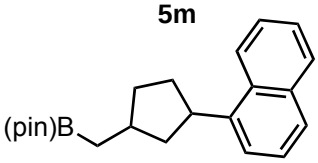
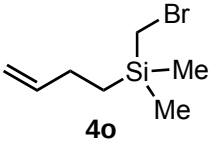
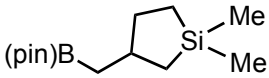
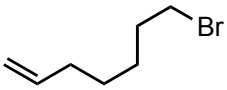
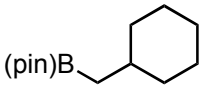
Scheme 2. Borylative Cyclization of 5-Bromopentene (**4b**)



The synthesis of a variety of different cyclic compounds was then investigated (Table 3). The reactions of secondary alkenyl bromides (**4c** and **4d**) proceeded smoothly to give the corresponding cyclopropylmethy boronates (**5c**, 94% and **5d**, 92%, respectively; cyclization/substitution = >95:5) (entries 1 and 2). Unfortunately, however, the diastereoselectivity in these cases was poor (trans/cis = 1:1). This reaction can be applied to the construction of spirocyclic frameworks bearing the boryl group, which would otherwise be difficult to synthesize through a one-step procedure. Spiro[3.4]octan-2-ylmethylboronate (**5e**) and spiro[3.5]nonan-2-methylboronate (**5f**) in particular were successfully obtained in high yields as singularly borylated products (90% and 92%, respectively) (entries 3 and 4). The application of a substrate containing a Boc-protected piperidine moiety (**4g**) gave the desired nitrogen-containing spirocyclic boronate (**5g**) in good yield (90%) with excellent chemoselectivity (**5g**/**6g** >95:5) (entry 5). Tri-substituted cyclobutanes (**5h** and **5i**) were formed in high yields (90% and 83%, respectively) from the corresponding alkenyl bromides (entries 6 and 7). The reactions of substrates containing aromatic rings (**4j** and **4k**) afforded the di-substituted cyclobutylmethyl boronates (**5j** and **5k**) in excellent yields (entries 8 and 9). Pleasingly, the reaction of a dienyl halide (**4l**) proceeded smoothly to produce the desired bis-boryl products (**5l**) bearing spiro[3.3]framework via double borylative cyclization (entry 10). The five-membered ring products (**5m** and **5n**) were also successfully synthesized with a high degree of chemoselectivity (>95:5) (entries 11 and 12). A silicon-containing product **5o** was obtained in good yield (entry 13) with a minor amount of the *endo*-cyclization product (7%). Notably, with the exception of entry 13, the *endo*-cyclization products originating from the regioisomeric insertion were not detected in the reactions shown in Table 3. Unfortunately, this reaction could not be successfully applied to the formation of six-membered rings (entry 14).

Table 3. Copper(I)-Catalyzed Borylative *exo*-Cyclization of Unactivated Alkenyl Halides[a]

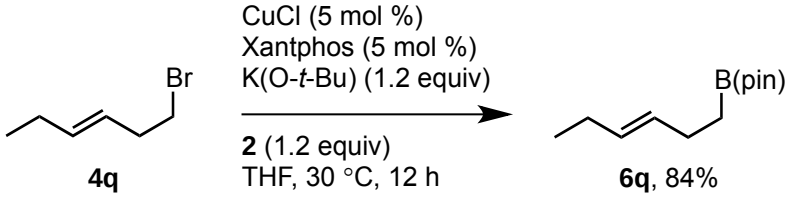
entry	substrate	product	time (h)	**5/6** selectivity	yield[b] (%)
1	 **4c**	 **5c**	1.5	>95:5	94 (1:1)
2	 **4d**	 **5d**	1	>95:5	92 (1:1)
3	 **4e**	 **5e**	4	>95:5	90
4	 **4f**	 **5f**	4	>95:5	92
5	 **4g**	 **5g**	4	>95:5	90
6	 **4h**	 **5h**	3	>95:5	90
7	 **4i**	 **5i**	4	>95:5	83
8	 **4j**	 **5j**	4	>95:5	91 (1.3:1)
9	 **4k**	 **5k**	4	>95:5	95 (1.4:1)

10[c]	 **4l**	 **5l**	4	>95:5	88
11	 **4m**	 **5m**	24	>95:5	86
12	 **4n**	 **5n**	6	>95:5	87 (1.1:1)
13[d]	 **4o**	 **5o**	4	>95:5	74
14[e]	 **4p**	 **5p**	20	>95:5	4

[a]Conditions: **4** (0.5 mmol), CuX (0.025 mmol), ligand (0.025 mmol), K(O-*t*-Bu)/THF (0.6 M, 1.0 mL), **2** (0.6 mmol), 30 °C . [b]Isolated yield. Values in parenthese are the stereoselectivity determined by GC analysis. [c]Conditions: **4l** (0.5 mmol), CuCl (0.1 mmol), Xantphos (0.1 mmol), K(O- *t*-Bu)/THF (0.73 M, 1.5 mL), **2** (1.1 mmol), 30 °C. [d]The endo-cyclization product (7%) was detected. [e]The reaction resulted in a complex mixture.

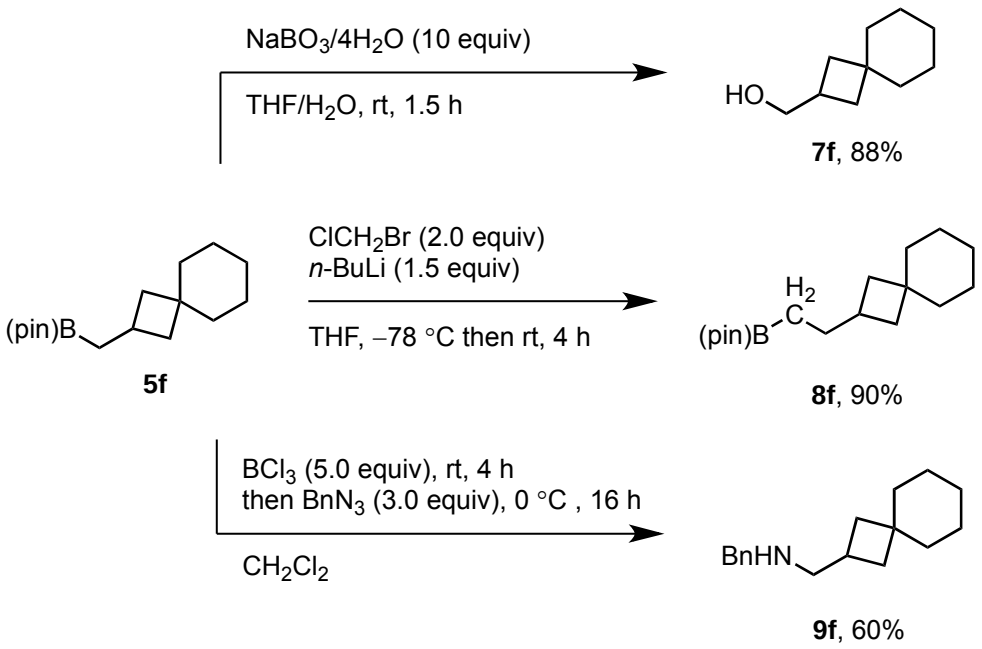
As shown in Scheme 3, reaction of an alkenyl bromide **4q** with an internal double bond afforded the simple boryl substitution product **6q** in 84% yield exclusively. The cyclization product could not be detected.[14]

Scheme 3. Copper(I)-Catalyzed Borylation of Alkenyl Bromide **4q**



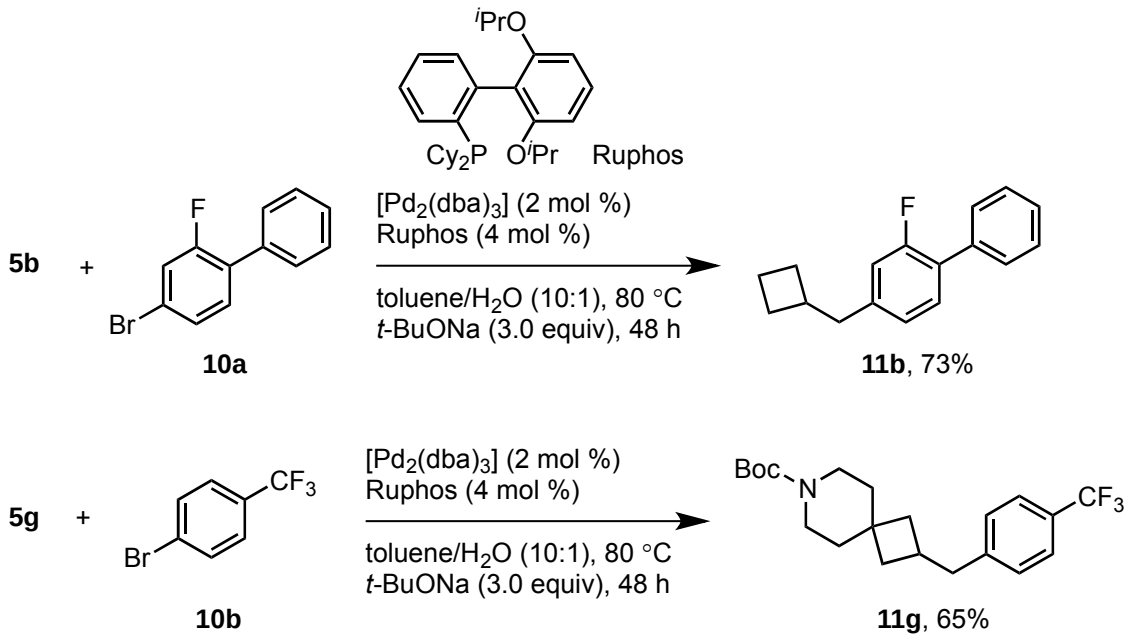
The borylative cyclization products are a useful synthetic block for preparation of carbocyclic compounds. The cyclization product **5f** was subjected to $NaBO_3$ oxidation, homologation with a halomethyl lithium reagent, or amination with benzyl azide (Scheme 4).[15–17] These reaction afforded the corresponding alcohol **7f** (88%, isolated yield), alkyl boronate **8f** (90%), and benzyl amine **9f** (60%), respectively.

Scheme 4. Derivatization of Borylative Cyclization Products



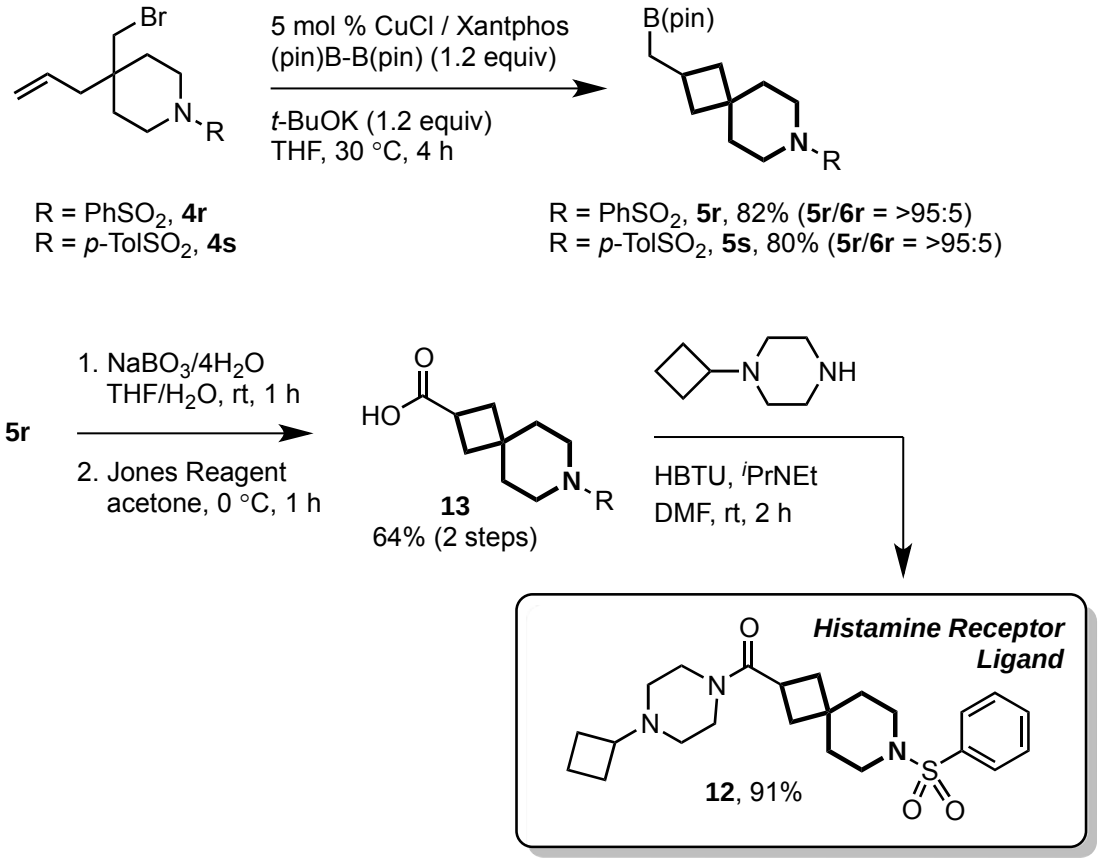
Suzuki-Miyaura cross-coupling reaction of borylative cyclization products (**5b** and **5g**) with aryl halides (**9a** and **9b**) also proceeded in the presence of Pd/Ruphos catalyst system to produce arylated products in reasonable yields (**11b** and **11g**, 73% and 65% respectively) (Scheme 5).[9a,18]

Scheme 5. Suzuki-Miyaura Cross-Coupling Reaction of Borylative Cyclization Products **5b** and **5g**



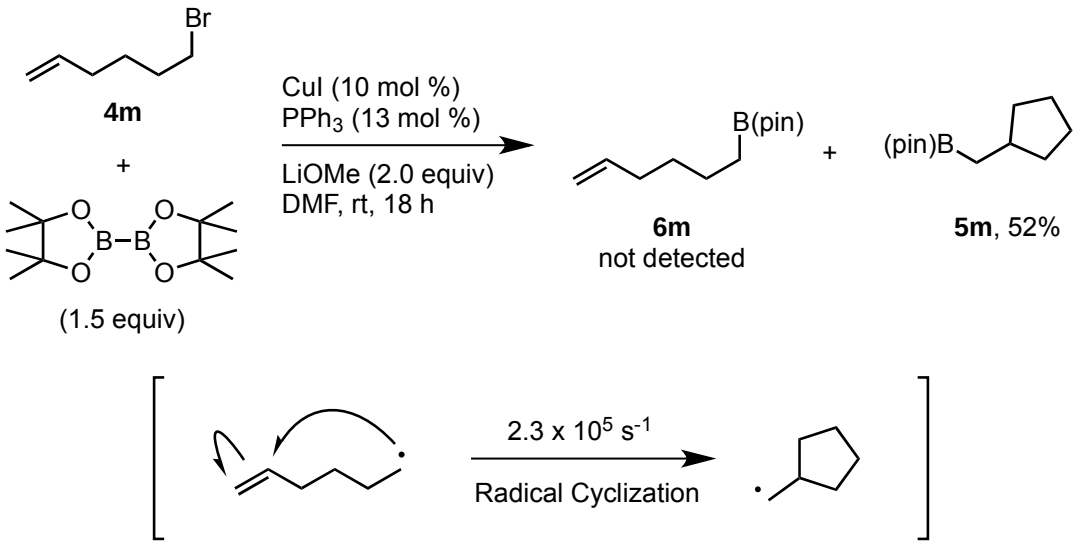
To further demonstrate the synthetic utility of this reaction, the author synthesized a biologically active compound, a histamine H3 receptor ligand **12** (IC_{50}: 6.56 nM), containing a piperidine sulfonamide structure (Scheme 6).[19] The author first checked the tolerance of sulfonamide functionality in this reaction; sulfonamides **4r** and **4s** gave the desired spirocyclic boronates (**5r** and **5s**) in good yields with excellent chemoselectivity (cyclization/substitution, >95:5). The boronate ester group in the borylative cyclization product **5r** was functionalized through $NaBO_3$ oxidation and Jones oxidation to afford carboxylic acid **13**, which was then coupled with 1-cyclobutylpiperazine to afford the histamine H3 receptor ligand **12**.

Scheme 6. Synthesis of Spirocyclobutyl Piperidine Structure through Borylative Cyclization: Application to the Sysnthesis of Histamine H3 Receptor Ligand **12**



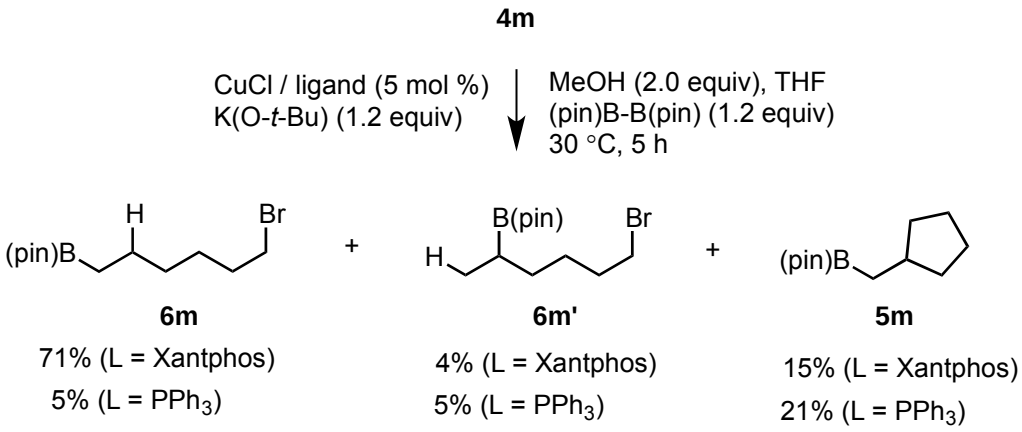
Liu, Steel, and Marder et al. reported the cyclization of **4m** to **5m** in their mechanistic studies of the boryl substitution reactions with a copper(I)/PPh_3 catalyst system (Scheme 7).[9a,10] The cyclization was suggested the possibility of a radical-process, in which the borylcopper(I) species initially attacked the C–Br bond and then underwent a radical-mediated cyclization. However, the radical scavenger experiment did not support this idea. The copper(I)/Xantphos catalyst system also gave the same product (Table 3, entry 11), although the reaction should proceed via the addition of borylcopper(I) to the alkene followed by an intermolecular substitution.

Scheme 7. Borylation of **4m** in the presence of Copper(I)/PPh3 Catalysis



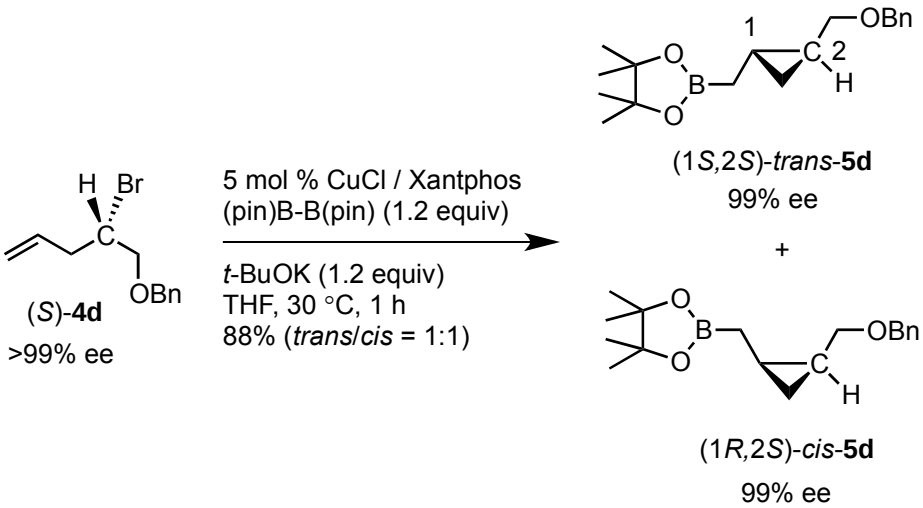
The difference in the mechanisms between the two processes was evidenced by the protonation experiments (Scheme 8). When Xantphos was used as the ligand, the protonated compounds (**6m** and **6m'**) were isolated as the major products. In contrast, the reaction with PPh_3 predominantly gave the cyclization product (**5m**) even in the presence of MeOH. The author supposes that the reaction with PPh_3 proceeds through a radical-related mechanism. The product switch for **4a** and **4b** (Table 2 and Scheme 2) also corresponds well with the difference highlighted for the above mechanisms. The alkylcopper(I) mediated substitution can afford cyclization of three- and four-membered rings; however, radical-mediated cyclization of both three- and four-membered rings is highly unfavorable.[20]

Scheme 8. Borylation Reactions of **4m** in the Presence of Proton Source



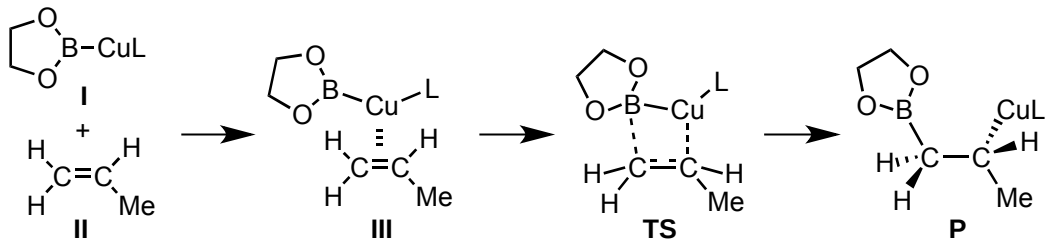
The borylative *exo*-cyclization of chiral substrates was also investigated to observe the stereochemistry of the leaving group (Scheme 9). Optically active (*S*)-**4d** was subjected to the $B_2(pin)_2$/CuCl/K(O-*t*-Bu)/Xantphos borylation system. The reaction proceeded in a perfect stereoselective manner in terms of the substitution at the C2 position, in that the alkyl halide substitution showed inversion of stereochemistry, whereas no selectivity was observed around the C1 position, reflecting the lack of stereoselectivity during the initial borylcopper(I) addition to the double bond. This high level of stereoselectivity also excluded the possibility of a radical-related mechanism during the cyclization step.

Scheme 9. Borylative Cyclization of Optically Active Substrate



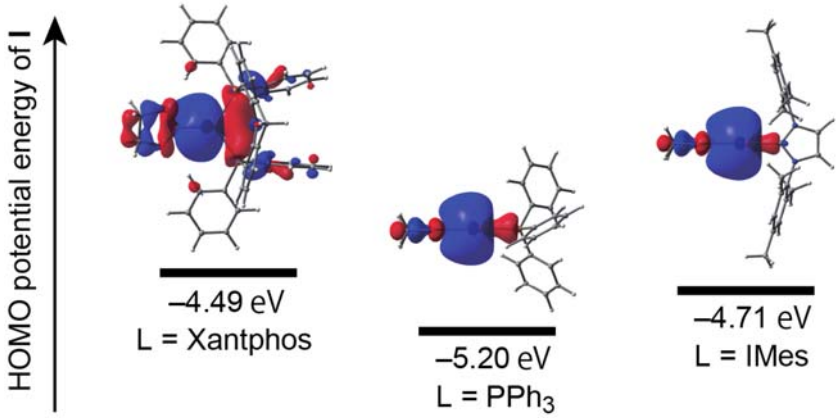
Preliminary density functional theory (DFT) calculations (B3PW91/cc-pVDZ) were used to explain the strong ligand influence observed in this reaction. The activation free energy for the addition of a model borylcopper(I)/Xantphos intermediate (**I**) to ethylene (**II**) was lower than those with the PPh_3 and NHC (IMes) complexes by 1.43 and 1.35 kcal/mol (Table 4). The HOMO level of **I** with Xantphos (–4.49 eV) was considerably higher than those of the PPh_3 (–5.20 eV) and NHC (–4.71 eV) complexes, indicating that the Xantphos complex had a stronger back donation ability to alkenes, which is considered to be important for the addition of borylcopper(I) to alkenes.[12] To understand the ligand effect, distortion/interaction analysis was also performed.[21] When the structures of the borylcopper(I) complexes (**I**) with PPh_3 and NHC were distorted to the structure in the transition states, the additional free energies were needed by 16.2 and 18.6 kcal/mol, respectively (Supporting Information). Contrary, the Xantphos complex only required 11.7 kcal/mol for the conformation change from **I** to **TS**, indicating the pre-activation nature of the Xantphos complex (**I**) in the addition to alkenes.

Table 4. DFT Calculations (B3PW91/cc-pVDZ) of Alkene Addition Step in Copper(I)-Catalyzd Borylation



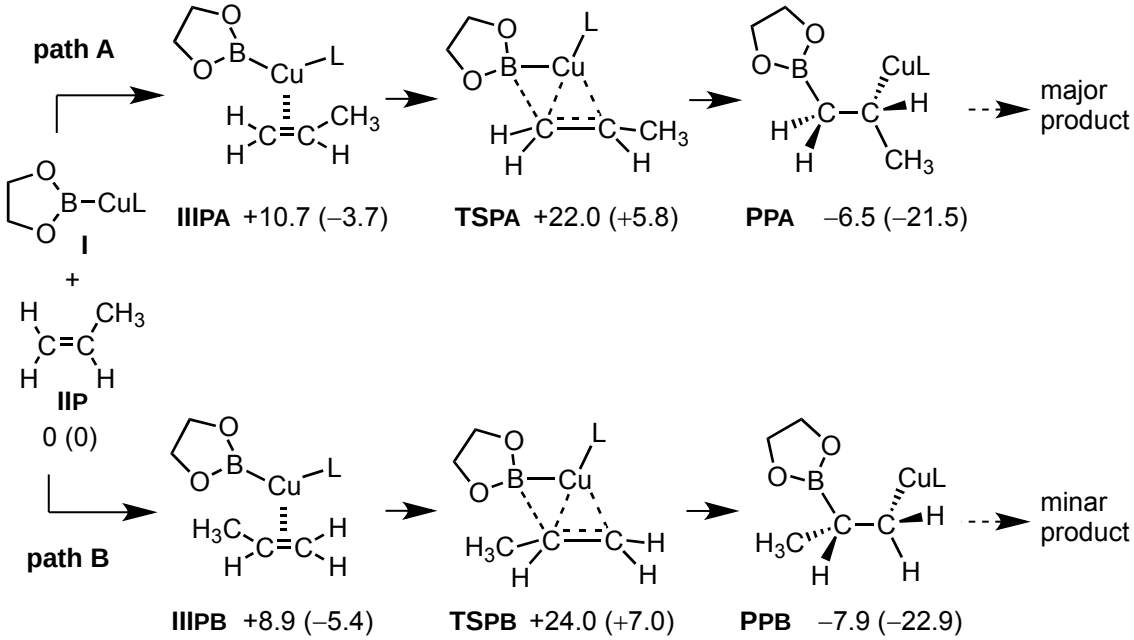
	ΔG (298K, 1.0 atm, gas-phase)[a] / kcal mol^{-1}			
L	**I+II**	**III**	**TS**	**P**
Xantphos	0	7.1 (–6.5)	17.6 (2.1)	–11.4 (–24.9)
PPh_3	0	3.5 (–10.4)	19.0 (3.6)	–16.2 (–30.5)
IMes	0	7.3 (–8.1)	18.9 (3.0)	–14.2 (–30.1)

[a]Electronic energies are shown in parentheses.



DFT calculations revealed that the activation barrier difference is a key factor for this regioselectivity (Scheme 10). In the proposed alkylcopper intermediate, the less bulky Cu(xantphos) moiety is placed at the sterically congested internal carbon. Based on the structure of the addition product, this seems to be unfavorable. DFT calculations with propene substrate for the two diastereomeric pathways were conducted. Path A can afford the major product for the addition of borylcopper(I), whereas path B corresponds to the formation of the minor product. The activation free energy for path A was lower than that of path B by 1.94 kcal/mol. Contrary, -complex **III**$_P$ and the alkylcopper product **P**$_P$ were more stabilized in path B than in path A. In the transition state, the C1 carbon, which will bind to boron atom in the product, formed a transient five-coordinated geometry with highly congested environment. The substituent on the C1 atom thus causes destabilization of the transition state. This can explain the transition state in path A has the lower barrier as compared to those in path B.

Scheme 10. DFT Calculations (B3PW91/cc-pVDZ) for Two Diastereomeric Pathways

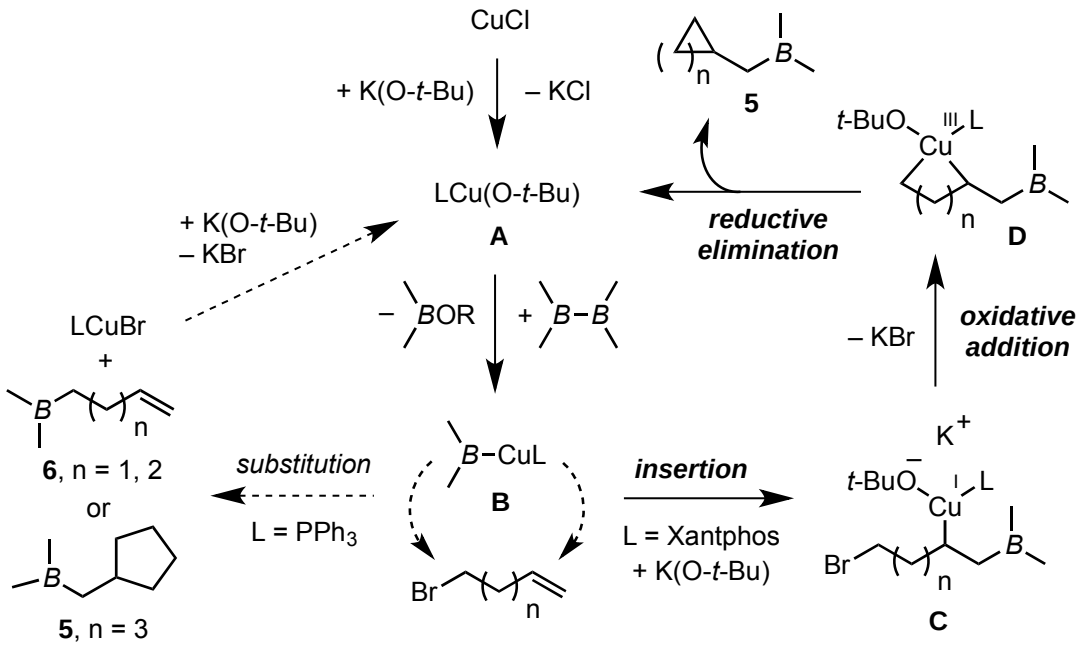


[a]Relative G value (kcal / mol) at 298 K, 1.0 atm, gas phase. Electronic energies are shown in parentheses.

A proposesd reaction mechanism for the process is shown in Scheme 11. The copper(I) alkoxide (**A**) formed via the reaction of the CuCl, ligand, and K(O-*t*-Bu) mixture initially reacts with diboron to form the borylcopper(I) intermediate (**B**). When Xantphos was used as the ligand, the borylcopper(I) intermediate possessed the ability to add to the C–C double bond of the substrate **4** (path **a**) to form the alkylcopper(I) species with concomitant formation of an ate complex (**C**) by coordination of the alkoxide. Subsequent sequential oxidative addition and elimination of bromide with inversion of the stereochemistry gives the cyclic copper(III) intermediate (**D**), in a manner similar to that of the S_N2 reaction postulated for the alkyl substitution of alkyl halides with cuprates.[22] Subsequent reductive elimination of the copper moiety from the **D** produces the cyclization product **5**, as well as reproducing **A**. The cyclization of six membered rings would not proceed according to

this mechanism because the seven membered ring intermediate (**D**, n = 4) appeared to be unstable (Table 3, entry 14). When a monophosphine were used as the ligand, the reactivity of the borylcopper(I) towards alkene addition would be less favourable (path **b**), with boryl substitution (n = 1,2) or radical cyclization proceeding (n = 3) instead.

Scheme 11. Possible Reaction Pathway



Conclusion

In summary, the auther have identified an unprecedented reactivity of borylcopper(I) toward unactivated terminal alkenes and developed a borylative *exo*-cyclization reaction, which allows for the one-step construction of alkylboronates with complex structures, such as spirocyclic frameworks, from simple starting materials. The undesired boryl substitution of the alkyl bromide moiety in the starting materials was suppressed by choosing an appropriate ligand (Xantphos), which enhanced the reactivity of

the key borylcopper(I) intermediate towards addition to the carbon-carbon double bonds.

Experimental

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 spectrometer (^{1}H: 400 MHz and ^{13}C: 100 MHz). Tetramethylsilane (^{1}H) and $CDCl_3$ (^{31}C) were employed as external standards, respectively. CuCl (ReagentPlus® grade, 224332-25G, ≥99%) and K(O-*t*-Bu) / THF (1.0 M, 328650-50ML) were purchased from Sigma-Aldrich Co. and used as received. 1,4-Diisopropylbenzene was used as an internal standard to determine GC yield. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with 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. Recycle preparative gel permeation chromatography was conducted with a JAI LC-9101 using $CHCl_3$ as the eluent. Elemental analyses and high-resolution mass spectra were recorded at the Center for Instrumental Analysis, Hokkaido University.

A Representative Procedure for the Copper(I)-Catalyzed Hydroboration of 1a (Table 1):

Copper chloride (2.5 mg, 0.025 mmol) and bis(pinacolato)diboron (152.4 mg, 0.6 mmol), Xantphos (14.5 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. THF (0.4 mL) and K(O-*t*-Bu)/THF (1.0 M, 0.6 mL, 0.6 mmol) were added in the vial through the rubber septum. After 1-hexene (**1a**, 42 mg, 0.5 mmol) was added to the

mixture at 30 °C, MeOH (415 μL, 1.0 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short silica gel column eluting with Et_2O/hexane (20:80). The crude mixture was further purified by flash column chromatography (SiO_2, Et_2O/hexane, 0:100–4:96) to give the corresponding alkylboronate **3a** as a colorless oil. The flash column chromatography should be done within 5 min after the crude mixture was applied on the silica gel surface; otherwise the products are obtained in low yield.

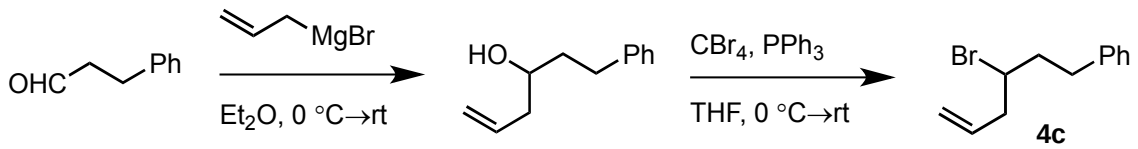
A Representative Procedure for the Copper(I)-Catalyzed Borylative Cyclization of Alkenyl Halides 4.

Copper chloride (2.5 mg, 0.025 mmol) and bis(pinacolato)diboron (152.4 mg, 0.6 mmol), Xantphos (14.5 mg, 0.025 mmol) were placed in an oven-dried reaction vial. 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, evacuated and backfilled with nitrogen. THF (0.4 mL) and K(O-*t*-Bu)/THF (1.0 M, 0.6 mL, 0.6 mmol) were added in the vial through the rubber septum. Then alkenyl halide **4** (0.5 mmol) was added dropwise at 30 °C. After the reaction was complete, the reaction mixture was passed through a short silica gel column eluting with Et_2O/hexane (20:80). The crude mixture was further purified by flash column chromathography (SiO_2, Et_2O/hexane, 0:100–4:96) to give the corresponding cyclization product **5**.

Starting Materials.

The starting materials (**1a**, **4a**, **4b**, **4m**, and **4p**) were purchased from commercial suppliers. (*E*)-1-Bromohex-3-ene (**4p**) was prepared by bromination of (*E*)-hex-3-en-1-ol with CBr4/PPh3 reagents.[23] The starting materials were dried over MS4A before use, without further purification.

Preparation of (3-bromohex-5-en-1-yl)benzene (4c).

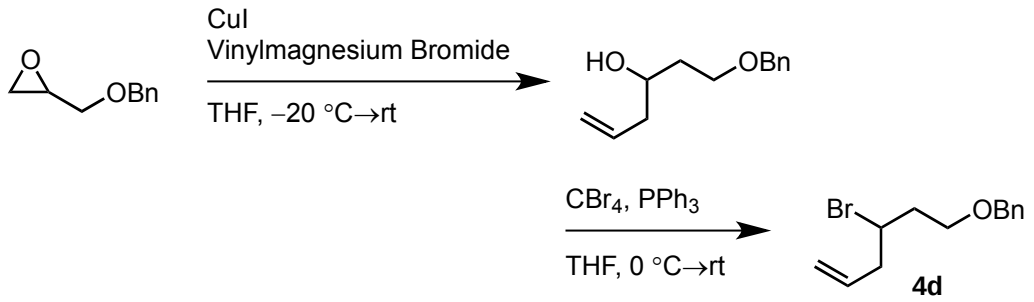


In a vacuum dried 100 mL round bottomed flask, 3-phenylpropanal (1.3 mL, 10 mmol) was dissolved in dry Et_2O (10 mL) and was cooled to 0 °C under nitrogen atmosphere. A Et_2O solution of allyl magnesium bromide (1.3 M, 11.5 mL, 15 mmol) was then added dropwise for 10 min. After stirred for 3 h, the reaction mixture was quenched by addition of 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 homoallylic alcohol (1.058 g, 6.0 mmol, 60%) as a colorless oil.

In a 50 mL round bottomed flask, CBr_4 (1.094 g, 3.3 mmol) and the homoallylic alcohol (529 mg, 3.0 mmol) were dissolved in dry THF (12 mL) and mixture was cooled to 0 °C. PPh_3 (866 mg, 3.3 mmol) was then added portion wise and the reaction mixture was stirred for 20 min. 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 hexane suspension of the crude mixture was filtered and concentrated by evaporation. The crude product was purified by silica gel chromatography and bulb-to-bulb distillation (20 Pa, 90 °C) to obtain **4c** (395 mg, 1.65 mmol, 55%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.08–2.13 (m, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.75 (dt, *J* = 8.2, 13.9 Hz, 1H), 2.91 (dt, *J* = 7.0, 13.9 Hz, 1H), 3.99 (quin, *J* = 6.7 Hz, 1H), 5.10–5.14 (m, 2H), 5.78–5.88 (m, 1H), 7.19–7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 33.6 (CH_2), 39.9 (CH_2), 43.3 (CH_2), 55.3 (CH), 117.9 (CH_2), 126.0 (CH), 128.4 (CH), 128.5 (CH), 134.6 (CH), 140.8 (C). HRMS–EI (*m*/*z*): $[M–Br]^+$ calcd for $C_{12}H_{15}$, 159.11737; found, 159.11655. Anal. Calcd for $C_{12}H_{15}Br$: C, 60.27; H, 6.32. Found: C, 60.16; H, 6.37.

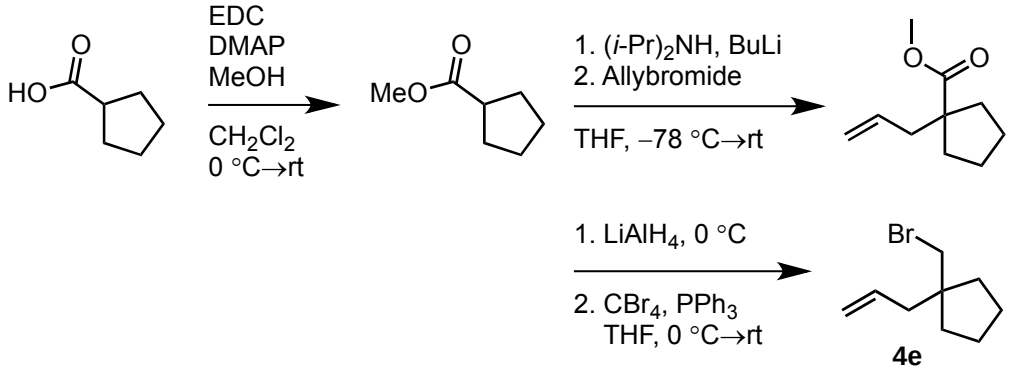
Preparation of {[(2-bromopent-4-en-1-yl)oxy]methyl} benzene (4d).



Anhydrous copper(I) iodide (285.7 mg, 1.5 mmol) was placed into a 100 mL round-bottomed flask equipped with a mechanical stirrer and a low-temperature thermometer. Then 4 mL of THF were added and the flask was cooled to –20 °C. Vinylmagnesium bromide (1.0 M in THF, 30 mL, 30 mmol) was added dropwise. After stirring for 20 min at –20 °C, benzyl glycidyl ether (2.3 mL, 15 mmol) in 2 mL of THF was added dropwise. After stirring for 12 h at –20 °C, the reaction mixture was quenched by addition of saturated NH_4Cl aq. and extracted with Et_2O three times. The combined organic layer was dried over Na_2SO_4. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain the homoallylic alcohol (2.556 g, 13.3 mmol, 89%) as a colorless oil. **4d** was then synthesized by bromination with CBr4/PPh3 reagents according to the same procedure described above (445 mg, 1.7 mmol, 35%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.54–2.62 (m, 1H), 2.74–2.81 (m, 1H), 3.65–3.75 (m, 2H), 4.09–4.16 (m, 1H), 4.58 (s, 2H), 5.12–5.17 (m, 2H), 5.78–5.88 (m, 1H), 7.28–7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 37.8 (CH_2), 69.6 (CH), 73.3 (CH_2), 73.8 (CH_2), 117.6 (CH_2), 127.66 (CH), 127.71 (CH), 128.4 (CH), 134.2 (CH), 137.9 (*C*). HRMS–EI (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{15}BrO$, 277.02040; found, 277.02013. Anal. Calcd for $C_{12}H_{15}BrO$: C, 56.49; H, 5.93. Found: C, 56.25; H, 5.86.

Preparation of 1-allyl-1-(bromomethyl)cyclopentane (4e).



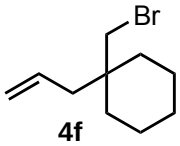
In a vacuum dried 300 mL of a round bottomed flask, cyclopentanecarboxylic acid (2.17 mL, 20 mmol) and MeOH (971 L, 24 mmol) were dissolved in dry CH_2Cl_2 (110 mL) and the flask was cooled to 0 °C under nitrogen atmosphere. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (4.60 g, 24 mmol) and *N*,*N*-dimethyl-4-aminopyridine (DMAP) (2.44 g, 20 mmol) were then added portion wise. After stirred for 4 h at room temperature, the reaction mixture was quenched by addition of saturated NH_4Cl aq. and extracted with CH_2Cl_2 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 methyl ester (1.839 g, 14.3 mmol, 72%) as a colorless oil.

To a 0 °C solution of *i*-Pr_2NH (2.0 mL, 14.5 mmol) in THF (15 mL) was added a hexane solution of *n*-BuLi (1.62 M, 6.8 mL, 11 mmol) dropwise. The reaction mixture was stirred for 20 min and then cooled to –78 °C. The methyl ester (1.282 g, 10 mmol) was added dropwise and the reaction mixture was stirred for 1 h at –78 °C. Allylbromide (1.3 mL, 15 mmol) was then added dropwise into the mixture. It was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched by addition of 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 methyl ester (1.009 g, 6.0 mmol, 60%) as a colorless oil.

To a slurry of $LiAlH_4$ (342 mg, 9 mmol) in Et_2O (10 mL) was added a solution of the methyl ester (1.001g, 6 mmol) in Et_2O (6 mL) dropwise at 0 °C. After stirred for 2 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 solvents were removed by evaporation under reduced pressure to obtain the alcohol (789 mg, 5.6 mmol, 94%) with acceptable purity. **4e** was then synthesized by bromination with CBr4/PPh3 reagents according to the same procedure described for **4d** (224 mg, 1.1 mmol, 22%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.49–1.69 (m, 8H), 2.23 (dt, *J* = 1.1, 6.7 Hz, 2H), 3.37 (s, 2H), 5.76 (ddt, *J* = 7.7, 10.2, 17.6 Hz, 2H), 5.70–5.81 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 25.0 (CH_2), 36.2 (CH_2), 42.1 (CH_2), 44.1 (CH_2), 46.6 (*C*), 118.0 (CH_2), 134.6 (*C*H). HRMS–EI (*m*/*z*): $[M–C_3H_6]^+$ calcd for C_6H_9Br, 159.98875; found, 159.98845.

Preparation of 1-allyl-1-(bromomethyl)cyclohexane (4f).

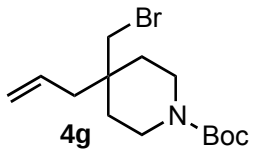


4f

4f was prepared from the corresponding methyl ester according to the procedure described above.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.36–1.48 (m, 10H), 2.16 (d, *J* = 7.7 Hz, 2H), 3.37 (s, 2H), 5.09–5.16 (m, 2H), 5.75 (ddt, *J* = 7.7, 10.2, 17.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 21.5 (CH_2), 26.0 (CH_2), 33.9 (CH_2), 36.7 (*C*), 40.1 (CH_2), 43.8 (CH_2), 118.2 (CH_2), 133.5 (*C*H). HRMS–EI (*m*/*z*): $[M–C_3H_5]^+$ calcd for $C_7H_{12}Br$, 175.01223; found, 175.01211. Anal. Calcd for $C_{10}H_{17}Br$: C, 55.31; H, 7.89. Found: C, 55.09; H, 7.87.

Preparation of *tert*-butyl 4-allyl-4-(bromomethyl)piperidine -1-carboxylate (4g).

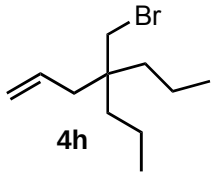


4g

4g was prepared from the corresponding methyl ester according to the procedure described above.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.46 (s, 9H), 1.48–1.56 (m, 4H), 2.23 (d, *J* = 7.8 Hz, 2H), 3.29–3.51 (m, 6H), 5.12–5.19 (m, 2H), 5.66–5.78 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 28.4 (CH_3), 33.2 (CH_2), 35.5 (*C*), 39.0 (CH_2), 41.9 (CH_2), 79.5 (*C*), 119.2 (CH_2), 132.4 (*C*H), 154.8 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{24}BrNO_2Na$, 340.08826; found, 340.08825.

Preparation of 4-(bromomethyl)-4-propylhept-1-ene (4h).

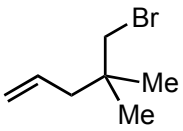


4h

4h was prepared from the corresponding methyl ester according to the procedure described above.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.87–0.93 (m, 6H), 1.18–1.30 (m, 8H), 2.07 (dt, *J* = 1.1, 7.7 Hz, 2H), 3.27 (s, 2H), 5.72 (ddt, *J* = 7.6, 10.2, 17.6 Hz, 2H), 5.67–5.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.7 (CH_3), 16.3 (CH_2), 37.1 (CH_2), 39.4 (CH_2), 39.5 (*C*), 42.4 (CH_2), 118.1 (CH_2), 133.7 (*C*H). HRMS–EI (*m*/*z*): $[M–C_3H_5]^+$ calcd for $C_8H_{16}Br$, 191.04353; found, 191.04340.

Preparation of 5-bromo-4,4-dimethylpent-1-ene (4i).

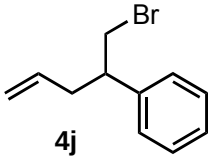


4i

4i was prepared from the corresponding methyl ester according to the procedure described above.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.02 (s, 6H), 2.10 (d, *J* = 7.7 Hz, 2H), 3.28 (s, 2H), 5.07–5.12 (m, 2H), 5.72–5.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 25.6 (CH_3), 34.8 (*C*), 44.1 (CH_2), 46.2 (CH_2), 118.1 (CH_2), 134.1 (*C*H). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_7H_{13}Br$, 176.02006; found, 176.01966.

Preparation of (1-bromopent-4-en-2-yl)benzene (4j).

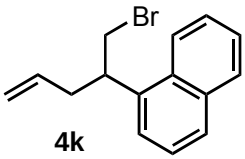


4j

4j was prepared from the corresponding methyl ester according to the procedure described above.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.42–2.50 (m, 1H), 2.61–2.68 (m, 1H), 3.02–3.09 (m, 1H), 3.56–3.64 (m, 2H), 4.98–5.08 (m, 2H), 5.65 (ddt, *J* = 7.2, 10.3, 17.5 Hz, 1H), 7.18–7.36 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 38.0 (CH_2), 38.3 (CH_2), 47.4 (*C*H), 117.2 (CH_2), 127.0 (*C*H), 127.6 (*C*H), 128.4 (*C*H), 135.3 (*C*H), 141.7 (*C*). HRMS–EI (*m*/*z*): $[M–C_3H_5]^+$ calcd for C_8H_8Br, 182.98093; found, 182.98085. Anal. Calcd for $C_{11}H_{13}Br$: C, 58.69; H, 5.82. Found: C, 58.42; H, 5.83.

Preparation of 1-(1-bromopent-4-en-2-yl)naphthalene (4k).



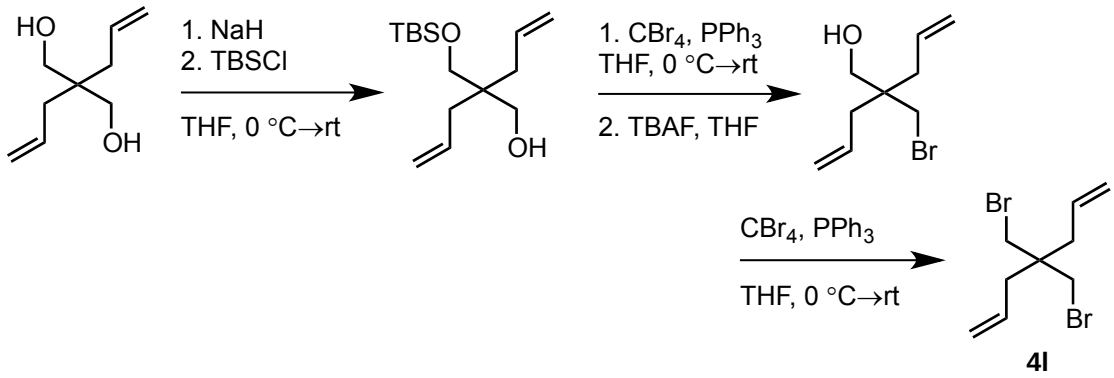
4k

4k was prepared from the corresponding methyl ester according to the procedure described above.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.63–2.71 (m, 1H), 2.81–2.89 (m, 1H), 3.68–3.78 (m, 2H), 3.99 (quin, *J* = 7.7 Hz, 1H), 4.98–5.14 (m, 2H), 5.69 (ddt, *J* = 7.1, 10.3, 17.4 Hz, 1H), 7.37 (dd, *J* = 0.7, 7.3 Hz, 1H), 7.45–7.57 (m, 3H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.87–7.89 (m, 1H), 8.06 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 37.5 (CH_2), 37.6 (CH_2), 41.0 (*C*H), 117.4 (CH_2), 122.6 (*C*H), 123.8 (*C*H), 125.2 (*C*H), 125.5 (*C*H), 126.3 (*C*H), 127.5 (*C*H), 129.1 (*C*H), 131.6 (*C*),

134.0 (*C*), 135.2 (*C*H), 137.3 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{15}Br$, 274.03571; found, 274.03529. Anal. Calcd for $C_{15}H_{15}Br$: C, 65.47; H, 5.49. Found: C, 65.47; H, 5.54.

Preparation of 4,4-bis(bromomethyl)hepta-1,6-diene (4l).

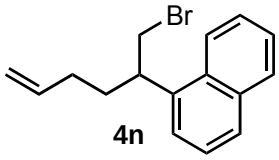


The starting material, (2,2-diallylpropane-1,3-diol), was prepared by $LiAlH_4$ reduction of the diethyl diallylmalonate. To a suspension of NaH (60wt.%, 400 mg, 10 mmol) in THF (20 mL) was added dropwise the diol (1.562 g, 10 mmol) at room temperature, TBSCl (1.73 mL, 10 mmol) was then added and the reaction mixture was stirred for 6 h. The resulting suspension was diluted with ether and quenched with saturated aqueous Na_2CO_3. The mixture was extracted with Et_2O three times and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the silyl protected product (2.587 g, 9.6 mmol, 96%) as a colorless oil. The monobromo compound was synthesized by bromination with CBr_4/PPh_3 reagents. The TBS group was then removed with TBAF (1.0 M in THF) to obtain the alcohol (701 mg, 3.2 mmol, 32%, 2 step) as a colorless oil. **4l** was also prepared by bromination of the alcohol with CBr4/PPh3 reagents according to the same procedure described above (279 mg, 1.0 mmol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.19 (d, *J* = 7.7 Hz, 4H), 3.38 (s, 4H), 5.18–5.26 (m, 4H), 5.75 (ddt, *J* = 7.6, 10.0, 17.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 37.0 (CH_2), 39.2 (CH_2), 41.1 (*C*), 119.9 (CH_2), 132.0 (*C*H). HRMS–EI (*m*/*z*): [M–

$CH_2Br]^+$ calcd for $C_8H_{12}Br$, 187.01223; found, 187.01154. Anal. Calcd for $C_9H_{14}Br_2$: C, 38.33; H, 5.00. Found: C, 38.06; H, 4.89.

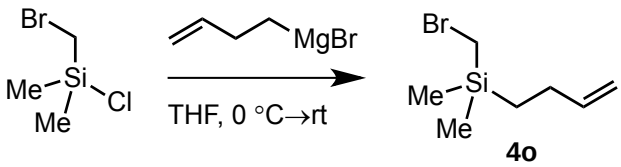
Preparation of 1-(1-bromohex-5-en-2-yl)naphthalene (4n).



4n was prepared from the corresponding methyl ester according to the procedure described above.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.92–2.05 (m, 3H), 2.20–2.31 (m, 1H), 3.61–3.72 (m, 2H), 3.92 (brs, 1H), 4.90–4.97 (m, 2H), 5.72–5.83 (m, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.46–7.56 (m, 3H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.86–7.89 (m, 1H), 8.07 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 31.1 (CH_2), 32.6 (CH_2), 38.5 (CH_2), 40.6 (*C*H), 115.1 (CH_2), 122.6 (*C*H), 123.4 (*C*H), 125.3 (*C*H), 125.5 (*C*H), 126.1 (*C*H), 127.5 (*C*H), 129.0 (*C*H), 131.9 (*C*), 133.9 (*C*), 137.8 (*C*H), 137.8 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{17}Br$, 288.05136; found, 288.05068. Anal. Calcd for $C_{16}H_{17}Br$: C, 66.45; H, 5.92. Found: C, 66.26; H, 5.94.

Preparation of (bromomethyl)(but-3-en-1-yl)dimethylsilane (4o).

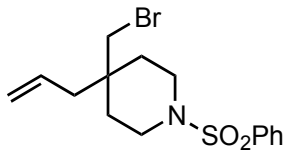


In a vacuum dried 100 mL of a round bottomed flask, (bromomethyl)chlorodimethylsilane (1.364 ml, 10 mmol) was dissolved in dry Et_2O (10 mL) and was cooled to 0 °C under nitrogen atmosphere. A Et_2O solution of homoallyl magnesium bromide (1.3 M, 10 mL, 13 mmol) was then added dropwise for 10 min. After stirred overnight, the reaction mixture was quenched by addition of 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. Because the purity of the product was not enough even after the flash column chromatography, the product was then subjected to a recycle gel permeation chromatography to obtain the pure homoallylsilane **4o** (255 mg, 1.2 mmol, 12%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.14 (s, 6H), 0.74–0.80 (m, 2H), 2.07–2.14 (m, 2H), 2.48 (s, 2H), 4.92 (dq, *J* = 1.6, 10.3 Hz, 1H), 5.02 (dq, *J* = 1.8, 17.4 Hz, 1H), 5.87 (ddt, *J* = 6.5, 10.5, 17.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –4.0 (CH_3), 13.2 (CH_2), 17.0 (CH_2), 27.6 (CH_2), 113.2 (CH_2), 140.9 (CH). HRMS–EI (*m*/*z*): $[M–C_4H_7]^+$ calcd for C_3H_8BrSi, 150.95786; found, 150.95753. Anal. Calcd for $C_7H_{15}BrSi$: C, 40.58; H, 7.30. Found: C, 40.44; H, 7.17.

Preparation of 4-allyl-4-(bromomethyl)-1-(phenylsulfonyl)piperidine (4r).

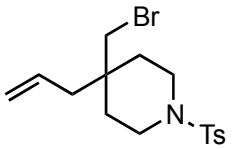


4r

4r was prepared from the corresponding methyl ester according to the procedure described above.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.60–1.71 (m, 4H), 2.08 (d, *J* = 7.7 Hz, 2H), 2.98–3.09 (m, 4H), 3.22 (s, 2H), 5.07–5.14 (m, 2H), 5.64 (ddt, *J* = 7.6, 10.2, 17.9 Hz, 1H), 7.54–7.58 (m, 2H) 7.61–7.65 (m, 1H) 7.76–7.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 32.5 (CH_2), 34.7 (C), 38.9 (CH_2), 41.0 (CH_2), 41.6 (CH_2), 119.3 (CH_2), 127.3 (CH), 129.0 (CH), 131.7 (CH), 132.7 (CH), 135.9 (C). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{20}BrNO_2SNa$, 380.02903; found, 380.02911.

Preparation of 4-allyl-4-(bromomethyl)-1-tosylpiperidine (4s).

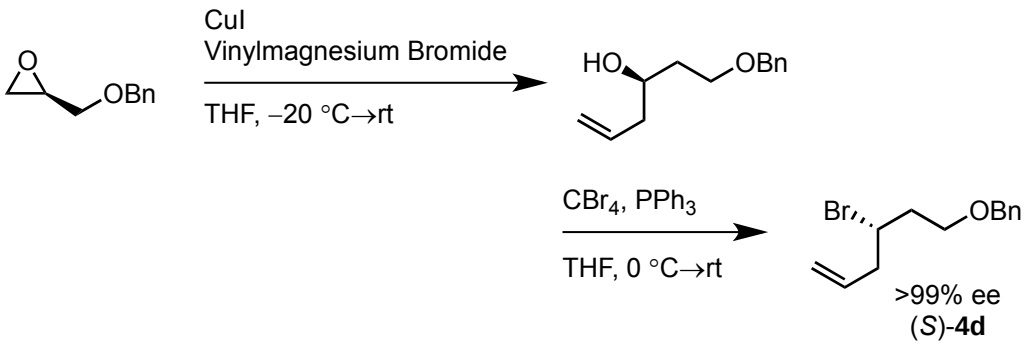


4s

4g was prepared from the corresponding methyl ester according to the procedure described above.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.60–1.71 (m, 4H), 2.08 (d, *J* = 7.8 Hz, 2H), 2.45 (s, 4H), 2.94–3.07 (m, 4H), 3.22 (s, 1H), 5.07–5.14 (m, 2H), 5.65 (ddt, *J* = 7.5, 10.0, 17.3 Hz, 1H), 7.34 (d, *J* =8.2 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 21.5 (CH_3), 32.6 (CH_2), 34.8 (*C*), 39.1 (CH_2), 41.0 (CH_2), 41.7 (CH_2), 119.4 (CH_2), 127.5 (*C*H), 129.7 (*C*H), 131.9 (*C*H), 132.9 (*C*), 143.6 (*C*). HRMS–EI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{22}BrNO_2SNa$, 394.04523; found, 394.04481.

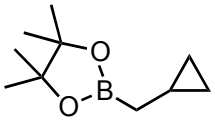
Preparation of optically active (*S*)-{[(2-bromopent-4-en-1-yl)oxy]methyl}benzene [(*S*)-4d].



(*S*)-**4d** was prepared from the corresponding (*R*)-benzyl glycidyl ether according to the procedure described above. The enantiomeric purity was determined by HPLC analysis on a chiral phase of a *p*-nitorobenzoate derivative of the alcohol obtained by Pd/C catalyzed hydrogenation of (*S*)-**4d** (Daicel CHIRALPAK® OJ-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C). (*R*)-**4d**: tR = 29.29 min, (*S*)-**4d**: tR = 31.28 min. $[\alpha]_D^{25.0}$ –7.70 (deg cm^3 g^{-1} dm^{-1}) (*c* 1.0 in CHCl3).

Characterization of Borylation Products.

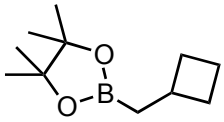
2-(Cyclopropylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5a).



5a

^{1}H NMR (400 MHz, $CDCl_3$, δ): –0.01–0.03 (m, 2H), 0.40–0.45 (m, 2H), 0.74–0.78 (m, 3H), 1.23 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 5.7 (CH_2), 5.9 (*C*H), 16.0 (br, B–CH_2), 24.8 (CH_3), 82.9 (*C*). HRMS–EI (*m*/*z*): $[M–CH_3]^+$ calcd for $C_9H_{16}BO_2$, 167.12433; found, 167.12411.

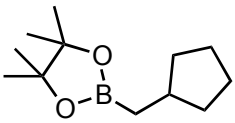
2-(Cyclobutylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5b).



5b

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.94 (d, *J* = 7.8 Hz, 2H), 1.23 (s, 12H), 1.54–1.64 (m, 2H), 1.72–1.85 (m, 2H), 2.04–2.11 (m, 2H), 2.47 (sep, *J*= 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 18.3 (CH_2), 20.0 (br, B–CH_2), 24.8 (CH_3), 30.8 (CH_2), 32.4 (*C*H), 82.8 (*C*). HRMS–EI (*m*/*z*): $[M–CH_3]^+$ calcd for $C_{10}H_{17}BO_2$, 181.14017; found, 181.13968.

2-(Cyclopentylmethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5m).

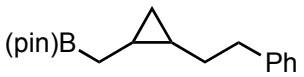


5m

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.84 (d, *J* = 7.3 Hz, 2H), 1.01–1.11 (m, 2H), 1.25 (s, 12H), 1.47–1.65 (m, 4H), 1.74–1.82 (m, 2H), 1.89–2.02 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.8 (CH_3), 25.1 (CH_2), 35.0 (CH_2), 36.1 (*C*H), 82.8 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (*m*/*z*): $[M–CH_3]^+$ calcd for $C_{10}H_{20}BO_2$, 195.15563; found, 196.15926. Anal. Calcd for $C_{12}H_{23}BO_2$: C, 68.59; H, 11.03.

Found: C, 68.63; H, 11.12.

4,4,5,5-Tetramethyl-2-[(2-phenethylcyclopropyl)methyl)]-1,3,2-dioxaborolane (5c).

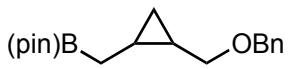


5c

The product (**5c**) was obtained as a diastereomeric mixture (1:1). The stereoselectivity was determined by ^{1}H NMR analysis of the alcohol derived from H_2O_2/NaOH oxidation of **5c.**

^{1}H NMR (400 MHz, $CDCl_3$, δ): –0.29 (q, *J* = 4.9 Hz, 0.5H), 0.17–0.27 (m, 1H), 0.42–0.57 (m, 1H), 0.61–0.90 (m, 3.5H), 1.26 (s, 12H), 1.40–1.68 (m, 2H), 2.68–2.73 (m, 2H), 7.14–7.29 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 9.8 (br, B–CH_2), 10.7 (*C*H), 11.9 (*C*H_2), 13.1 (*C*H_2), 13.8 (*C*H), 15.4 (*C*H), 15.7 (br, B–*C*H_2), 19.6 (*C*H), 24.7 (*C*H_3), 30.8 (*C*H_2), 35.9 (*C*H_2), 36.2 (*C*H), 36.5 (*C*H_2), 82.8 (*C*), 82.9 (*C*), 125.39 (*C*H), 125.42 (*C*H), 128.1 (*C*H), 128.33 (*C*H), 128.35 (*C*H), 142.71 (*C*), 142.73 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{27}BO_2$, 286.21041; found, 286.21040.

2-({2-[(Benzyloxy)methyl]cyclopropyl}methyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5d).



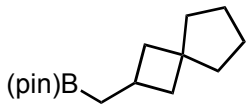
5d

The product (**5d**) was obtained as a diastereomeric mixture (1:1). The stereoselectivity was determined by GC analysis of the crude reaction mixture.

^{1}H NMR (400 MHz, $CDCl_3$, δ): –0.1 (q, *J* = 5.3 Hz, 0.5H), 0.31–0.42 (m, 1H), 0.66–1.13 (m, 4.5H), 1.24 (s, 12H), 3.23–3.52 (m, 2H), 4.49–4.56 (m, 2H), 7.24–7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 10.7 (*C*H), 10.9 (*C*H), 11.5 (*C*H_2), 12.3 (*C*H), 15.2 (*C*H), 19.3 (*C*H), 24.69 (*C*H_3), 24.73 (*C*H_3), 70.5 (*C*H_2), 72.2 (*C*H_2), 72.6 (*C*H_2), 74.3 (*C*H_2), 83.0 (*C*), 127.3 (*C*H), 127.4 (*C*H), 127.6 (*C*H),

127.7 (*C*H), 128.2 (*C*H), 138.6 (*C*), 138.7 (*C*). HRMS–EI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{27}BO_3Na$, 325.19510; found, 325.19433. Anal. Calcd for $C_{18}H_{27}BO_2$: C, 71.54; H, 9.00. Found: C, 71.56; H, 9.26.

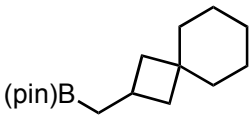
4,4,5,5-Tetramethyl-2-(spiro[3.4]octan-2-ylmethyl)-1,3,2-dioxaborolane (5e).



5e

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.93 (d, *J* = 7.3 Hz, 2H), 1.23 (s, 12H), 1.46–1.61 (m, 10H), 1.99 (dt, *J* = 2.8, 8.8 Hz, 2H), 2.35 (sep, *J*= 8.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 20.0 (br, B–CH_2), 23.6 (CH_2), 23.9 (CH_2), 24.7 (CH_3), 25.9 (*C*H), 39.1 (CH_2), 40.5 (CH_2), 42.2 (CH_2), 42.4 (*C*), 82.7 (*C*). HRMS–EI (*m*/*z*): $[M–CH_3]^+$ calcd for $C_{15}H_{24}BO_2$, 235.18720; found, 235.18696. Anal. Calcd for $C_{15}H_{27}BO_2$: C, 72.01; H, 10.88. Found: C, 71.78; H, 11.00.

4,4,5,5-Tetramethyl-2-(spiro[3.5]nonan-2-ylmethyl)-1,3,2-dioxaborolane (5f).

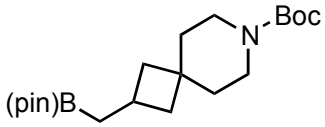


5f

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.93 (d, *J* = 8.1 Hz, 2H), 1.23 (s, 12H), 1.27–1.45 (m, 12H), 1.93 (dt, *J* = 2.6, 8.8 Hz, 2H), 2.34 (sep, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 20.4 (br, B–CH_2), 22.8 (CH_2), 23.0 (CH_2), 24.7 (CH_3), 25.0 (*C*H), 26.1 (CH_2), 35.4 (*C*), 37.1 (CH_2), 41.0 (CH_2), 41.2 (CH_2), 82.7 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{29}BO_2$, 264.22606; found, 264.22586. Anal. Calcd for $C_{16}H_{29}BO_2$: C, 72.73; H, 11.06. Found: C, 72.46; H, 11.12.

7-(phenylsulfonyl)-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-7

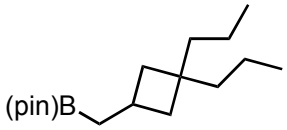
azaspiro[3.5]nonane (5g).



5g

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.96 (d, *J* = 8.0 Hz, 2H), 1.23 (s, 12H), 1.34–1.41 (m, 4H), 1.44 (s, 9H), 1.54 (t, *J* = 5.1 Hz, 2H), 1.98–2.03 (m, 2H), 2.41 (sep, *J* = 8.4 Hz, 1H), 2.87 (t, *J* = 5.7 Hz, 2H), 2.96 (t, *J* = 5.7 Hz, 2H), 7.50–7.54 (m, 2H) 7.57–7.61 (m, 1H) 7.74–7.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 20.0 (br, B–CH_2), 24.8 (CH_3), 25.0 (*C*H), 28/4 (CH_3), 33.7 (*C*), 36.1 (CH_2), 39.7 (CH_2), 40.2 (CH_2), 79.0 (*C*), 82.9 (*C*) 155.0 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{36}BNO_4Na$, 388.26296; found, 388.26309.

2-[(3,3-Dipropylcyclobutyl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5h).

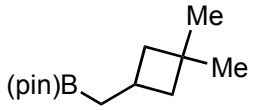


5h

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.83–0.93 (m, 8H), 1.06–1.41 (m, 10H), 1.23 (s, 12H), 1.86–1.92 (m, 2H), 2.34 (sep, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.8 (CH_3), 14.9 (CH_3), 17.0 (CH_2), 17.3 (CH_2), 20.3 (br, B–CH_2), 24.7 (CH_3), 25.0 (*C*H), 37.2 (*C*), 39.9 (CH_2), 40.8 (CH_2), 43.2 (CH_2), 82.7 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{17}H_{33}BO_2$, 280.25736; found, 264.25722. Anal. Calcd for $C_{17}H_{33}BO_2$: C, 72.86; H, 11.87. Found: C, 72.82; H, 11.98.

2-[(3,3-Dimethylcyclobutyl)methyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

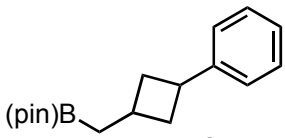
(5i).



5i

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.92 (d, *J* = 8.0 Hz, 2H), 1.02 (s, 3H), 1.10 (s, 3H), 1.23 (s, 12H), 1.40 (dt, *J* = 2.6, 9.3 Hz, 2H), 1.90 (dt, *J* = 2.7, 9.0 Hz, 2H), 2.37 (sep, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 20.0 (br, B–CH_2), 24.5 (*C*H), 24.8 (*C*H_3), 28.5 (*C*H_3), 31.3 (*C*H_3), 43.4 (*C*H_2), 82.7 (*C*). HRMS–EI (*m*/*z*): [M–CH_3]$^+$ calcd for $C_{12}H_{22}BO_2$, 209.17151; found, 209.17127.

4,4,5,5-Tetramethyl-2-((3-phenylcyclobutyl)methyl)-1,3,2-dioxaborolane (5j).



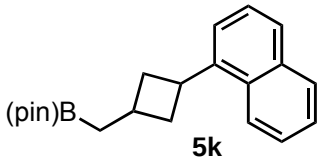
5j

The product (**5j**) was obtained as a diastereomeric mixture (1.3:1). The stereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.98 (d, *J* = 7.7 Hz, 2H), 1.16 (d, *J* = 8.1 Hz, 2H), 1.24 (s, 12H), 1.25 (s, 24H), 1.69–1.78 (m, 2H), 2.04–2.10 (m, 2H), 2.31–2.59 (m, 6H), 3.24–3.34 (m, 1H), 3.62 (quin, *J* = 8.3 Hz, 1H), 7.13–7.32 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.0 (br, B–CH_2), 24.5 (*C*H_3), 24.7 (*C*H_3), 27.4 (*C*H), 28.0 (*C*H), 35.9 (*C*H), 36.35 (*C*H), 36.41 (*C*H_2), 82.77 (*C*), 82.80 (*C*), 125.36 (*C*H), 125.44 (*C*H), 126.3 (*C*H), 128.0 (*C*H), 128.1 (*C*H), 146.0 (*C*), 146.6 (*C*). HRMS–EI (*m*/*z*): [M–CH_3]$^+$ calcd for $C_{16}H_{22}BO_2$, 257.17128; found, 257.17105.

4,4,5,5-Tetramethyl-2-{[3-(naphthalen-1-yl)cyclobutyl]methyl}-1,3,2-dioxabo

rolane (5k).

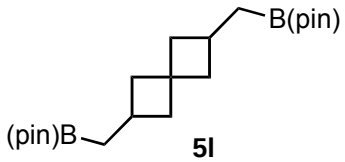


5k

The product (**5k)** was obtained as a diastereomeric mixture (1.4:1). The stereoselectivity was determined by GC analysis of the crude reaction mixture.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.99 (d, *J* = 7.7 Hz, 2H), 1.22–1.27 (m, 2H), 1.23 (s, 12H), 1.25 (s, 12H), 1.84–1.92 (m, 2H), 2.22–2.28 (m, 2H), 2.46–2.65 (m, 5H), 2.71–2.78 (m, 1H), 3.84–3.93 (m, 1H), 4.23 (quint, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.40–7.51 (m, 8H), 7.67–7.71 (m, 2H), 7.81–7.91 (m, 3H), 7.97–8.00 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.0 (br, B–CH_2), 24.7 (CH_3), 27.7 (*C*H), 28.5 (*C*H), 33.3 (*C*H), 34.1 (*C*H), 35.4 (CH_2), 37.7 (CH_2), 82.78 (*C*), 82.82 (*C*), 121.9 (*C*H), 122.5 (*C*H), 124.15 (*C*H), 124.25 (*C*H), 125.2 (*C*H), 125.3 (*C*H), 125.4 (*C*H), 126.1 (*C*H), 126.2 (*C*H), 128.45 (*C*H), 128.54 (*C*H), 131.50 (*C*), 131.54 (*C*), 133.6 (*C*), 133.7 (*C*), 141.5 (*C*), 141.6 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{27}BO_2$, 322.21041; found, 322.21022.

2,6-Bis[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]spiro[3.3]heptan e (5l).

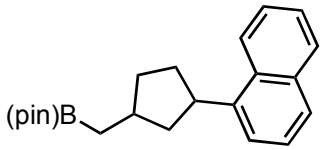


5l

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.88 (d, *J* = 7.7 Hz, 4H), 1.22 (s, 24H), 1.47–1.60 (m, 4H), 1.97–2.03 (m, 2H), 2.16–2.33 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.5 (br, B–CH_2), 24.7 (CH_3), 26.4 (*C*H), 35.8 (*C*), 43.3 (CH_2), 43.9 (CH_2), 82.7 (*C*). HRMS–EI (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{22}BO_2Na$, 399.28539; found, 399.28515.

4,4,5,5-Tetramethyl-2-{[3-(naphthalen-1-yl)cyclopentyl]methyl}-1,3,2-dioxab

orolane (5n).

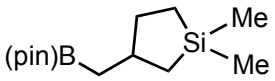


5n

The product (**5n)** was obtained as a diastereomeric mixture (1.1:1). The stereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.99–1.02 (m, 4H), 1.18–1.22 (m, 1H), 1.25 (s, 24H), 1.33–1.54 (m, 3H), 1.75–2.14 (m, 6H), 2.19–2.46 (m, 4H), 3.79–3.88 (m, 1H), 3.95 (quin, *J* = 8.2 Hz, 1H), 7.39–7.52 (m, 8H), 7.67–7.69 (m, 2H), 7.83–7.85 (m, 2H), 8.14 (t, *J* = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 18.5 (br, B–CH_2), 24.7 (CH_3), 33.1 (CH_2), 33.9 (*C*H), 34.1 (CH_2), 35.0 (*C*H), 35.4 (CH_2), 36.1 (*C*H), 39.7 (*C*H), 41.1 (*C*H), 42.0 (CH_2), 43.0 (CH_2), 82.8 (*C*), 121.9 (*C*H), 123.8 (*C*H), 124.0 (*C*H), 125.1 (*C*H), 125.36 (*C*H), 125.48 (*C*H), 125.52 (*C*H), 126.0 (*C*H), 126.1 (*C*H), 128.6 (*C*H), 132.0 (*C*), 132.1 (*C*), 133.8 (*C*), 142.2 (*C*), 142.7 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{29}BO_2$, 336.22606; found, 336.22559.

1,1-Dimethyl-3-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]silolan e (5o).

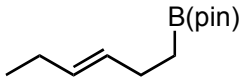


5o

This compound was obtained as a mixture with *endo*-cylization product (exo/endo 91:9).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.08 (s, 6H), 0.42–0.53 (m, 1H), 0.72 (ddd, *J* = 2.5, 7.1, 14.8 Hz, 1H), 0.81–0.93 (m, 3H), 0.99–1.10 (m, 1H), 1.25 (s, 12H), 1.76–1.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –1.23 (CH_3), –1.12 (CH_3), 13.2 (CH_2), 20.5 (br, B–CH_2), 23.0 (CH_2), 24.76 (CH_3), 24.79 (CH_3), 36.2 (CH_2), 37.1 (*C*H), 82.7 (*C*). HRMS–EI (*m*/*z*): $[M–CH_3]^+$ calcd for $C_{12}H_{24}BO_2Si$, 239.16386; found, 238.16649.

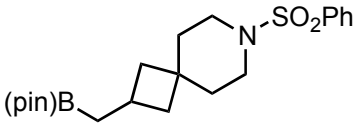
(*E*)-2-(hex-3-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6q)



6q

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.86 (t, *J* = 7.9 Hz, 2H), 0.95 (t, *J* = 7.7 Hz, 3H), 1.24 (s, 12H), 1.95–2.03 (m, 2H), 2.05–2.17 (m, 2H), 5.44 (dt, *J* = 2.56, 5.12 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 11.0 (br, B–CH_2), 14.0 (CH_3), 24.9 (CH_3), 25.6 (CH_2), 26.9 (CH_2), 83.0 (*C*), 130.9 (*C*H). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{23}BO_2$, 210.17934; found, 210.17924.

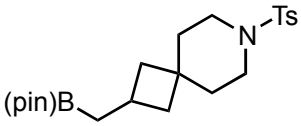
7-(phenylsulfonyl)-2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)-7 azaspiro[3.5]nonane (5r).



5r

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.89 (d, *J* = 7.7 Hz, 2H), 1.20 (s, 12H), 1.25–1.30 (m, 2H), 1.55–1.58 (m, 2H), 1.68 (t, *J* = 5.7 Hz, 2H), 1.85–1.90 (m, 2H), 2.34 (sep, *J* = 8.5 Hz, 1H), 2.87 (t, *J* = 2.9, 5.7 Hz, 2H), 2.96 (t, *J* = 3.0, 5.7 Hz, 2H), 7.50–7.54 (m, 2H), 7.57–7.61 (m, 1H), 7.74–7.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 21.0 (br, B–CH_2), 24.7 (CH_3), 24.8 (*C*H), 32.8 (*C*), 35.4 (CH_2), 38.8 (CH_2), 39.9 (CH_2), 43.0 (CH_2), 43.2 (CH_2), 82.8 (*C*), 127.5 (*C*H), 128.8 (*C*H), 132.5 (*C*H), 136.3 (*C*). HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{33}BNO_4S$, 406.22179; found, 406.22174.

2-[(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-7-tosyl-7-azaspiro[3. 5]nonane (5s).



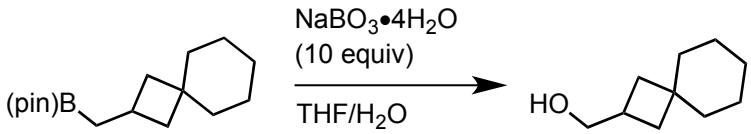
5s

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.89 (d, *J* = 7.7 Hz, 2H), 1.20 (s, 12H), 1.25–1.30 (m, 2H), 1.54–1.58 (m, 2H), 1.67 (t, *J* = 5.7 Hz, 2H), 1.85–1.90 (m, 2H), 2.33 (sep, *J* = 8.4 Hz, 1H), 2.43 (s, 3H), 2.86 (t, *J* = 5.5 Hz, 2H), 2.94 (t, *J* = 5.5 Hz, 2H),

7.31 (d, J = 8.0 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 19.9 (br, B–CH_2), 21.3 (*C*H), 24.6 (CH_3), 24.7 (CH_3), 32.7 (*C*), 35.3 (CH_2), 38.8 (CH_2), 39.8 (CH_2), 42.9 (CH_2), 43.1 (CH_2), 82.6 (*C*), 127.4 (*C*H), 129.4 (*C*H), 133.2 (*C*), 143.0 (*C*). HRMS–EI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{34}BNO_4SNa$, 442.21993; found, 442.21989.

Derivatization of Borylative Cyclization Products.

Experimental Procedure for the $NaBO_3$ Oxidation of 5f.



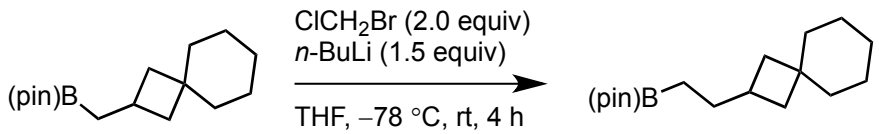
5f **7f**

The oxidation was performed according to the literature procedure.[24]

In a reaction vial, $NaBO_3$•$4H_2O$ (384.7 mg, 2.5 mmol) was dissolved in THF/H_2O (3:2, 5 mL). **5f** (66.1 mg, 0.25 mmol) was then added at room temperature. After stirred for 1.5 h, the reaction mixture was extracted three times with EtOAc, dried over $MgSO_4$, and filtered. The crude material was purified by flash column chromatography to obtain the corresponding alcohol **7f** (33.9 mg, 0.22 mmol, 88%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.19–1.58 (m, 12H), 1.81–1.86 (m, 2H), 2.40 (sep, J = 8.1 Hz, 1H), 3.58 (d, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 22.6 (CH_2), 22.8 (CH_2), 26.0 (CH_2), 30.5 (*C*H), 35.1 (CH_2), 35.7 (*C*), 37.7 (CH_2), 40.5 (CH_2), 68.4 (CH_2). HRMS–EI (*m*/*z*): $[M–OH_2]^+$ calcd for $C_{10}H_{16}$, 136.12520; found, 136.12493.

Experimental Procedure for the One Carbon-Homologation of 5f.



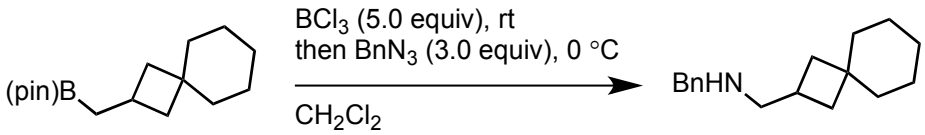
5f **8f**

The homologation was performed according to the literature procedure.[25]

In an oven-dried reaction vial, **5f** (66.2 mg, 0.25 mmol) and bromochloromethane (64.7 mg, 0.5 mmol) were dissolved in dry THF (2 mL). After the mixture was cooled to –78 °C, *n*-BuLi in hexane (1.64 M, 0.23 mL, 0.38 mmol) was added dropwise. The mixture was stirred at –78 °C for 10 min, and then stirred at room temperature for 4 h. The reaction was quenched with NH_4Cl aq., extracted three times with Et_2O, dried over $MgSO_4$, and filtered. The crude material was then purified by flash column chromatography to obtain the corresponding homologation product **8f** (62.7 mg, 0.225 mmol, 90%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.66 (t, *J* = 8.2 Hz, 2H), 1.22–1.49 (m, 14H), 1.24 (s, 12H), 1.80–1.85 (m, 2H), 2.06 (sep, *J* = 8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 9.0 (br, B–CH_2), 22.8 (CH_2), 23.0 (CH_2), 24.8 (CH_3), 26.1 (CH_2), 31.0 (CH_2), 32.1 (CH_2), 35.2 (*C*), 37.6 (CH_2), 38.5 (CH_2), 40.9 (CH_2), 82.8 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{17}H_{31}BO_2$, 278.24202; found, 278.24193.

Experimental Procedure for the Amination of 5f.



5f **9f**

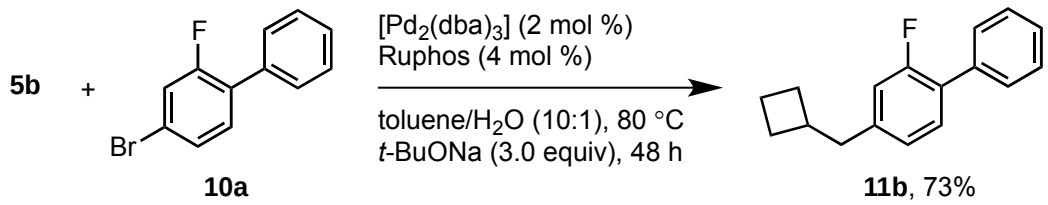
The amination was performed according to the literature procedure.[26]

In an oven-dried reaction vial, CH_2Cl_2 solution of BCl_3 (1.0 M, 1.25 mL, 1.25 mmol) was added under nitrogen atmosphere. **5f** (66.1 mg, 0.25 mmol) was added to the reaction vial with stirring at room temperature. After 4 h, the volatile materials were removed under reduced pressure, and dry CH_2Cl_2 (1.5

mL) was added to the resultant product. The reaction vial was cooled to 0 °C, and benzyl azide (100 mg, 0.75 mmol) was added to the mixture. After stirred for 16 h at 0 °C, the reaction mixture was quenched by adding aqueous NaOH (2.0 M), extracted three times with EtOAc, dried over Na_2SO_4, and filtered. The crude material was then purified by flash column chromatography to obtain the corresponding amine **9f** (36.5 mg, 0.15 mmol, 60%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.22–1.47 (m, 12H), 1.83–1.89 (m, 2H), 2.37 (sep, *J* = 8.2 Hz, 1H), 2.64 (d, *J* = 7.3 Hz, 2H), 3.77 (s, 2H), 7.22–7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 22.7 (CH_2), 22.8 (CH_2), 26.0 (CH_2), 28.6 (*C*H), 36.0 (*C*), 37.1 (CH_2), 37.5 (CH_2), 40.7 (CH_2), 54.0 (CH_2), 56.5 (CH_2), 126.9 (*C*H), 128.1 (*C*H), 128.3 (*C*H), 140.3 (*C*). HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{26}N$, 244.20598; found, 244.20593.

Procedure for the Suzuki-Miyaura Cross-Coupling Reaction of 5b between 4-Bromo-2-fluoro-1,1′-biphenyl (10a):



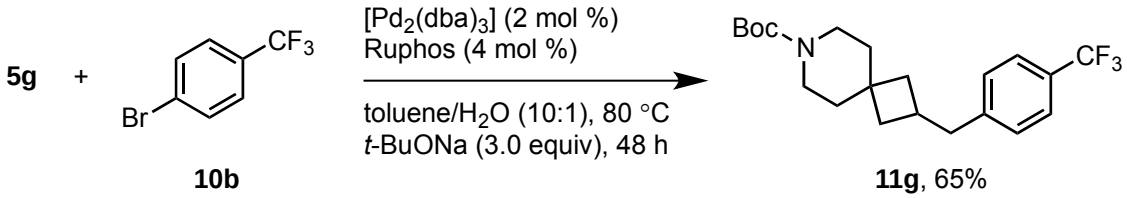
Suzuki-Miyaura cross-coupling reaction was performed according to the literature procedure.[27]

$Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), Na(O-*t*-Bu) (72 mg, 0.75 mmol), Ruphos (4.7 mg, 0.01 mmol), and 4-bromo-2-fluoro-1,1′-biphenyl (62.7 mg, 0.25 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. Toluene (0.5 mL) and H_2O (0.05 mL) and **5b** (58.8 mg, 0.30 mmol) were added in the vial through the rubber septum. The resulting mixture was stirred at 80 °C for 48 h. The reaction mixture was passed through a short silica gel

column eluting with Et_2O. The crude mixture was further purified by flash column chromatography to give the corresponding coupling product **11b** (43.1 mg, 73%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.70–1.79 (m, 2H), 1.82–1.94 (m, 2H), 2.04–2.12 (m, 2H), 2.59 (sep, *J* = 7.9 Hz, 1H), 2.72 (d, *J* = 7.8 Hz, 2H), 6.92–6.99 (m, 2H), 7.24–7.36 (m, 2H), 7.41–7.44 (m, 2H), 7.53–7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 18.3 (CH_2), 28.2 (CH_2), 36.9 (*C*H), 42.4 (CH_2), 115.9 (d, *J* = 22.0 Hz, *C*H), 124.5 (d, *J* = 2.8 Hz, *C*H), *126.2 (d, J = 13.4 Hz, C)*, 127.3 (*C*H), 128.4 (*C*H), 128.9 (d, *J* = 2.9 Hz, *C*H), 130.3 (d, *J* = 3.8 Hz, *C*H), 135.9 (*C*), 143.0 (d, *J* = 6.7 Hz, *C*), 159.6 (d, *J* = 248.1 Hz, *C*). ^{19}F NMR ($CDCl_3$, 372.5 MHz): –118.9. HRMS–ESI (*m*/*z*): $[M]^+$ calcd for $C_{17}H_{17}F_1$, 240.13143; found, 240.13090.

Procedure for the Suzuki-Miyaura Cross-Coupling Reaction of 5g between 1-Bromo-4-(trifluoromethyl)benzene (10b):



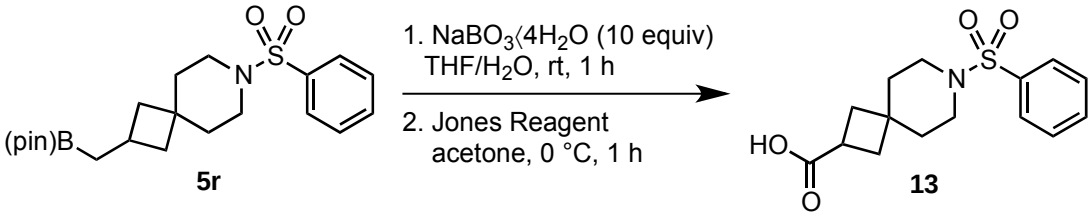
Suzuki-Miyaura cross-coupling reaction was performed according to the literature procedure with slight modification.[27]

$Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), Na(O-*t*-Bu) (72 mg, 0.75 mmol), Ruphos (4.7 mg, 0,01 mmol), and **5g** (91.3 mg, 0.25 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. Toluene (0.5 mL) and H_2O (0.05 mL) and bromo-4-(trifluoromethyl)benzene (**10b**) (112.5 mg, 0.5 mmol) were added in the vial through the rubber septum. The resulting mixture was stirred at 80 °C for 48 h. The reaction mixture was passed through a short silica gel column eluting with Et_2O. The crude

mixture was further purified by flash column chromatography to give the corresponding coupling product **11g** (62.3 mg, 65%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.44–1.60 (m, 15H), 1.93–1.98 (m, 2H), 2.52 (sep, *J* = 8.2 Hz, 1H), 2.77 (d, *J* = 7.7 Hz, 2H), 3.27 (t, *J* = 5.3 Hz, 2H) 3.32 (t, *J* = 5.3 Hz, 2H), 7.22–7.27 (m, 2H), 7.52 (d, J = 7.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 28.4 (CH_3), 30.0 (*C*H), 34.0 (*C*), 36.1 (CH_2), 37.8 (CH_2), 39.6 (CH_2), 40.5 (br, CH_2), 43.4 (CH_2), 79.2 (*C*), 125.1 (q, *J* = 3.5 Hz, *C*H), 128.7 (*C*H), 145.0 (*C*), 154.9 (*C*). ^{19}F NMR ($CDCl_3$, 372.5 MHz): –62.2. HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{28}O_2NF_3Na$, 406.19643; found, 406.19645.

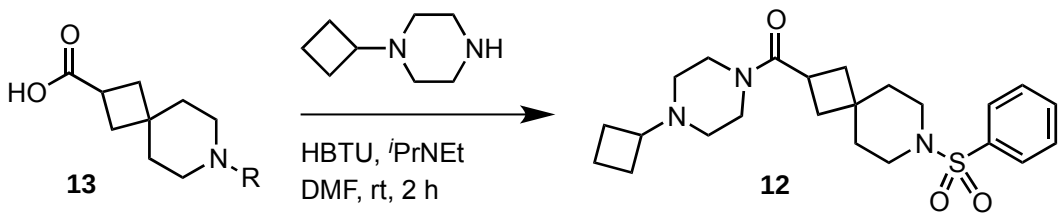
Preparation of 7-(phenylsulfonyl)-7-azaspiro[3.5]nonane-2-carboxylic acid (13).



In a reaction vial, $NaBO_3$•$4H_2O$ (769.3 mg, 5 mmol) and **5r** (202.4 mg, 0.5 mmol) was dissolved in THF/H_2O (3:2, 5 mL) at room temperature. After stirred for 1 h, the reaction mixture was extracted three times with Et_2O, dried over $MgSO_4$, and filtered. The crude material was purified by flash column chromatography to give the corresponding alcohol (128.6 mg) as a white solid. The obtained alcohol was subjected to the oxidation reaction using Jones reagent (ca. 2.5 M, 0.25 mL, 0.625 mmol) in acetone at 0 °C. After 1 h, the reaction was quenched by saturated aqueous NH_4Cl, extracted three times with Et_2O. The combined organic layer was washed with aqueous NaOH (0.1 M) and then aqueous layer was acidified with saturated aqueous NH_4Cl, extracted six times with Et_2O. The combined organic layer was dried over $MgSO_4$ followed by evaporation to obtain the corresponding carboxylic acid **13** (100.1 mg, 64%, 2 steps) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.67 (t, *J* = 5.9 Hz, 2H), 1.71 (t, *J* = 5.7 Hz, 2H), 1.97 (d, *J* = 8.8 Hz, 4H), 2.91 (t, *J* = 5.7 Hz, 2H), 2.97 (t, *J* = 5.7 Hz, 2H), 3.32 (quint, *J* = 8.9 Hz, 1H), 7.51–7.55 (m, 2H), 7.58–7.62 (m, 1H) 7.74–7.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 31.4 (*C*H), 33.5 (*C*), 34.1 (CH_2), 35.6 (CH_2), 37.2 (CH_2), 42.6 (CH_2), 42.9 (CH_2), 127.4 (*C*H), 128.9 (*C*H), 132.7 (*C*H), 136.0 (*C*), 181.8 (*C*). HRMS–ESI (*m*/*z*): $[M–H]^+$ calcd for $C_{15}H_{18}NO_4S$, 308.09620; found, 308.09676.

Preparation of (4-cyclobutylpiperazin-1-yl)(7-(phenylsulfonyl)-7-azaspiro[3.5]nonan-2-yl)methanone (12).



The condensation was performed according to the literature procedure.[28]

In a vacuum dried 20 mL of a round bottomed flask, carboxylic acid (61.8 mg, 0.2 mmol) and *N*,*N*-diisopropylethylamine (DIEA) (41 μL) were dissolved in DMF (3 mL) under nitrogen atmosphere. A solution of *O*-benzotriazole-*N*,*N*,*N′*,*N′*-tetramethyluronium hexafluorophosphate (HBTU) (83.4 mg, 0.22 mmol) and 1-cyclobutylpiperazine (28.1 mg, 0.2 mmol) in DMF (3 mL) was then added dropwise. After stirred for 2 h at room temperature, the solvent was removed under reduced pressure. The crude product was then purified by flash column chromatography to obtain the corresponding condensation product **12** (78.4 mg, 91%) as a white solid. ^{1}H NMR was in agreement with those in the literature.[29] ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.62–1.76 (m, 6H), 1.80–1.90 (m, 4H), 1.99–2.04 (m, 4H), 2.24 (dt, *J* = 5.7, 11.7 Hz, 4H), 2.68 (quint, *J* = 8.0 Hz, 1 H), 2.91 (t, *J* = 5.3 Hz, 2 H), 2.98 (t, *J* = 5.1 Hz, 2 H), 3.10 (quint, *J* = 8.8 Hz, 1 H), 3.29 (t, *J* = 4.9 Hz, 2H), 3.59 (t, *J* = 4.8 Hz, 2H), 7.52–7.56 (m, 2H), 7.59–7.63 (m, 1H), 7.74–7.76 (m, 2H).

Determination of Absolute Configuration of *trans*-5d and *cis*-5d.

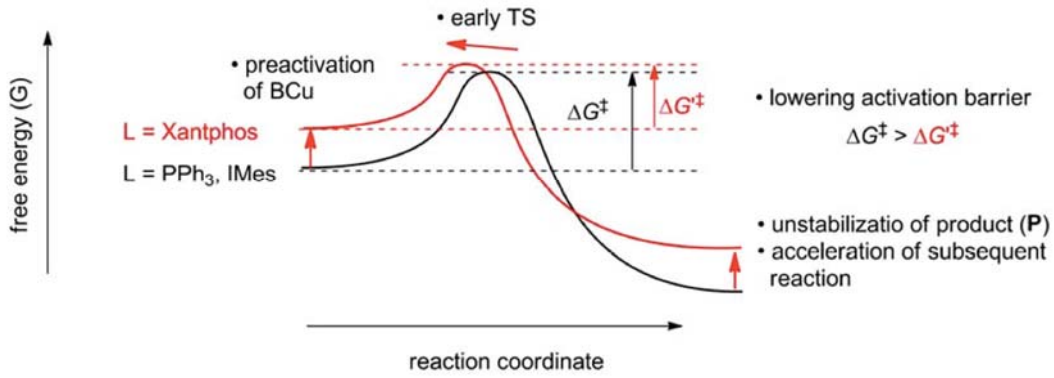
The absolute configuration of *trans*-**5d** and *cis*-**5d** were determined by comparing the optical rotation of the cyclopropylmethyl alcohol obtained by H_2O_2 oxidation.[7] The ee values were determined by HPLC analysis (Daicel CHIRALPAK® OJ-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C). (*S*,*S*)-**7d**: tR = 36.71 min., (*R*,*R*)-**7d**: tR = 40.92 min, (*R*,*S*)-**7d**: tR = 23.17 min., (*S*,*R*)-**7d**: tR = 25.43 min. (*S*,*S*)-**7d**: $[\alpha]_D^{25.1}$ +10.56 (deg cm^3 g^{-1} dm^{-1}) (*c* 0.9 in CHCl3), (*R*,*S*)-**7d**: $[\alpha]_D^{23.9}$ –38.75 (deg cm^3 g^{-1} dm^{-1}) (*c* 0.8 in $CHCl_3$).

Details of DFT calculations

All calculations were performed with the Gaussian 09W (revision C.01) program package.[30] Geometry optimizations were performed with B3PW91/cc-pVDZ in the gas-phase. Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) ligand was modeled by 4,5-bis(diphenylphosphino)-9,9-xanthene. Molecular orbitals were drawn by the GaussView 5.0 program. Frequency calculations were conducted on gas-phase optimized geometries to check the all the stationary points as either minima or transition states. Fragment distortion and interaction energies were calculated with B3PW91/cc-pVDZ in the gas-phase.

To understand the ligand effect observed in the borylative *exo*-cyclization reaction, the author conducted distortion/interaction analysis and structure change analysis of stationary points. Comparison of the calculation results of ligands indicate that the low activation barrier for the reaction with Xantphos is due to the preactivation effect on the starting borylcopper(I)/Xantphos complex as summarized in Figure S1.

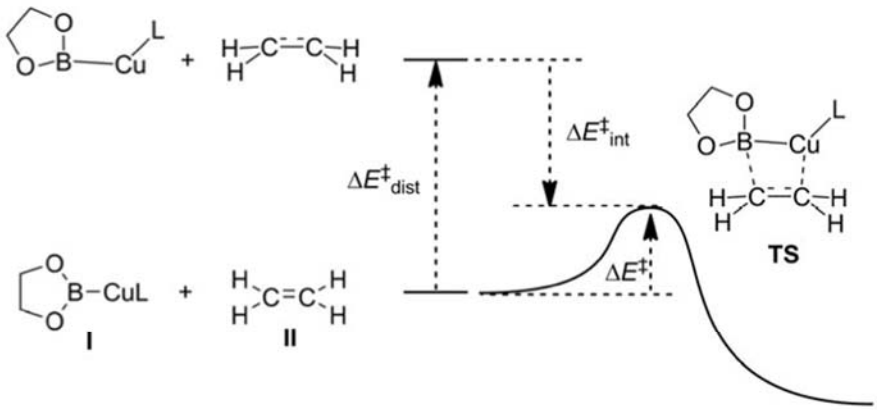
Figure S1. Summary of Ligand Effect of Xantphos on the Energy Profile in Addition of Borylcopper(I) to Alkene



Distortion/Interaction Analysis

The distortion/interaction analysis for the transition states in addition reaction of borylcopper(I) to ethylene indicated the preactivation nature of the Xantphos ligated borylcopper(I) complex. The energies to deform the isolated reactants to the transition geometry ($E^{\ddagger}_{dist}$) and the energy of interaction between these deformed reactants are summarized in Table S1. The -complex (**III**) was omitted because G_{III} values (complexation) were positive. The deformation energy for borylcopper(I) complex [$E^{\ddagger}_{dist}$ (Cu–B)] with Xantphos ligand (11.7 kcal/mol) is significantly smaller than those of PPh_3 and IMes (16.2 and 18.6 kcal/mol, respectively). The deformation energy for ethylene [$E^{\ddagger}_{dist}$ ($H_2C{=}CH_2$)] shows smaller difference. The interaction energy ($E^{\ddagger}_{int}$) of Xantphos complex (–38.8 kcal/mol) is largely smaller than those of PPh_3 and IMes (–44.8 and –49.1 kcal/mol, respectively). This analysis indicates that a major factor for the low activation barrier of Xantphos complex at the addition transition state is attributable to the preactivation nature of borylcopper(I)/Xantphos complex and the resultant early transition state. In other words, Xantphos ligand make the borylcopper(I) complex more close to the TS.

Table S2. Distortion/Interaction Analysis for Addtion TS



	energy difference (kcal/mol)			
ligand (L)	$\Delta E^{\ddagger}$	$\Delta E^{\ddagger}_{dist}$ (Cu–B)	$\Delta E^{\ddagger}_{dist}$ ($H_2C{=}CH_2$)	$\Delta E^{\ddagger}_{int}$
Xantphos	2.1	**11.7**	**29.2**	**–38.8**
PPh_3	3.6	16.2	32.1	–44.8
IMes	3.0	18.6	33.5	–49.1

Structure Analysis of Stationary Points for Various Ligands

Comparison of optimization structures of Xantphos (**I**$_x$, **III**$_x$, **TS**$_x$, **P**$_x$), PPh_3 (**I**$_t$, **III**$_t$, **TS**$_t$, **P**$_t$) and IMes (**I**$_i$, **III**$_i$, **TS**$_i$, **P**$_i$) are consistent with the preactivation nature of Xantphos ligand. Summary of structural parameter and optimized structures are shown in Table S2 and Figure S2. Among the starting borylcopper(I) complexes, **I**$_x$ (L = Xantphos) has the longest Cu–B bond, indicating the higher degree of activation in Cu–B as compared to **I**$_t$ (X = PPh_3) and **I**$_i$ (X = IMes). The longest Cu–B is also observed in **III**$_x$; on the contrary, the coordinated carbon-carbon double bond (C1–C2) is most weakened in **III**$_i$. **TS**$_x$ has the longest Cu–B bond and the shortest C1–C2 bond length among structures with other ligands. This indicated that, in Xantphos complexes, the Cu–B bonds are activated throughout the reaction and that the transition state (**TS**$_x$) lies early in terms of the bond scission of C1–C2 bond as compared to the reaction with other ligands.

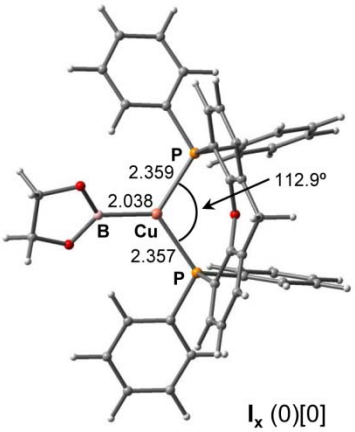
Table S2. Selected Bond Lengths of Optimized Structures

	bond length (Å)

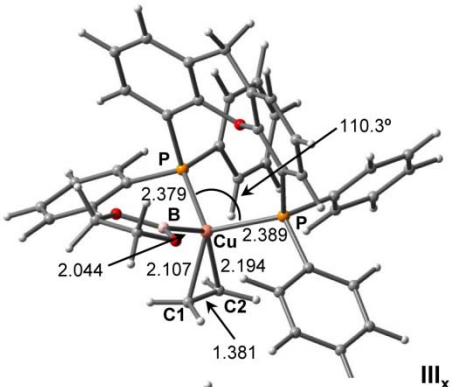
	ligand	Cu–B[a]	Cu–P	C1–C2[b]
ethylene	-	-	-	1.332
I_x	Xantphos	**2.038**	2.358, 2.357	-
I_t	PPh_3	2.012	2.238	-
I_i	IMes	2.011	-	-
III_x	Xantphos	**2.044**	2.379, 2.389	**1.381**
III_t	PPh_3	2.029	2.286	1.390
III_i	IMes	2.034	-	1.397
TS_x	Xantphos	**2.094**	2.305, 2.300	**1.471**
TS_t	PPh_3	2.067	2.181	1.490
TSi_t	IMes	2.068	-	1.492

[a]The longest Cu–B bond length in the comparative stationary points were indicated by boldface. [b]The shortest C1–C2 bond length in the comparative stationary points were indicated by boldface.

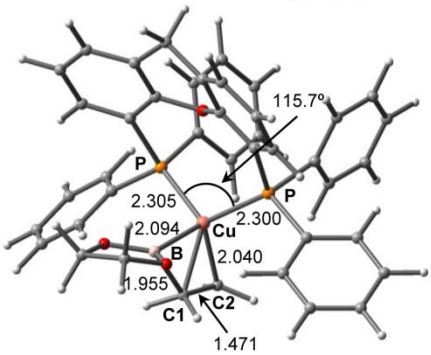
Figure S2. Optimized Structures (I, III, TS, P) for Xantphos, PPh_3 and IMes with Structural Parameters and Free (in parentheses) and Electronic (in bracket) Energies



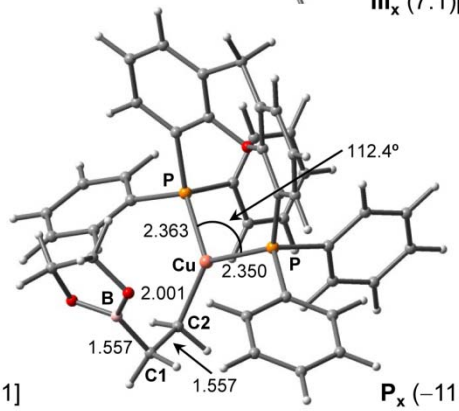
I_x (0)[0]



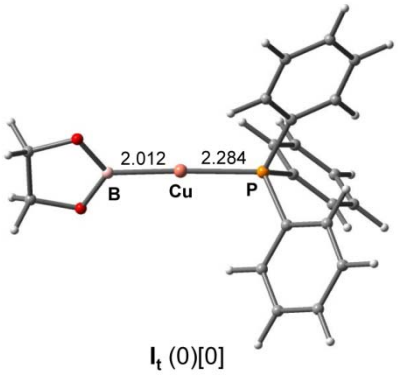
III_x (7.1)[−6.5]



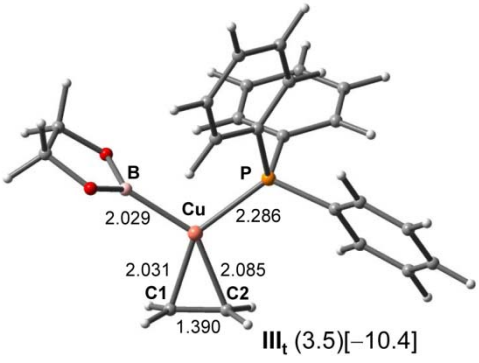
TS_x (17.6)[2.1]



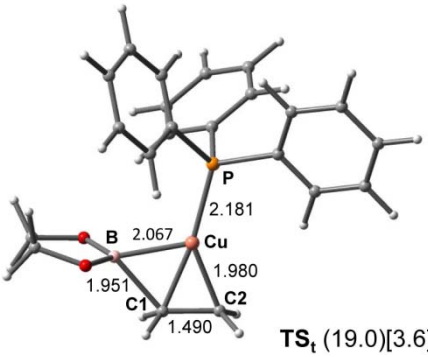
P_x (−11.4)[−24.9]



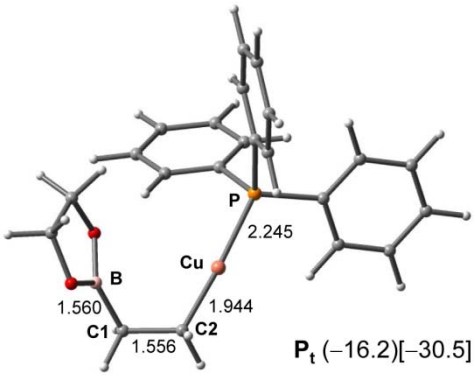
I_t (0)[0]



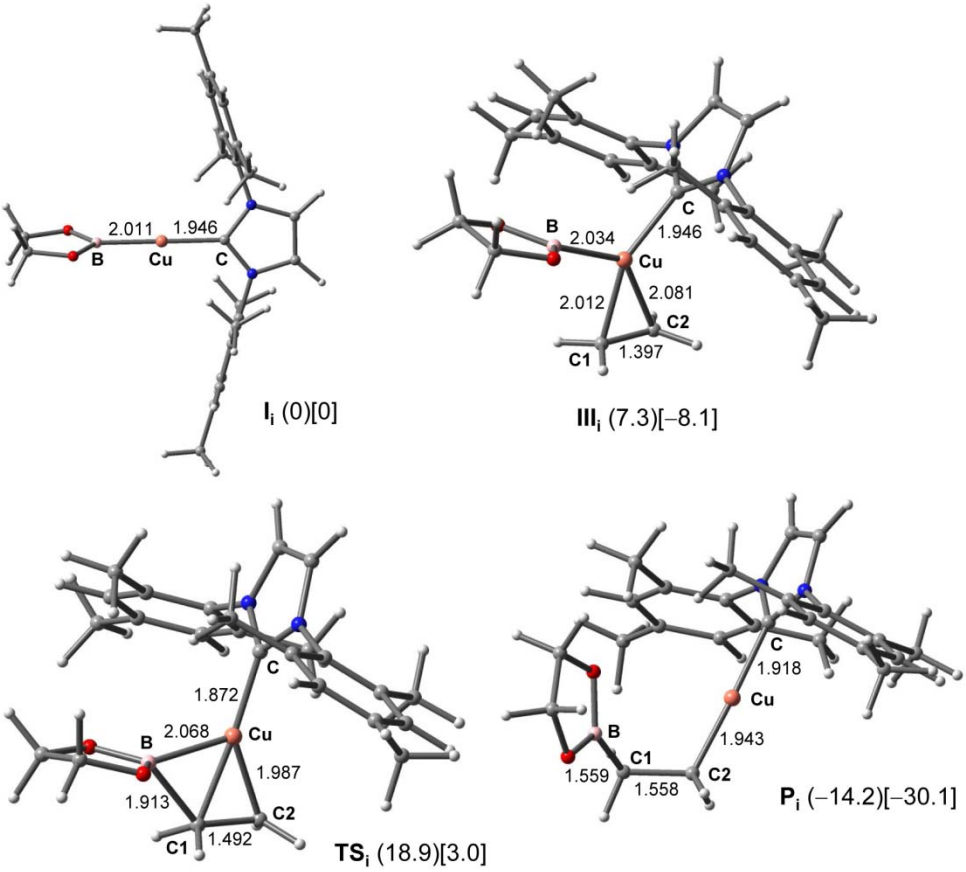
III_t (3.5)[−10.4]



TS_t (19.0)[3.6]



P_t (−16.2)[−30.5]



Structure Analysis of Reaction Pathways in the Reaction of Propene

Coparison of the optimized structures in two different pathways, A and B gives important information on the regioselectivity (Figure S3). The distance between C2 and Cu of **III**$_{PA}$ is larger than that of **III**$_{PB}$. This distortion in **III**$_{PA}$ would be caused by the steric congestion between C2-CH_3 moiety and the bulky Xantphos ligand. This could destabilize the **III**$_{PA}$ as compared to **III**$_{PB}$. In the transition states, both boron atoms and copper centers are placed at much closer to the C1 atom as compared to those in the π-complexes. In addition, C1 atom took congested five-coordinated structure containing the newly forming C1-B and the breaking C1-Cu bonds. These structure alternation make the steric congestion around C1 atom more important than those of C2 atom in the transition states. Furthermore, C2 atoms take take more sp^3-like configuration in transition states. This could decrease the steric interaction between the substituents around C2 atoms and Xantphos ligand.

These reversal structural features of the transition state against the π-complexe can cause the destabilization in **TS**$_{PB}$ as compared to **TS**$_{PA}$. In the products (**P**$_{PA}$ and **P**$_{PB}$), interactions between C2 and the bulky Cu moiety become an important factor again, causing destabilization of **P**$_{PA}$. The difference in electronic properties between -CH_2 and -$CHCH_3$ may influence the energy profiles in path A and B, although further analysis is required to clear this.

Figure S3. Two Diastereomeric Pathways for Addition Step of Borylcopper(I)(Xantphos) Intermediate (I) to Propene (IIp)

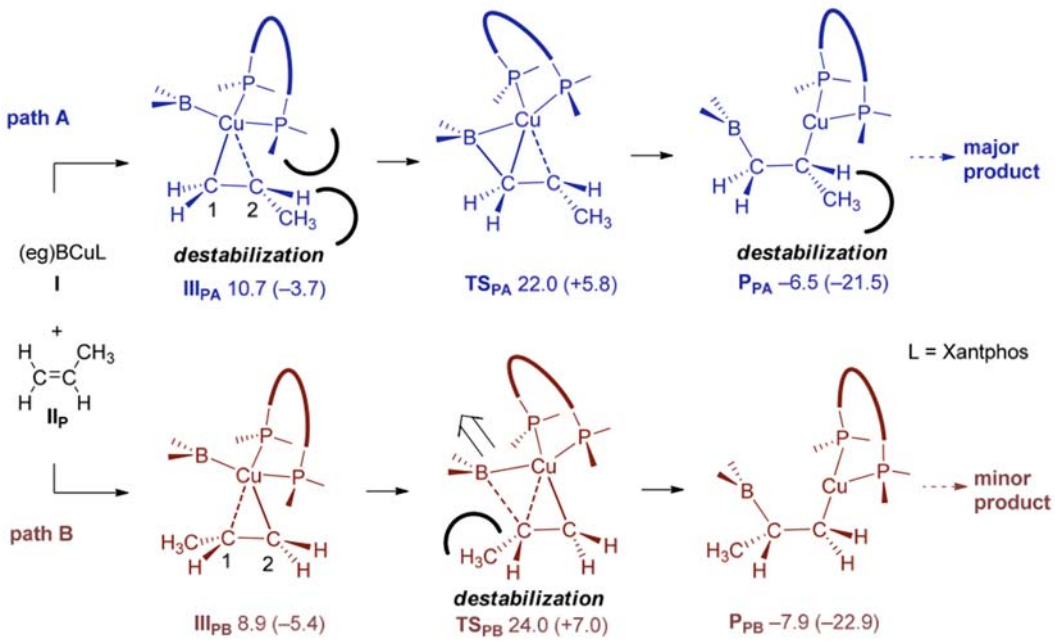
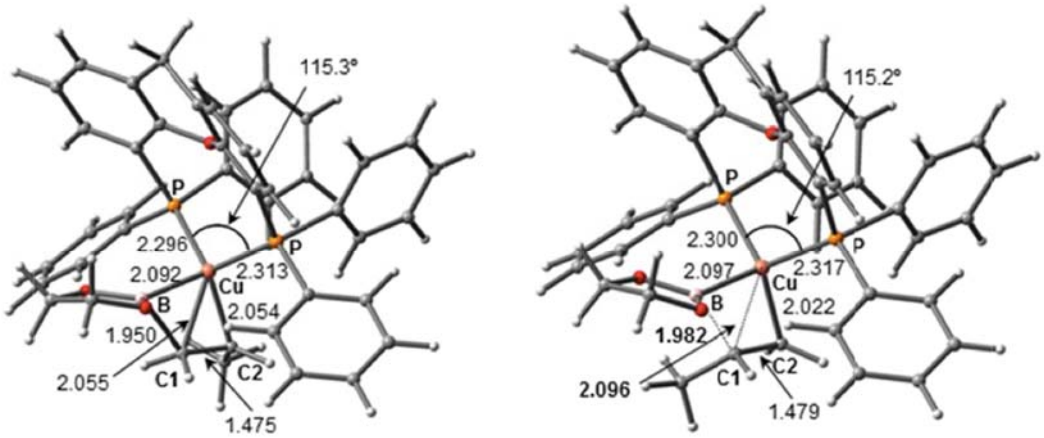


Figure S4. Optimized Structures for the Transition States (TSX, TSPA, TSPB) with Structural Parameters and Free (in parentheses) and Electronic (in bracket) Energies



TS_{PA} (+22.0)[+5.8] TS_{PB} (+24.0)[+7.0]

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Chapter 3.

Copper(I)-Catalyzed Regio- and Enantioselective Monoborylation of Alkenylsilanes

Abstract

An asymmetric monoborylation of alkenylsilanes catalyzed by a copper(I) complex with chiral bisphosphine ligand BenzP* is reported. The reaction proceeded with excellent regioselectivity and high enantioselectivity to afford the corresponding optically active organoboronate esters with a stereogenic C−B bond containing a vicinal silyl group. The synthetic utility of the product is demonstrated through stepwise transformations to multifunctional optically active compounds in a stereospecific manner.

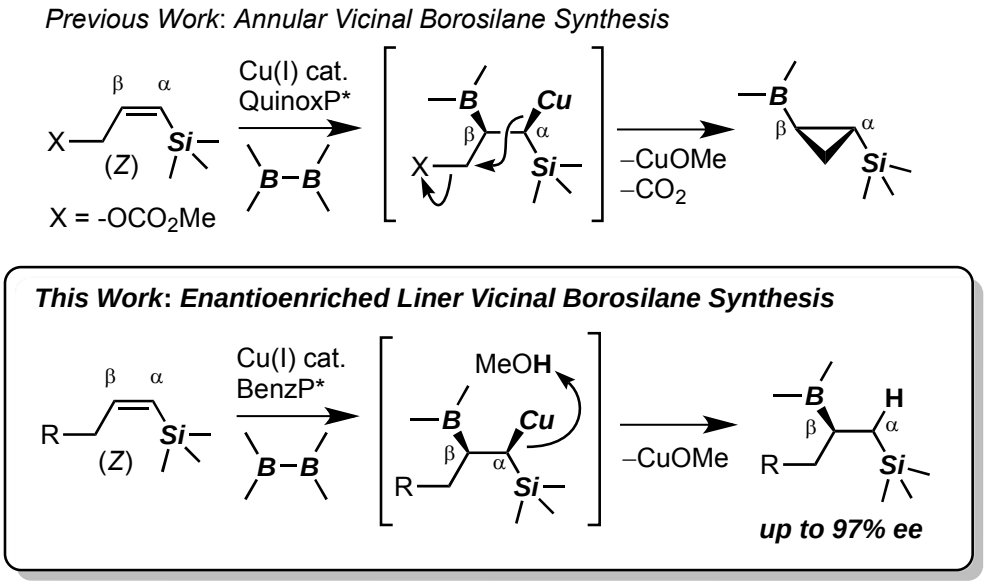
Introduction

Enantioenriched chiral organoboron compounds have been recognized as important chiral building blocks in organic synthesis because they undergo

stereospecific transformations of the stereogenic C−B bonds to form C−O, C−N, or C−C bonds.[1] The copper(I)-catalyzed asymmetric borylation reactions of C−C double bonds have emerged as a powerful tool to prepare various optically active organoboronates, which has been researched extensively recently.[2-7] The key step for the efficient construction of a stereogenic C−B bond is the regio- and enantioselective addition of the borylcopper(I) species to prochiral alkene substrates.[4,6,7]

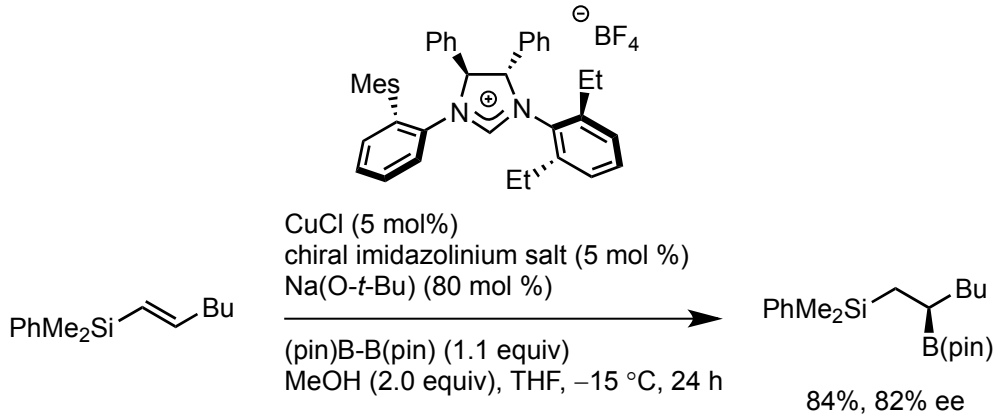
An asymmetric *β*-borylation of alkenylsilanes can provide enantiomerically enriched vicinal borosilanes, which can be derivatized through stepwise, stereospecific transformations of the boron and silicon functionalities.[3c,8] Ito and Sawamura group previously reported highly enantioselective copper(I)-catalyzed intramolecular 1,2-carboboration of (*Z*)-alkenylsilane derivatives.[3c] This reaction involved the addition of a chiral borylcopper(I)/bisphosphine complex to the C−C double bonds in the substrate to form *β*-borylated alkylcopper(I) intermediate **A**, which is stabilized by the electronic effect of the silicon group, followed by stereospecific intramolecular substitution to give the corresponding annular vicinal borosilane (Scheme 1a).[9] The author anticipated that efficient protonation of the alkylcopper(I) intermediate **A′** could also afford optically active linear vicinal borosilanes (Scheme 1b).[10]

Scheme 1. Copper(I)-Catalyzed Asymmetric Borylation Reactions of (*Z*)-Alkenylsilane Substrates



At the time that the author initiated this investigation, there were no reports of such asymmetric borylation; however, Hoveyda and co-workers have since reported that chiral *N*-heterocyclic carbene copper complexes catalyze enantioselective *β*-borylation of (*E*)-alkenylsilanes.[11] Although the reaction proceeded with high regioselectivity, the degree of enantioselection was moderate in most cases and depended on the structure of the substrates (68–93% *ee*).

Scheme 2. Chiral NHC-Copper(I)-Catalyzed Asymmetric Borylation of (*E*)-Alkenylsilanes



Herein the author reports an efficient catalysis using a copper(I) complex of the chiral electron-donating ligand BenzP* to produce optically active linear vicinal borosilanes with a high degree of enantioselectivity (88–97% *ee*) from (*Z*)-alkenylsilane substrates. Stepwise transformation of the borylated products is also demonstrated through the preparation of chiral 1,2-diol and 1,2-aminoalcohol derivatives.

Results and Discussion

Following on from previous research, the reaction of (*Z*)-**1a** was first investigated with CuCl/(*R*,*R*)-QuinoxP* chiral catalyst (5 mol%) in the presence of bis(pinacolato)diboron **2** (1.5 equiv), K(O-*t*-Bu) base (1.2 equiv) and MeOH (4.0 equiv) as a proton source in THF at 30 ºC (Table 1). Pleasingly, the reaction proceeded with good enantioselectivity (92% *ee*), but gave only moderate yield (68%) (entry 1). To his disappointment, using the chiral ligand (*R*,*R*)-segphos, which has previously been found to catalyze intermolecular 1,2-carboboration of (*Z*)-alkenylsilane derivatives,[3c] instead of (*R*,*R*)-QuinoxP* resulted in almost no reaction (entry 2). A series of other chiral ligands were also screened, including (*R*,*R*)-Me-Duphos, (*S*,*S*)-BDPP,

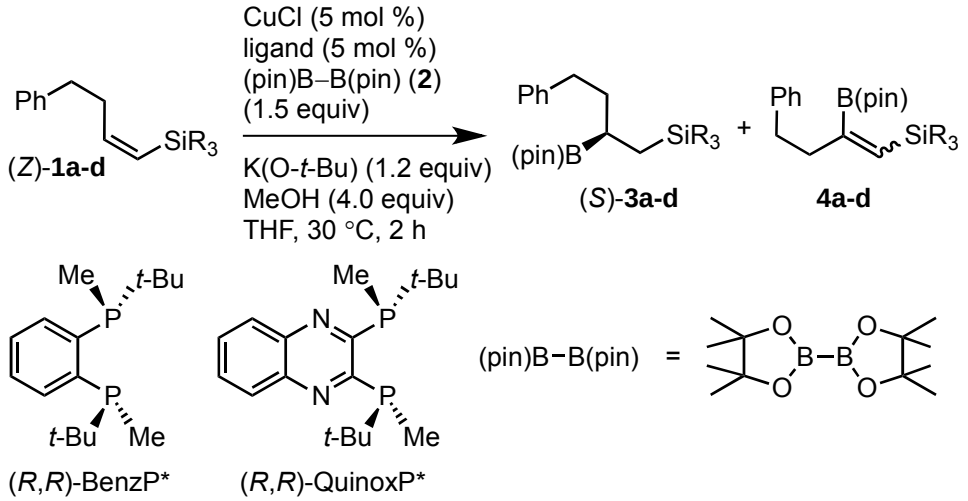
(*R*)-BINAP and the ferrocenyl chiral ligand (*R*,*S*)-Josiphos; they too showed poor results (entries 3–6).

Then, the author investigated the reaction with (*R*,*R*)-BenzP*,[12] which has a similar structure to QuinoxP*. However, BenzP* is more electron donating than QuinoxP*, which can facilitate the interaction between the HOMO of the borylcopper(I) complex and LUMO of the alkenylsilane substrate, enhancing reactivity while keeping high enatioselectivity.[13,14] As a result, the author successfully improved the yield (91%) and enantioselectivity (95% *ee*) of the reaction using chiral ligand (*R*,*R*)-BenzP* (entry 7). A small amount of a *β*-elimination product, **4a** (5%) was also detected. Enantiomerically enriched organoboronates with dimethylphenylsilyl or benzyldimethylsilyl group, which can be converted into other functional groups more easily than trimethylsilyl group, were also synthesized with excellent enantioselectivity (94% *ee*) through reaction with the copper(I)/(*R*,*R*)-BenzP* catalytic system (entries 8 and 9, respectively). The reaction of the substrate with a more sterically hindered diphenylmethylsilyl group also gave a good result (entry 10). Higher enantioselectivity (97% *ee*) was obtained when the reaction was conducted at 0 C without *β*-elimination side-product **4a** (entry 11).

Various alkenylsilanes were then subjected to the asymmetric monoborylation in the presence of the copper(I)/(*R*,*R*)-BenzP* catalyst (Table 2). Optically active organoboronates that possess alkyl substituents [R = CH_2CH_2Ph (**3a**), Me (**3e**), and *n*-Bu (**3f**)] were obtained with high enantioselectivity (94–97% *ee*) from the corresponding alkenylsilanes.

Although the reaction of a substrate with a *β*-branched alkyl substituent (R = CH_2Cy, **3g**) resulted in good enantioselectivity (89% *ee*), the reaction rate was relatively slower (58%) because of the considerable steric congestion around the C–C double bond. Alkenylsilanes with functional groups such as silyl ether (**3h**), benzyl ether (**3i**), and benzoate (**3j**) were compatible with the borylation reaction. A substrate containing a chloro group, which is reactive

Table 1. Copper(I)-Catalyzed Enantioselective Monoborylation of Alkenylsilanes 1 with Bis(pinacolate)diboron 2 under Various Conditions[a]

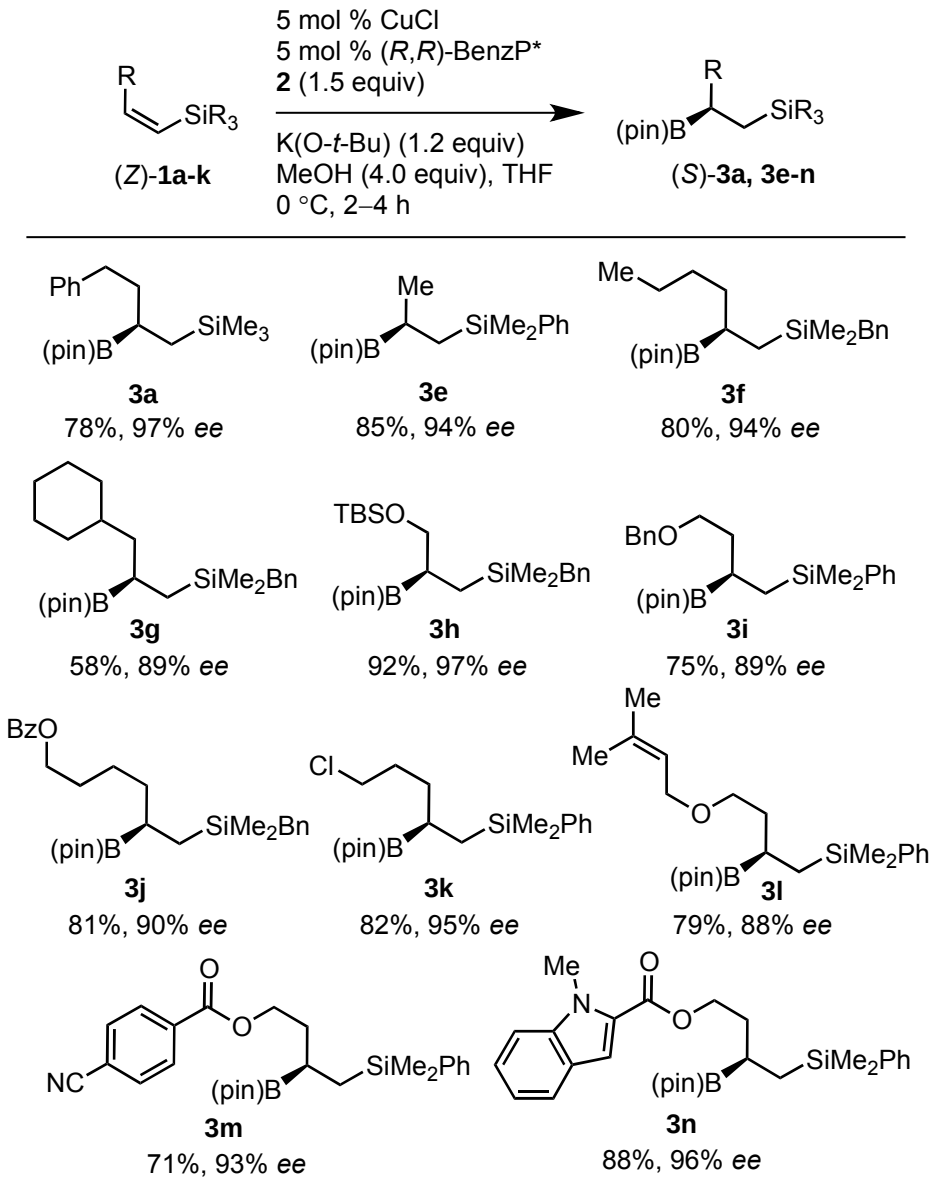


entry	R_3Si	temp. (°C)	Ligand	yield (%)[b] **3**	**4**	ee (%)
1	Me_3Si	30	(*R*,*R*)-QuinoxP*	68	<1	92
2	Me_3Si	30	(*R*,*R*)-Me-Duphos	64	<1	92
3	Me_3Si	30	(*S*,*S*)-BDPP	29	<1	74
4	Me_3Si	30	(*R*)-BINAP	<1	<1	85 (*R*)
5	Me_3Si	30	(*R*)-Segphos	<1	<1	–
6	Me_3Si	30	(*R*,*S*)-Josiphos	<1	<1	–
7	Me_3Si	30	(*R*,*R*)-BenzP*	91	5	95
8	$PhMe_2Si$	30	(*R*,*R*)-BenzP*	94	5	94
9	$BnMe_2Si$	30	(*R*,*R*)-BenzP*	92	6	94
10	Ph_2MeSi	30	(*R*,*R*)-BenzP*	74	9	91
11	Me_3Si	0	(*R*,*R*)-BenzP*	81	<1	97

[a]Conditions: **1** (0.5 mmol), CuCl (0.025 mmol), ligand (0.025 mmol), K(O-*t*-Bu)/THF (0.6 M, 1.0 mL), **2** (0.6 mmol), MeOH (2.0 mmol). [b]Yield was determined by ^{1}H NMR analysis of the crude mixture. [c]Determined by GC or ^{1}H NMR analysis of the crude reaction mixture.

for the copper(I)-catalyzed boryl substitution, was also applicable (82%, 95% *ee*) with no side-product detected.[15] Furthermore, the reaction also proceeded in the presence of prenyloxy ether (**3l**), cyano group (**3m**) and *N*-protected indole (**3n**) substrates, resulting in good yields with excellent enantioselectivities (88–96% *ee*).

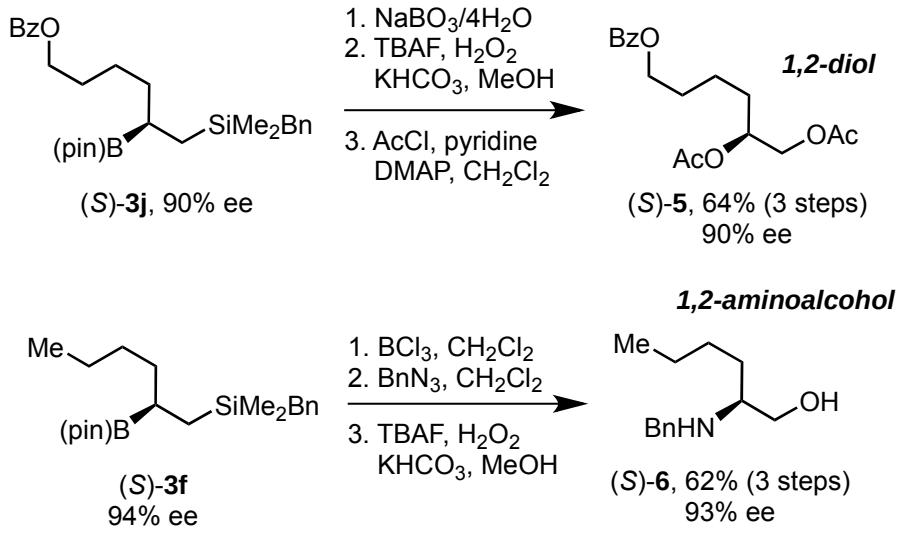
Table 2. Copper(I)-Catalyzed Enantioselective Monoborylation of Various Alkenylsilanes



The synthetic utility of the monoborylation products was demonstrated through selective derivatization. The product **3j** was subjected to sequential $NaBO_3$ and Tamao oxidation to afford the desired enantiomerically enriched 1,2-diol **5** (64%, 3 steps; 90% *ee*) in a stereospecific manner for the C–B bond (Scheme 3).[8a,16] The author also conducted the stereospecific amination of **3f** with benzyl azide to give the corresponding amine, followed by oxidation of

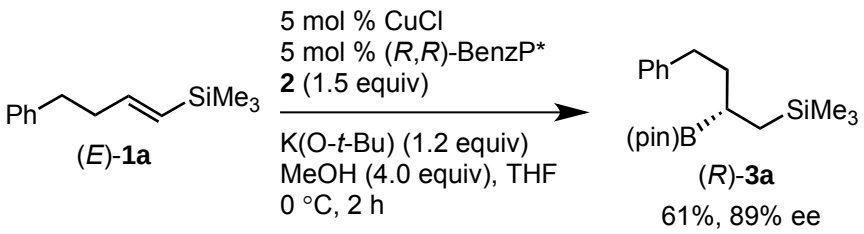
the Si–C bond to obtain the optically active 1,2-aminoalcohol **6** in good yield with excellent enantiomeric purity (62%, 3 steps; 93% *ee*).[17]

Scheme 3. Stepwise Transformation of Monoborylation Products: Synthesis of 1,2-Diol and 1,2-Aminoalcohol Derivatives



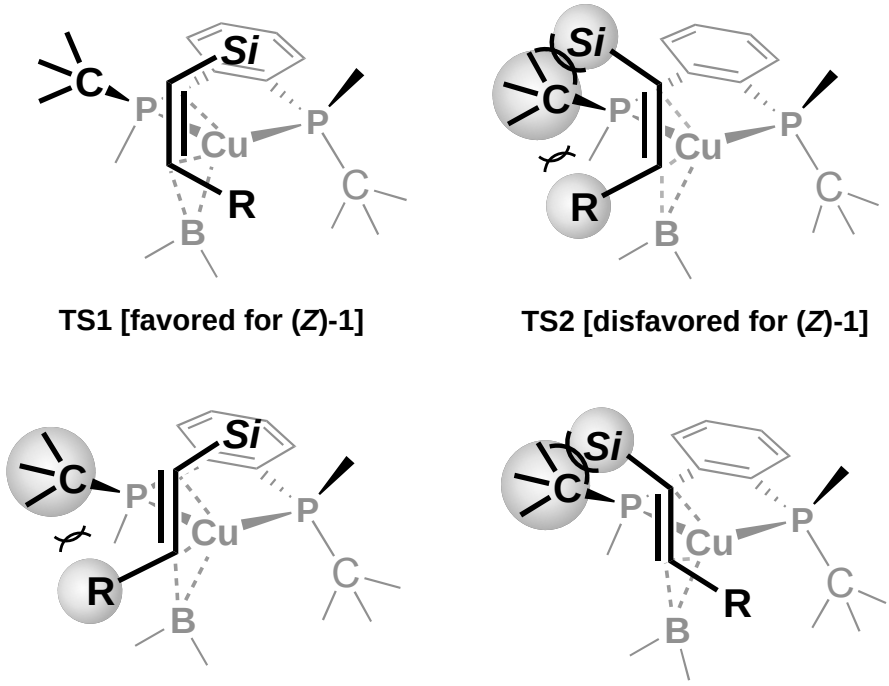
The *E* or *Z* configuration of the substrate strongly influenced the enantioselectivity of the borylation reaction (Scheme 4). Reaction of (*E*)-**1a** under standard conditions gave (*R*)-**3a** in lower yield and enantioselectivity (61%, 89% *ee*) than those obtained for the same reaction with (*Z*)-**1** (81%, 97% *ee*).[11]

Scheme 4. Copper(I)-Catalyzed Enantioselective Monoborylation of (*E*)-**1a**



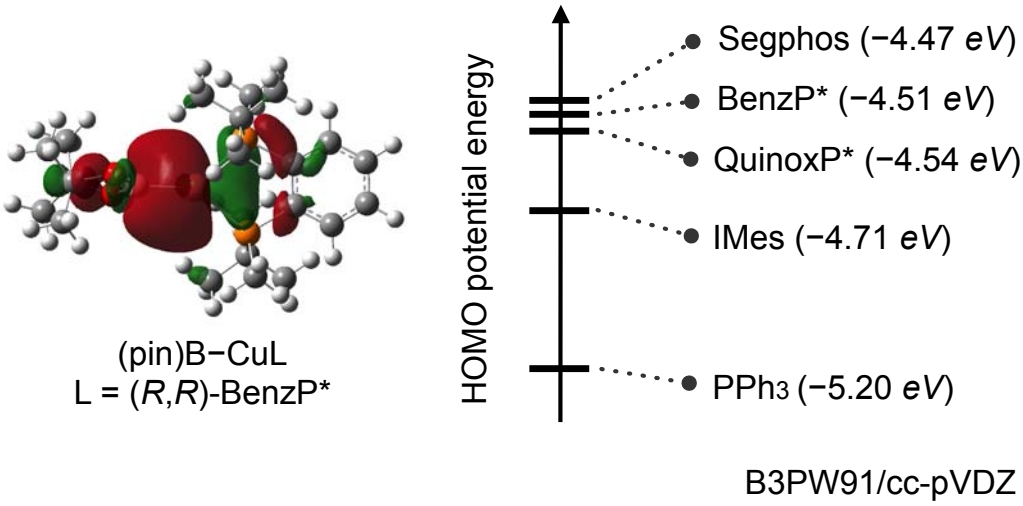
The observed stereochemical outcome of the copper(I)-catalyzed monoborylation of (*Z*)- or (*E*)-alkenylsilanes can be explained by the transition states of Cu−B addition across the C−C double bond, as shown in Figure 1. In the case of the reaction with (*Z*)-**1**, the favored transition state **TS1** is free from steric congestion between the substituents of (*Z*)-**1** and the *t*-Bu group of the BenzP* chiral ligand, thus producing (*S*)-**3** as the major enantiomer. In contrast, the less favored transition state **TS2** is destabilized because one of the *t*-Bu groups of the ligand is close to both the silyl groups and substituents of (*Z*)-**1**. In the case of (*E*)-**1**, one of the *t*-Bu groups of the ligand is involved in steric interactions with either the substituents (**TS3**) or silyl groups of (*E*)-**1** (**TS4**). Thus, the energy difference between **TS3** and **TS4** is smaller than that between **TS1** and **TS2**, resulting in higher enantioselectivity for the substrates with (*Z*)-configuration.

Figure 1. Transition State Models for the Enantioselection



Preliminary DFT calculations (B3PW91/cc-pVDZ) were used to explain the effect of the ligand on reactivity for the borylation of alkenylsilanes (Figure 2). Marder, Lin and co-workers reported that the interaction between the HOMO of the borylcopper(I) intermediate and the LUMO of the electrophile is crucial for insertion to unsaturated bonds.[13] The HOMO levels of the borylcopper(I) complexes with BenzP* (−4.51 *eV*) and QuinoxP* (−4.54 *eV*) were considerably higher than those containing IMes (4.71 *eV*) and PPh_3 (−5.20 *eV*).[18] This is consistent with the higher reactivity of copper(I)/BenzP*. Although the hydroboration of alkenylsilane with copper(I)/segphos catalyst showed poor result, the HOMO level of the segphos complex was higher than that of BenzP*. This inconsistency would be caused by the steric effect in the transition state. Further theoretical investigations including the transition states are required for the full explanation of the reactivity of borylcopper(I) complexes.

Figure 2. DFT Calculation (B3PW91/cc-pVDZ) of the HOMO Levels of Borylcopper(I) Complexes



Conclusion

In summary, the auther have developed the copper(I)/BenzP* complex catalyzed highly regio- and enantioselective hydroboration of alkenylsilanes to afford the synthetically useful optically active liner vicinal borosilanes. The reaction proceeded with excellent regioselectivity and high enantioselectivity. The synthetic utility of the protocol was demonstrated by the stepwise and stereoselective transformation of the products into the enantioenriched 1,2-diol and 1,2-aminoalcohol derivatives.

Experimental

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 spectrometer (^{1}H: 400 MHz and ^{13}C: 100 MHz). Tetramethylsilane (^{1}H) and $CDCl_3$ (^{31}C) were employed as external standards, respectively. CuCl (ReagentPlus® grade, 224332-25G, ≥99%) and K(O-*t*-Bu) / THF (1.0 M, 328650-50ML) were purchased from Sigma-Aldrich Co. and used as received. Mesitylene was used as an internal standard to determine NMR yield. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with 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. Elemental analyses and high-resolution mass spectra were recorded at the Center for Instrumental Analysis, Hokkaido University. All DFT calculations were performed with the Gaussian 09W (revision C.01) program package.[19] Geometry optimizations were performed with B3PW91/cc-pVDZ in the gas-phase. Molecular orbitals were drawn by the GaussView 5.0 program. Frequency calculations were conducted on gas-phase optimized geometries to check the all the stationary points as either minima or transition states. Fragment distortion and interaction energies were calculated with B3PW91/cc-pVDZ in the gas-phase.

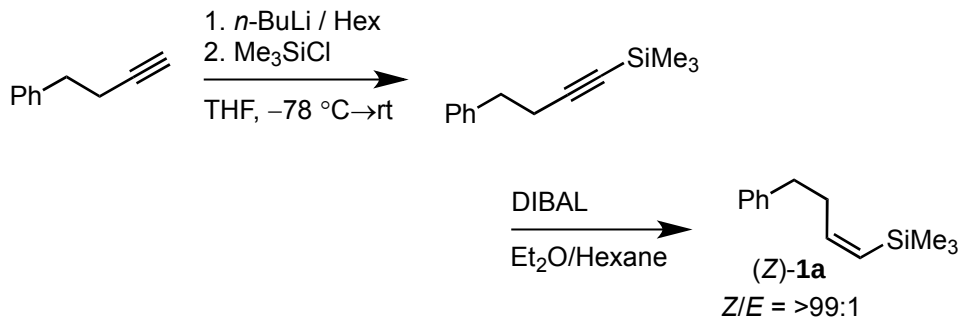
A Representative Procedure for the Copper(I)-Catalyzed Asymmetric Monoborylation of (*Z*)-1a (Table 1):

Copper chloride (2.5 mg, 0.025 mmol) and bis(pinacolato)diboron (190.5 mg, 0.75 mmol), (*R*,*R*)-BenzP* (7.1 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. THF (0.4 mL) and K(O-*t*-Bu)/THF (1.0 M, 0.6 mL, 0.6 mmol) were added in the vial through the rubber septum. After (*Z*)-alkenylsilane **1a** (102.2 mg, 0.5 mmol) was added to the mixture at 0 °C, MeOH (80.9 μL, 2.0 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short silica gel column eluting with Et_2O/hexane (20:80). The crude mixture was further purified by flash column chromatography (SiO_2, Et_2O/hexane, 0:100–4:96) to give the corresponding hydroboration product **3a** as a colorless oil. The flash column chromatography should be done within 5 min after the crude mixture was applied on the silica gel surface; otherwise the products are obtained in a low yield.

Preparation of Substrates.

Preparation of (*Z*)-trimethyl(4-phenylbut-1-en-1-yl)silane (1a).



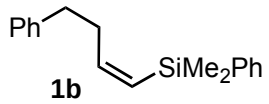
In a vacuum dried 100 mL round bottomed flask, 4-phenyl-1-butyne (1.92 g, 15.0 mmol) was dissolved in dry THF (15.0 mL) and was cooled to –78 °C under nitrogen atmosphere. A hexane solution of *n*-BuLi (1.62 M, 10.2 mL, 16.5 mmol) was then added dropwise for 10 min. After stirred for 20 min, chlorotrimethylsilane was added dropwise and the reaction mixture was stirred at –78 °C for 10 min. Then, it was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched by addition of saturated NH_4Cl aq. 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. The crude product was purified by flash column chromatography to obtain the corresponding silylacetylene (2.82 g, 13.9 mmol, 93%) as a colorless oil.

In a 200 mL round bottomed flask, silylacetylene (2.82 g, 13.9 mmol) was dissolved in dry Et_2O (15.0 mL) and mixture was cooled to 0 °C. A hexane solution of diiobuylaluminium hydride (DIBAL) (1.0 M, 22.5 mL, 22.5 mmol) was then added portion wise and the reaction mixture was warmed to room temperature. After stirred for 12 h, the reaction mixture was quenched by addition of NH_4Cl aq. at 0 °C. After filtration, the mixture was 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 silica gel chromatography to obtain (*Z*)-**1a** (*Z*/*E* = >99:1) (2.28 g, 11.2 mmol, 80%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.09 (s, 9H), 2.43 (q, *J* = 7.5 Hz, 2H), 2.68 (t, *J* = 8.1, 2H), 5.52 (d, *J* = 14.3 Hz, 1H), 6.34 (dt, *J* = 7.3, 14.5 Hz, 1H), 7.17–7.21 (m, 3H), 7.25–7.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 0.18 (CH_3), 35.5 (CH_2), 36.1 (CH_2), 125.9 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 129.7 (*C*H), 141.7 (*C*), 147.8 (*C*H). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{20}Si$, 204.13343; found, 204.13325.

Preparation of (*Z*)-dimethyl(phenyl)(4-phenylbut-1-en-1-yl)silane (1b). **1b** was prepared from the corresponding chlorosilane according to the procedure described above.



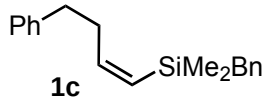
1b

Z/*E* = >99:1

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.35 (s, 6H), 2.34 (q, *J* = 7.9 Hz, 2H), 2.58 (t, *J* = 7.8 Hz, 2H), 5.68 (d, *J* = 14.2 Hz, 1H), 6.46 (quint, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 6.8, 2H), 7.13–7.19 (m, 1H), 7.20–7.27 (m, 2H), 7.32–7.38 (m, 3H), 7.50–7.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –0.89 (CH_3), 35.7 (CH_2), 125.8 (*C*H), 127.5 (*C*H), 127.8 (*C*H), 128.2 (*C*H), 128.4 (*C*H), 128.8 (*C*H), 133.7 (*C*H), 139.5 (*C*), 141.6 (*C*), 149.6 (*C*H). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{22}Si$, 266.14908;

found, 266.14877.

Preparation of (*Z*)-benzyldimethyl(4-phenylbut-1-en-1-yl)silane (1c). **1c** was prepared from the corresponding chlorosilane according to the procedure described above.

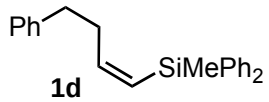


1c

Z/*E* = >99:1

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.065 (s, 3H), 0.067 (s, 3H), 2.12 (s, 2H), 2.36 (q, *J* = 7.9 Hz, 2H), 2.64 (t, *J* = 8.1 Hz, 2H), 5.48 (d, *J* = 14.3 Hz, 1H), 6.37 (dt, *J* = 7.3, 14.6 Hz, 1H), 6.98 (d, *J* = 7.7 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 5.10–5.14 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 1.7 (CH_3), 26.6 (CH_2), 35.6 (CH_2), 35.9 (CH_2), 124.0 (*C*H), 125.9 (*C*H), 127.6 (*C*H), 128.1 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 140.0 (*C*), 141.6 (*C*), 148.9 (*C*H). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{24}NaSi$, 303.15395; found, 303.15374.

Preparation of (*Z*)-dimethyl(phenyl)(prop-1-en-1-yl)silane (1d). **1d** was prepared from the corresponding chlorosilane according to the procedure described above.



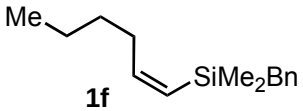
1d

Z/*E* = >99:1

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.62 (s, 3H), 2.28 (q, *J* = 7.8 Hz, 2H), 2.50 (t, *J* = 8.0 Hz, 2H), 5.87 (dd, *J* = 1.3, 14.1 Hz, 1H), 6.61 (dt, *J* = 7.41, 14.6 Hz, 1H), 6.86–6.92 (m, 2H), 7.10–7.23 (m, 3H), 7.30–7.41 (m, 6H), 7.50–7.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –1.9 (CH_3), 35.4 (CH_2), 36.0 (CH_2), 125.6 (*C*H), 125.7 (*C*H), 127.9 (*C*H), 128.2 (*C*H), 128.4 (*C*H), 129.1 (*C*H), 134.6 (*C*H), 137.4 (*C*), 141.5 (*C*), 151.2 (*C*H). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{23}H_{24}Si$, 328.16473; found, 328.16396.

Preparation of (Z)-benzyl(hex-1-en-1-yl)dimethylsilane (1f).

1f was prepared from the corresponding terminal alkyne according to the procedure described above.



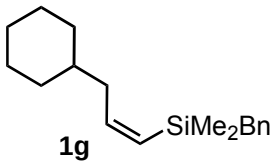
1f

Z/*E* = >99:1

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.091 (s, 3H), 0.093 (s, 3H), 0.89 (t, *J* = 7.1 Hz, 3H), 1.25–1.37 (m, 4H), 2.04 (q, *J* = 7.0 Hz, 2H), 2.16 (s, 2H), 5.43 (dd, *J* = 0.7, 14.3 Hz, 1H), 6.34 (dt, *J* = 7.3, 14.5 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –1.6 (CH_3), 14.0 (CH_3), 22.4 (CH_2), 26.7 (CH_2), 31.8 (CH_2), 33.5 (CH_2), 123.9 (CH), 126.5 (CH), 128.1 (CH), 128.2 (CH), 140.1 (C), 150.4 (CH). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{24}Si$, 232.16473; found, 232.16415.

Preparation of (Z)-benzyl(3-cyclohexylprop-1-en-1-yl)dimethylsilane (1g).

1g was prepared from the corresponding terminal alkyne according to the procedure described above.



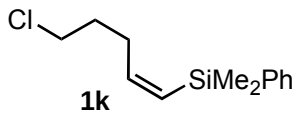
1g

Z/*E* = >99:1

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.08 (s, 6H), 0.88 (q, *J* = 11.2 Hz, 2H), 1.08–1.33 (m, 4H), 1.60–1.73 (m, 5H), 1.96 (t, *J* = 7.1 Hz, 2H), 2.16 (s, 2H), 5.46 (d, *J* = 14.7 Hz, 1H), 6.36 (dt, *J* = 7.4, 14.7 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 2H), 7.06 (t, *J* = 7.1 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –1.6 (CH_3), 26.4 (CH_2), 26.5 (CH_2), 26.8 (CH_2), 33.2 (CH_2), 38.3 (CH), 41.4 (CH_2), 123.9 (CH), 127.2 (CH), 128.1 (CH), 128.2 (CH), 140.2 (C), 149.1 (CH). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{28}Si$, 272.19603; found, 272.19541.

Preparation of (Z)-benzyl(5-chloropent-1-en-1-yl)dimethylsilane (1k).

1k was prepared from the corresponding terminal alkyne according to the procedure described above.

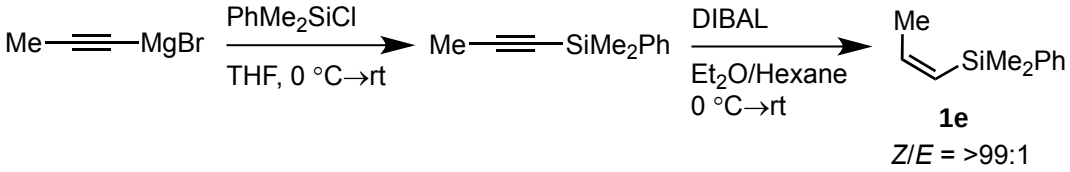


1k

Z/*E* = >99:1

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.39 (s, 6H), 1.75 (quint, *J* = 7.2 Hz, 2H), 2.16 (s, 2H), 2.18 (q, *J* = 7.6 Hz, 2H), 3.39 (t, *J* = 6.8 Hz, 2H), 5.71 (d, *J* = 14.3, 1H), 6.37 (dt, *J* = 7.3, 14.5 Hz, 1H), 7.32–7.38 (m, 3H), 7.51–7.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –1.0 (CH_3), 30.8 (CH_2), 32.3 (CH_2), 44.2 (CH_2), 127.7 (*C*H), 128.4 (*C*H), 128.8 (*C*H), 133.6 (*C*H), 139.3 (*C*), 148.4 (*C*H). HRMS–ESI (*m*/*z*): $[M–CH_3]^+$ calcd for $C_{12}H_{16}ClSi$, 223.07098; found, 223.07058.

Preparation of (*Z*)-dimethyl(phenyl)(prop-1-en-1-yl)silane (1e).



1e

Z/*E* = >99:1

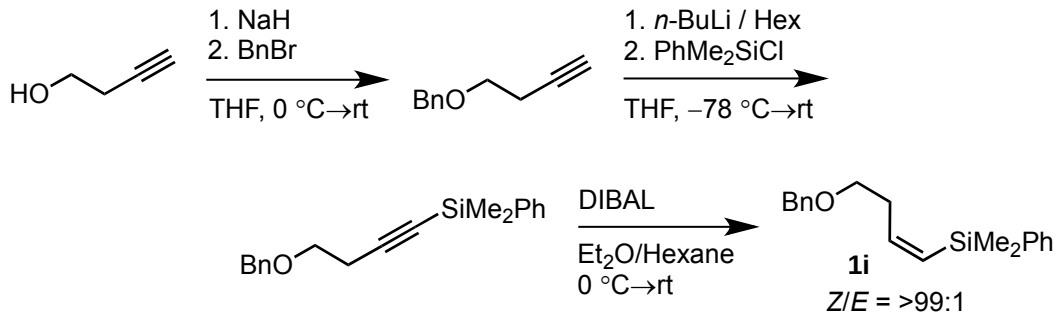
In a 200 mL round bottomed flask, chlorodimethylphenylsilane (3.36 mL, 20.0 mmol) was dissolved in dry THF (20.0 mL) and mixture was cooled to 0 °C. A THF solution of propynyl magnesium bromide (0.5 M, 44.0 mL, 22.0 mmol) was then added portion wise and the reaction mixture was stirred for 1 h. The reaction mixture was quenched by addition of NH_4Cl aq. 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 reaction mixture was purified by silica gel chromatography and to give the corresponding silylacetylene (2.68 g, 15.4 mmol, 77%) as a colorless oil.

In a 50 mL round bottomed flask, silylacetylene (872 mg, 5.00 mmol) was dissolved in dry Et_2O (5.00 mL) and mixture was cooled to 0 °C. A hexane solution of DIBAL (1.0 M, 7.50 mL, 7.50 mmol) was then added dropwise and the reaction mixture was warmed to room temperature. After stirred for 18 h, the reaction mixture was quenched by addition of NH_4Cl aq. at 0 °C. After

filtration, the mixture was 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 silica gel chromatography to obtain (*Z*)-**1e** (*Z*/*E* = >99:1) (714 mg, 4.10 mmol, 81%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.39 (s, 6H), 1.72 (d, *J* = 7.0 Hz, 3H), 5.66 (dt, *J* = 1.5, 14.3 Hz, 1H), 6.54 (sextet, *J* = 7.0 Hz, 1H), 7.32–7.38 (m, 3H), 7.51–7.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –0.92 (CH_3), 19.4 (CH_3), 127.6 (*C*H), 127.8 (*C*H), 128.8 (*C*H), 133.7 (*C*H), 139.6 (*C*), 145.1 (*C*H). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{11}H_{16}Si$, 176.10213; found, 176.10222.

Preparation of (*Z*)-(4-(benzyloxy)but-1-en-1-yl)dimethyl(phenyl)silane (1i).



To a suspension of NaH (60%, dispersion in Liquid Paraffin) (1.20 g, 30.0 mmol) in THF (20.0 mL), 3-butyn-1-ol (1.51 mL, 20.0 mmol) was added dropwise at 0 °C. After gas evaluation stopped, benzyl bromide (3.60 mL, 30.0 mmol) was added dropwise with stirring at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 4 h. After the reaction was quenched by addition of NH_4Cl aq. 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 mixture was purified by silica gel chromatography to afford the corresponding benzyl ether (2.88 g, 18.0 mmol, 90%) as a colorless oil.

In a vacuum dried 200 mL round bottomed flask, the obtained benzyl ether (2.80 g, 17.5 mmol) was dissolved in dry THF (20.0 mL) and was cooled to –

78 °C under nitrogen atmosphere. A hexane solution of *n*-BuLi (1.62 M, 12.0 mL, 19.0 mmol) was then added dropwise for 10 min. After stirred for 1 h, chlorodimethylphenylsilane was added dropwise and the reaction mixture was stirred at –78 °C for 10 min. Then, it was warmed to room temperature and stirred for 1 h. The reaction mixture was quenched by addition of saturated NH_4Cl aq. 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. The crude product was purified by flash column chromatography to obtain the corresponding silylacetylene (4.53 g, 15.4 mmol, 88%) as a colorless oil.

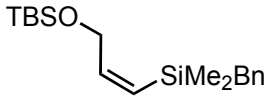
In a 100 mL round bottomed flask, the obtained silylacetylene (2.94 g, 10.0 mmol) was dissolved in dry Et_2O (10.0 mL) and mixture was cooled to 0 °C. A hexane solution of DIBAL (1.0 M, 15.0 mL, 15.0 mmol) was then added portion wise and the reaction mixture was warmed to room temperature. After stirred for 20 h, the reaction mixture was quenched by addition of NH_4Cl aq. at 0 °C. After filtration, the mixture was 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 silica gel chromatography to obtain (*Z*)-**1i** (*Z*/*E* = >99:1) (2.28 g, 7.70 mmol, 77%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.38 (s, 6H), 2.39 (q, *J* = 7.1 Hz, 2H), 3.42 (t, *J* = 7.0 Hz, 2H), 4.43 (s, 2H), 5.76 (d, *J* = 14.3 Hz, 1H), 6.46 (dt, *J* = 7.2, 14.4 Hz, 1H), 7.27–7.36 (m, 8H), 7.51–7.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –0.83 (CH_3), 34.1 (CH_2), 69.6 (CH_2), 72.8 (CH_2), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.4 (CH), 128.9 (CH), 129.2 (CH), 133.8 (CH), 138.5 (*C*), 139.5 (*C*), 146.5 (CH). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –0.83 (CH_3), 34.1 (CH_2), 69.6 (CH_2), 72.8 (CH_2), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.4 (CH), 128.9 (CH), 129.2 (CH), 138.5 (*C*), 139.5 (*C*), 146.6 (CH). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{24}ONaSi$, 319.14886; found, 319.14868.

Preparation of Alkenyl Alcohols.

The (*Z*)-alkenyl alcohols for preparation of (*Z*)-**1h**, **1j**, **1l**, **1m** and **1n** were synthesized by DIBAL reduction of the corresponding silyl-protected alkynyl alcohols according to the procedure described above.

Preparation of (*Z*)-benzyl{3-[(*tert*-butyldimethylsilyl)oxy]prop-1-en-1-yl}dimethylsilane (1h).



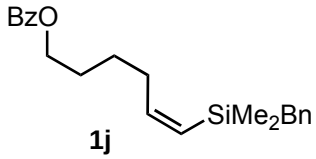
1h

Z/*E* = >99:1

1h was prepared from the corresponding alkenyl alcohol by standard silylation procedure.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.05 (s, 6H), 0.10 (s, 6H), 0.89 (s, 9H), 2.15 (s, 2H), 4.07 (dd, *J* = 2.6, 6.0 Hz, 2H), 5.55 (dt, *J* = 1.6, 14.9 Hz, 1H), 6.41 (dt, *J* = 6.1, 14.9 Hz, 1H), 7.00 (d, *J* = 7.3 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –5.1 (CH_3), –1.8 (CH_3), 18.3 (*C*), 26.0 (CH_3), 26.5 (CH_2), 63.7 (CH_2), 124.1 (*C*H), 127.4 (*C*H), 128.1 (*C*H), 128.2 (*C*H), 139.7 (*C*), 149.1 (*C*H). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{32}ONaSi_2$, 343.18839; found, 343.18821.

Preparation of (*Z*)-6-(benzyldimethylsilyl)hex-5-en-1-yl benzoate (1j).



1j

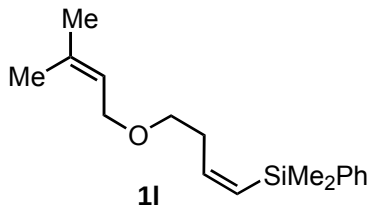
Z/*E* = >99:1

1j was prepared from the corresponding alkenyl alcohol by standard acylation procedure.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.10 (s, 6H), 1.49 (q, *J* = 7.9 Hz, 2H), 1.75 (quint, *J* = 7.3 Hz, 2H), 2.10 (q, *J* = 7.7 Hz, 2H), 2.16 (s, 2H), 4.3 (t, *J* = 6.8 Hz, 2H), 5.48 (d, *J* = 14.3 Hz, 1H), 6.33 (dt, *J* = 7.3, 14.5 Hz, 1H), 7.01 (d, *J* = 7.3 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.7 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 2H),

7.52–7.58 (m, 1H), 7.52–7.58 (m, 2H), 8.01–8.07 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –1.7 (CH_3), 25.9 (CH_2), 26.6 (CH_2), 28.3 (CH_2), 33.1 (CH_2), 64.6 (CH_2), 123.9 (*C*H), 127.2 (*C*H), 128.0 (*C*H), 128.1 (*C*H), 128.2 (*C*H), 129.4 (*C*H), 130.3 (*C*), 132.7 (*C*H), 139.8 (*C*), 149.3 (*C*H), 166.4 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{28}O_2NaSi$, 375.17508; found, 375.17480.

Preparation of (*Z*)-dimethyl{4-[(3-methylbut-2-en-1-yl)oxy]but-1-en-1-yl}(phenyl)silane (1l).

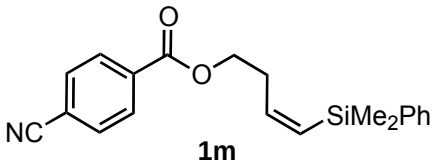


1l
Z/*E* = >99:1

1l was prepared from the corresponding alkenyl alcohol and prenyl bromide by standard etherification procedure.

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.39 (s, 6H), 1.65 (s, 3H), 1.73 (s, 3H), 2.35 (dq, *J* = 1.5, 7.3 Hz, 2H), 3.35 (t, *J* = 7.1 Hz, 2H), 3.87 (d, *J* = 7.3 Hz, 2H), 5.27–5.34 (m, 1H), 5.75 (d, *J* = 14.3 Hz, 1H), 6.45 (dt, *J* = 7.3, 14.6 Hz, 1H), 7.30–7.37 (m, 3H), 7.51–7.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –1.04 (CH_3), 17.8 (CH_3), 25.6 (CH_3), 34.0 (CH_2), 67.1 (CH_2), 69.2 (CH_2), 121.1 (*C*H), 127.6 (*C*H), 128.7 (*C*H), 128.9 (*C*H), 133.5 (*C*H), 136.4 (*C*), 139.2 (*C*), 146.4 (*C*H). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{26}ONaSi$, 297.16451; found, 297.16425.

Preparation of (*Z*)-4-[dimethyl(phenyl)silyl]but-3-en-1-yl 4-cyanobenzoate (1m).

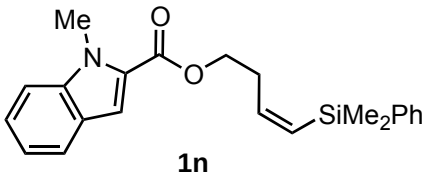


1m
Z/*E* = >99:1

1m was prepared from the corresponding alkenyl alcohol and 4-cyanobenzoic acid by standard condensation procedure using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.40 (s, 6H), 2.53 (q, *J* = 7.0 Hz, 2H), 4.31 (t, *J* = 6.6 Hz, 2H), 5.86 (d, *J* = 14.7 Hz, 1H), 6.46 (dt, *J* = 7.3, 14.5 Hz, 1H), 7.29–7.37 (m, 3H), 7.49–7.57 (m, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 8.04–8.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –1.12 (CH_3), 32.6 (CH_2), 64.6 (CH_2), 116.1 (*C*), 117.8 (*C*), 127.7 (*C*H), 128.8 (*C*H), 129.8 (*C*H), 130.1 (*C*H), 130.4 (*C*H), 131.9 (*C*H), 133.4 (*C*H), 133.8 (*C*), 138.7 (*C*), 144.6 (*C*H), 164.5 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{20}H_{21}O_2NNaSi$, 358.12338; found, 358.12304.

Preparation of (*Z*)-4-[dimethyl(phenyl)silyl]but-3-en-1-yl 1-methyl-1*H*-indole-2-carboxylate (1n).

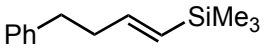


1n
Z/*E* = >99:1

1n was prepared from the corresponding alkenyl alcohol and 1-methyl-1*H*-indole-2-carboxylic acid by standard condensation procedure using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.41 (s, 6H), 2.53 (dq, *J* = 1.5, 7.0 Hz, 2H), 4.05 (s, 3H), 4.28 (t, *J* = 7.8 Hz, 1H), 5.85 (dt, *J* = 1.4, 14.3 Hz, 2H), 6.51 (dt, *J* = 7.2, 14.4 Hz, 1H), 7.15 (ddd, *J* = 1.7, 6.3, 8.1 Hz, 1H), 7.24–7.27 (m, 1H), 7.29–7.40 (m, 5H), 7.52–7.58 (m, 2H), 7.67 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –0.91 (CH_3), 31.5 (CH_3), 32.9 (CH_2), 63.6 (CH_2), 110.17 (*C*H), 110.21 (*C*H), 120.5 (*C*H), 122.5 (*C*H), 124.9 (*C*H), 125.8 (*C*), 127.7 (*C*), 127.8 (*C*H), 128.9 (*C*H), 130.2 (*C*H), 133.6 (*C*H), 139.1 (*C*), 139.6 (*C*), 145.3 (*C*H), 162.0 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{25}O_2NNaSi$, 386.15468; found, 386.15445.

Preparation of (*E*)-trimethyl(4-phenylbut-1-en-1-yl)silane (1a).



(*E*)-**1a**

Z/*E* = >99:1

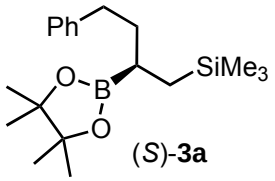
(*E*)-**1a** was prepared by Bu_3SnH-mediated isomerization reaction of (*Z*)-**1a**.[2]

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.04 (s, 9H), 2.37–2.45 (m, 2H), 2.71 (t, *J* = 8.2 Hz, 2H), 5.67 (dt, *J* = 1.6, 18.9 Hz, 1H), 6.08 (dt, *J* = 6.2, 18.6 Hz, 1H), 7.15–7.21 (m, 3H), 7.24–7.31 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –1.2 (CH_3), 35.2 (CH_2), 38.5 (CH_2), 125.7 (*C*H), 128.2 (*C*H), 128.4 (*C*H), 130.4 (*C*H), 142.0 (*C*), 146.1 (*C*H). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{20}Si$, 204.13343; found, 204.13331.

4. Characterization of Borylation Products.

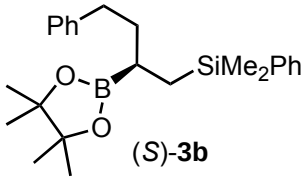
The absolute configuration of the hydroboration product (*S*)-**3k** was determined by comparison of the optical rotation of the alcohol, which was derived from (*S*)-**3k**, and the literature value for (*R*)-**3k**.[11]

(*S*)-Trimethyl[4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]silane [(*S*)-3a].



^{1}H NMR (400 MHz, $CDCl_3$, δ): –0.015 (s, 9H), 0.56 (dd, *J* = 5.9, 15.0, 1H), 0.78 (dd, *J* = 9.0, 14.8, 1H), 1.06–1.16 (m, 1H), 1.27 (s, 12H), 1.60–1.83 (m, 2H), 2.54–2.68 (m, 2H), 7.13–7.21 (m, 2H), 7.23–7.30 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –0.94 (CH_3), 17.4 (CH_2), 18.1 (br, B–CH), 24.9 (CH_3), 25.0 (CH_3), 35.4 (CH_2), 36.9 (CH_2), 82.9 (*C*), 125.5 (*C*H), 128.2 (*C*H), 128.4 (*C*H), 143.0 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{33}O_2BNaSi$, 354.22714; found, 354.22741. $[\alpha]_D^{24.5}$ –19.50 (*c* 1.0 in $CHCl_3$, 97% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, *S* isomer: t_R = 31.44 min., *R* isomer: t_R = 42.11 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

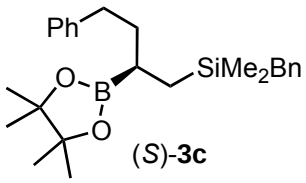
(*S*)-Dimethyl(phenyl)[4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]silane [(*S*)-3b].



^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.26 (s, 6H), 0.81 (dd, *J* = 5.9, 15.0, 1H), 1.04 (dd, *J* = 8.8, 15.0, 1H), 1.10–1.19 (m, 1H), 1.21 (s, 12H), 1.59–1.80 (m, 2H), 2.48–

2.62 (m, 2H), 7.10 (d, J = 7.0 Hz, 2H), 7.15 (q, J = 7.4 Hz, 1H), 7.24 (t, J = 7.5 Hz, 2H), 7.29–7.36 (m, 3H), 7.47–7.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –2.49 (CH_3), –2.28 (CH_3), 16.4 (CH_2), 18.0 (br, B–CH), 24.8 (CH_3), 24.9 (CH_3), 35.2 (CH_2), 36.8 (CH_2), 82.9 (*C*), 125.5 (*C*H), 127.6 (*C*H), 128.1 (*C*H), 128.3 (*C*H), 128.6 (*C*H), 133.6 (*C*H), 139.8 (*C*), 142.8 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{24}H_{35}O_2BNaSi$, 416.24279; found, 416.24263. $[\alpha]_D^{24.5}$ –13.18 (*c* 1.1 in $CHCl_3$, 94% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 2/98, 0.5 mL/min, 40 °C, *S* isomer: t_R = 16.03 min., *R* isomer: t_R = 16.93 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

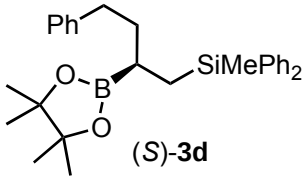
(*S*)-Benzyldimethyl[4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) butyl]silane [(*S*)-3c].



(*S*)-**3c**

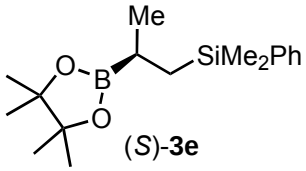
^{1}H NMR (400 MHz, $CDCl_3$, δ): –0.055 (s, 3H), –0.048 (s, 3H), 0.56 (dd, J = 5.5, 15.0, 1H), 0.80 (dd, J = 9.1, 15.0, 1H), 1.06–1.16 (m, 1H), 1.27 (s, 12H), 1.57–1.68 (m, 1H), 1.71–1.83 (m, 1H), 2.08 (s, 2H), 2.49–2.72 (m, 2H), 6.95–7.08 (m, 3H), 7.13–7.22 (m, 5H), 7.24–7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –3.05 (CH_3), –3.00 (CH_3), 15.6 (CH_2), 17.9 (br, B–CH), 24.8 (CH_3), 24.9 (CH_3), 25.9 (CH_2), 35.3 (CH_2), 37.0 (CH_2), 82.9 (*C*), 123.7 (*C*H), 125.5 (*C*H), 127.98 (*C*H), 128.02 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 140.3 (*C*), 142.8 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{37}O_2BNaSi$, 430.25844; found, 430.25824. $[\alpha]_D^{24.6}$ –12.73 (*c* 1.1 in $CHCl_3$, 94% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, *S* isomer: t_R = 23.25 min., *R* isomer: t_R = 31.05 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

(*S*)-Methyldiphenyl[4-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]silane [(*S*)-3d].



^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.55 (s, 3H), 1.09–1.29 (m, 2H), 1.16 (s, 6H), 1.17 (s, 6H), 1.38 (dd, *J* = 8.4, 15.0, 1H), 1.56 (s, 12H), 1.58–1.79 (m, 2H), 2.44–2.60 (m, 2H), 7.04 (m, 2H), 7.11–7.16 (m, 1H), 7.22 (t, J = 7.3 Hz, 2H), 7.28–7.38 (m, 6H), 7.48–7.54 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –3.94 (CH_3), 14.7 (CH_2), 18.0 (br, B–CH), 24.7 (CH_3), 24.9 (CH_3), 35.2 (CH_2), 36.8 (CH_2), 83.0 (*C*), 125.5 (*C*H), 127.68 (*C*H), 127.71 (*C*H), 128.1 (*C*H), 128.3 (*C*H), 129.0 (*C*H), 134.5 (*C*H), 134.6 (*C*H), 137.67 (*C*), 137.73 (*C*), 142.8 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{29}H_{37}O_2BNaSi$, 478.25844; found, 478.25839. $[\alpha]_D^{24.7}$ –36.07 (*c* 1.4 in $CHCl_3$, 91% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane =3/97, 0.5 mL/min, 40 °C, *S* isomer: t_R = 52.93 min., *R* isomer: t_R = 40.27 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

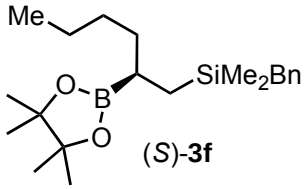
(*S*)-Dimethyl(phenyl)[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl] silane [(*S*)-3e].



^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.270 (s, 3H), 0.273 (s, 3H), 0.68 (dd, *J* = 6.6, 14.6, 1H), 0.99 (d, *J* = 7.3, 3H), 1.02–1.16 (m, 2H), 1.20 (s, 12H), 7.29–7.35 (m, 3H), 7.49–7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –2.32 (CH_3), –2.28 (CH_3), 12.0 (br, B–CH), 18.8 (CH_2), 19.4 (CH_3), 24.6 (CH_3), 24.7 (CH_3), 82.7 (*C*), 127.5 (*C*H), 128.5 (*C*H), 133.5 (*C*H), 140.0 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{29}O_2BNaSi$, 327.19275; found, 327.19256. $[\alpha]_D^{22.8}$ +13.50 (*c* 1.0 in $CHCl_3$,

94% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, *S* isomer: t_R = 39.57 min., *R* isomer: t_R = 42.13 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

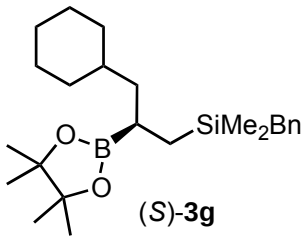
(*S*)-Benzyldimethyl[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexyl]silane [(*S*)-3f].



(*S*)-**3f**

^{1}H NMR (400 MHz, $CDCl_3$, δ): –0.052 (s, 3H), –0.047 (s, 3H), 0.50 (dd, *J* = 5.7, 15.2, 1H), 0.75 (dd, *J* = 9.2, 15.0, 1H), 0.88 (t, *J* = 7.14, 3H), 0.98–1.09 (m, 1H), 1.19–1.49 (m, 6H), 1.24 (s, 12H), 2.08 (s, 2H), 7.00 (d, *J* = 7.3 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –3.1 (CH_3), 14.1 (CH_3), 15.8 (CH_2), 18.0 (br, B–CH), 22.9 (CH_2), 24.8 (CH_3), 24.9 (CH_3), 26.0 (CH_2), 31.2 (CH_2), 34.7 (CH_2), 82.8 (*C*), 123.7 (*C*H), 128.0 (*C*H), 128.1 (*C*H), 140.5 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{37}O_2BNaSi$, 382.25844; found, 382.25829. $[\alpha]_D^{24.8}$ +7.00 (*c* 1.0 in $CHCl_3$, 94% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, *S* isomer: t_R = 28.07 min., *R* isomer: t_R = 31.60 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

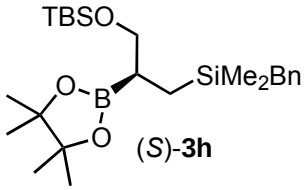
(*S*)-Benzyl[3-cyclohexyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl]dimethylsilane [(*S*)-3g].



(*S*)-**3g**

^{1}H NMR (400 MHz, $CDCl_3$, δ): –0.048 (s, 3H), –0.045 (s, 3H), 0.49 (dd, *J* = 5.7, 15.2, 1H), 0.69 (dd, *J* = 8.1, 15.0, 1H), 0.76–0.92 (m, 2H), 1.06–1.43 (m, 7H), 1.24 (s, 12H), 1.58–1.80 (m, 5H), 2.08 (s, 2H), 7.00 (d, *J* = 7.0 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –2.98 (CH_3), –2.93 (CH_3), 15.4 (br, B–CH), 15.9 (CH_2), 24.9 (CH_3), 26.1 (CH_2), 26.5 (CH_2), 26.7 (CH_2), 33.3 (CH_2), 33.7 (CH_2), 37.0 (CH), 42.6 (CH_2), 82.8 (*C*), 123.7 (CH), 128.0 (CH), 128.1 (CH), 140.5 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{24}H_{41}O_2BNaSi$, 422.28974; found, 422.28940. $[\alpha]_D^{21.9}$ –20.42 (*c* 1.2 in $CHCl_3$, 89% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, *S* isomer: t_R = 25.44 min., *R* isomer: t_R = 27.91 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

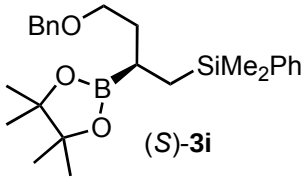
(*S*)-Benzyl{3-[(*tert*-butyldimethylsilyl)oxy]-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl}dimethylsilane [(*S*)-3h].



^{1}H NMR (400 MHz, $CDCl_3$, δ): –0.048 (s, 3H), –0.037 (s, 3H), 0.023 (s, 3H), 0.029 (s, 3H), 0.51 (dd, *J* = 4.8, 15.0, 1H), 0.67 (dd, *J* = 9.9, 15.0, 1H), 0.88 (s, 9H), 1.20–1.32 (m, 1H), 1.24 (s, 12H), 2.09 (s, 2H), 3.59 (d, *J* = 7.0 Hz, 2H), 6.99 (d, *J* = 7.3 Hz, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –5.39 (CH_3), –3.19 (CH_3), –3.06 (CH_3), 11.7 (CH_2), 18.3 (*C*), 22.3 (br, B–CH), 24.9 (CH_3), 25.86 (CH_2), 25.94 (CH_3), 67.6 (CH_2), 82.9 (*C*), 123.7 (CH), 128.00 (CH), 128.03 (CH), 140.4 (*C*). HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{46}O_3BSi_2$, 448.31094; found, 448.31116. $[\alpha]_D^{23.1}$ –10.56 (*c* 0.9 in $CHCl_3$, 97% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0/100, 0.5 mL/min, 40 °C, *S* isomer: t_R = 22.11 min., *R* isomer: t_R = 28.00 min.) of the corresponding alcohol after $NaBO_3$ oxidation of

the borylated product in comparison of the racemic sample.

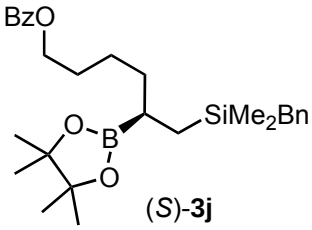
(*S*)-[4-(Benzyloxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]dimethyl(phenyl)silane [(*S*)-3i].



(*S*)-**3i**

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.27 (s, 6H), 0.74 (dd, *J* = 6.0, 15.2, 1H), 1.00 (dd, *J* = 8.4, 15.0, 1H), 1.12–1.19 (m, 1H), 1.15 (s, 12H), 1.61–1.81 (m, 2H), 3.39 (t, *J* = 7.0 Hz, 2H), 4.45 (s, 2H), 7.21–7.34 (m, 8H), 7.47–7.54 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –2.49 (CH_3), –2.30 (CH_3), 14.9 (br, B–CH), 16.3 (CH_2), 24.66 (CH_3), 24.74 (CH_3), 34.3 (CH_2), 69.3 (CH_2), 72.6 (CH_2), 82.8 (*C*), 127.3 (*C*H), 127.5 (*C*H), 128.1 (*C*H), 128.6 (*C*H), 133.5 (*C*H), 138.6 (*C*), 139.8 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{37}O_3BNaSi$, 446.25335; found, 446.25406. $[\alpha]_D^{22.3}$ –30.00 (*c* 1.2 in $CHCl_3$, 89% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, *S* isomer: t_R = 48.27 min., *R* isomer: t_R = 56.16 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

(*S*)-6-(Benzyldimethylsilyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexyl benzoate [(*S*)-3j].

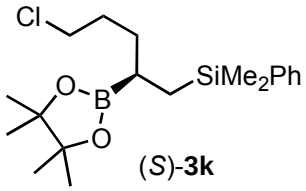


(*S*)-**3j**

^{1}H NMR (400 MHz, $CDCl_3$, δ): –0.047 (s, 3H), –0.039 (s, 3H), 0.50 (dd, *J* = 5.9, 15.0, 1H), 0.77 (dd, *J* = 9.2, 15.0, 1H), 1.02–1.11 (m, 1H), 1.22 (s, 12H), 1.35–1.54 (m, 4H), 1.69–1.80 (m, 2H), 2.08 (s, 2H), 4.30 (t, *J* = 6.6 Hz, 2H), 6.99 (d, *J* = 7.3 Hz, 2H), 7.04 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 2H), 7.43 (t, *J* = 7.9 Hz, 2H),

7.55 (tt, J = 1.6, 7.6 Hz, 1H), 8.01–8.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –2.88 (CH_3), –2.84 (CH_3), 15.9 (CH_2), 18.0 (br, B–CH), 24.9 (CH_3), 25.0 (CH_3), 25.6 (CH_2), 26.1 (CH_2), 29.1 (CH_2), 34.8 (CH_2), 65.2 (CH_2), 83.1 (*C*), 123.9 (*C*H), 128.17 (*C*H), 128.22 (*C*H), 128.4 (*C*H), 129.6 (*C*H), 130.6 (*C*), 132.9 (*C*H), 140.6 (*C*), 166.7 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{41}O_4BNaSi$, 502.27957; found, 502.27982. $[\alpha]_D^{24.3}$ –1.15 (deg cm^3 g^{-1} dm^{-1}) (*c* 1.3 in $CHCl_3$, 90% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, *S* isomer: t_R = 21.77 min., *R* isomer: t_R = 25.12 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

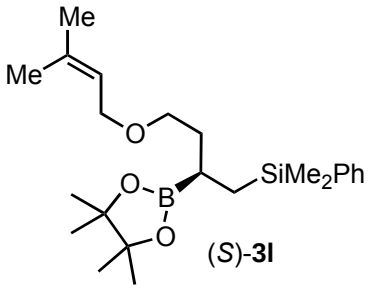
(*S*)-[5-Chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl]dimethyl(phenyl)silane [(S)-3k].[3]



(*S*)-**3k**

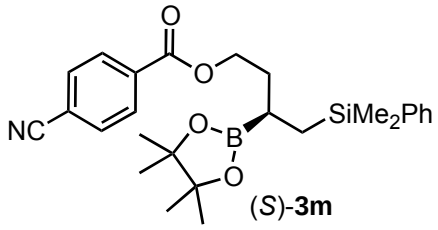
^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.28 (s, 6H), 0.72 (dd, J = 5.1, 14.3, 1H), 0.96–1.13 (m, 2H), 1.19 (s, 12H), 1.40–1.56 (m, 2H), 1.64–1.80 (m, 2H), 3.42 (t, J = 6.8 Hz, 2H), 7.29–7.36 (m, 3H), 7.47–7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –2.58 (CH_3), –2.34 (CH_3), 16.5 (CH_2), 17.4 (br, B–CH), 24.7 (CH_3), 24.8 (CH_3), 31.82 (CH_2), 31.84 (CH_2), 45.1 (CH_2), 82.9 (*C*), 127.6 (*C*H), 128.7 (*C*H), 133.5 (*C*H), 139.6 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{32}O_2BClNaSi$, 388.18817; found, 388.18872. $[\alpha]_D^{20.2}$ +4.12 (*c* 0.85 in $CHCl_3$, 95% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, *S* isomer: t_R = 45.41 min., *R* isomer: t_R = 50.88 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

(*S*)-Dimethyl{4-[(3-methylbut-2-en-1-yl)oxy]-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl}(phenyl)silane [(*S*)-3l].



^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.27 (s, 6H), 0.75 (dd, *J* = 5.9, 15.0, 1H), 1.01 (dd, *J* = 8.8, 15.0, 1H), 1.08–1.16 (m, 1H), 1.19 (s, 12H), 1.59–1.80 (m, 2H), 1.64 (s, 3H), 1.72 (s, 3H), 3.35 (t, *J* = 7.3 Hz, 2H), 3.89 (d, *J* = 7.3 Hz, 2H), 5.28–5.35 (m, 1H), 7.30–7.35 (m, 3H), 7.48–7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –2.54 (CH_3), –2.39 (CH_3), 14.8 (br, B–CH), 16.3 (CH_2), 17.8 (CH_3), 24.6 (CH_3), 24.7 (CH_3), 25.7 (CH_3), 34.4 (CH_2), 67.0 (CH_2), 69.2 (CH_2), 82.7 (*C*), 121.5 (*C*H), 127.5 (*C*H), 128.5 (*C*H), 133.5 (*C*H), 136.0 (*C*), 139.7 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{39}O_3BNaSi$, 424.26900; found, 424.26926. $[\alpha]_D^{24.0}$ +3.75 (*c* 1.2 in $CHCl_3$, 88% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, *S* isomer: t_R = 37.95 min., *R* isomer: t_R = 40.00 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

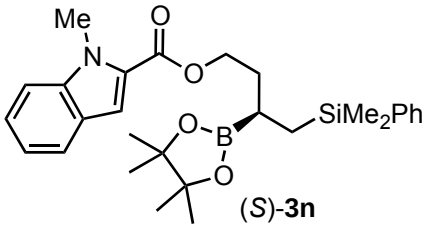
(*S*)-4-[Dimethyl(phenyl)silyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl 4-cyanobenzoate [(*S*)-3m].



^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.29 (s, 6H), 0.81 (dd, *J* = 6.0, 15.2, 1H), 1.06 (dd, *J* = 8.8, 15.0, 1H), 1.17–1.29 (m, 1H), 1.20 (s, 12H), 1.73–1.93 (m, 2H), 4.24–

4.38 (m, 2H), 7.27–7.33 (m, 3H), 7.47–7.54 (m, 2H), 7.71 (d, *J* = 8.8, 2H), 8.05 (d, *J* = 8.4, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): –2.61 (CH_3), –2.27 (CH_3), 14.4 (br, B–CH), 24.65 (CH_2), 24.74 (CH_3), 32.9 (CH_2), 64.9 (CH_2), 83.1 (*C*), 116.0 (*C*H), 117.9 (*C*), 127.6 (*C*H), 128.7 (*C*H), 130.0 (*C*H), 132.0 (*C*H), 133.5 (*C*H), 134.2 (*C*), 139.5 (*C*), 164.7 (*C*). HRMS–ESI (*m*/*z*): [M+Na]$^+$ calcd for $C_{26}H_{34}O_4NBNaSi$, 485.22787; found, 485.22816. $[\alpha]_D^{24.1}$ +17.08 (*c* 1.2 in $CHCl_3$, 95% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, *S* isomer: t_R = 18.61 min., *R* isomer: t_R = 19.75 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

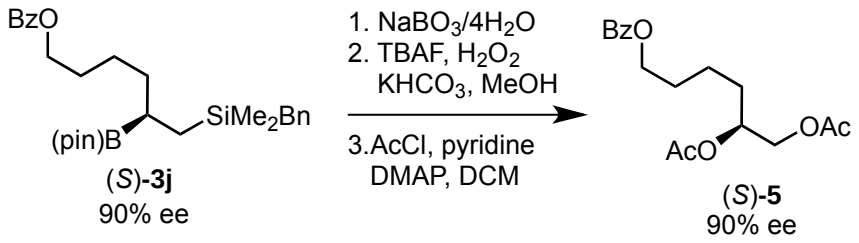
(*S*)-4-[Dimethyl(phenyl)silyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl-1-methyl-1*H*-indole-2-carboxylate [(*S*)-3n].



^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.30 (s, 3H), 0.31 (s, 3H), 0.79–0.88 (m, 1H), 1.02–1.11 (m, 1H) 1.20 (s, 12H), 1.23–1.34 (m, 1H), 1.74–1.95 (m, 2H), 4.04 (s, 3H), 4.20–4.35 (m, 2H), 7.11–7.18 (m, 1H), 7.21–7.25 (m, 1H), 7.27–7.39 (m, 5H), 7.49–7.55 (m, 2H), 7.67 (d, *J* = 8.4, 1H). ^{13}C NMR (1,00 MHz, $CDCl_3$, δ): –2.49 (CH_3), –2.27 (CH_3), 14.6 (br, B–CH), 16.2 (CH_2), 24.7 (CH_3), 24.8 (CH_3), 31.5 (CH_3), 33.1 (CH_2), 63.8 (CH_2), 83.0 (*C*), 110.1 (*C*H), 120.3 (*C*H), 122.4 (*C*H), 124.7 (*C*H), 125.8 (*C*), 127.6 (*C*H), 127.9 (*C*), 128.7 (*C*H), 133.5 (*C*H), 139.5 (*C*), 162.1 (*C*). HRMS–ESI (*m*/*z*): [M+Na]$^+$ calcd for $C_{28}H_{38}O_4NBNaSi$, 513.25917; found, 513.26000. $[\alpha]_D^{23.5}$ –3.82 (*c* 1.7 in $CHCl_3$, 96% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 3/97, 0.5 mL/min, 40 °C, *S* isomer: t_R = 13.07 min., *R* isomer :t_R = 16.15 min.) of the corresponding alcohol after $NaBO_3$ oxidation of the borylated product in comparison of the racemic sample.

5. Stepwise Transformations of Hydroboration Products.

Experimental Procedure for the Synthesis of Chiral 1,2-Diol (*S*)-5.[2]



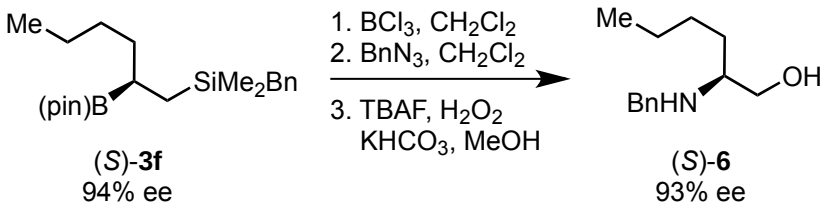
In a reaction vial, $NaBO_3 \bullet 4H_2O$ (184.6 mg, 1.20 mmol) was dissolved in THF/H_2O (1:1, 4.00 mL). (*S*)-**3j** (144.2 mg, 0.30 mmol) was then added at room temperature. After stirred for 12 h, the reaction mixture was extracted three times with EtOAc, dried over $MgSO_4$, and filtered. The crude material was purified by flash column chromatography to obtain the corresponding alcohol (92.3 mg, 0.250 mmol, 83%) as a colorless oil.

A THF solution of tetrabutylanmonium fluoride (1.0 M, 2.00 mL, 2.00 mmol) was added to a solution of the alcohol (92.3 mg, 0.25 mmol) in THF (3.50 mL) with stirring at room temperature. After 30 min, $KHCO_3$ (100.1 mg, 1.00 mmol), MeOH (2.00 mL) and 30% H_2O_2 (1.00 mL) were successively added to the reaction mixture. After 30 min, the reaction mixture was diluted with water, extracted with three times of $CHCl_3$, dried over $MgSO_4$, and filtered. After evaporation, the crude product was used in the next step without further purification.

In a reaction vial, the crude mixture of the diol and dimethylaminopyridine (DMAP) (30.5 mg, 0.25 mmol) were dissolved in CH_2Cl_2 (1.00 mL). After addition of pyridine (59.4 μL, 0.75 mmol), the reaction mixture was cooled to 0 °C. Acetyl chloride (53.3 μL, 0.75 mmol) was added dropwise to the mixture and stirred for 1 h. The reaction was quenched by addition of water, extracted with Et_2O there 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 give the diol (*S*)-**5** (62.1 mg, 0.19 mmol, 77%, 2 steps) as a colorless oil. (64% 3 steps)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.42–1.59 (m, 2H), 1.60–1.73 (m, 2H), 1.74–1.89 (m, 2H), 2.057 (s, 3H), 2.065 (s, 3H), 4.05 (dd, *J* = 6.4, 12.3 Hz, 2H), 4.24 (dd, *J* = 3.3, 12.1 Hz, 2H), 4.32 (t, *J* = 6.8 Hz, 2H), 5.07–5.14 (m, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.56 (tt, *J* = 1.5, 7.6 Hz, 1H), 8.00–8.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 20.7 (CH_3), 21.0 (CH_3), 21.7 (CH_2), 28.4 (CH_2), 30.2 (CH_2), 64.4 (CH_2), 64.9 (CH_2), 71.1 (CH_3), 128.3 (*C*H), 129.4 (*C*H), 130.2 (*C*), 132.8 (*C*H), 166.5 (*C*), 170.5 (*C*), 170.7 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{22}O_6Na$, 345.13086; found, 345.13062. $[\alpha]_D^{24.7}$ –9.23 (*c* 1.3 in $CHCl_3$, 90% ee). The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, (*S*)-**5**: t_R = 46.08 min., (*R*)-**5**: t_R = 49.87 min.).

Experimental Procedure for the Synthesis of Chiral 1,2-Aminoalcohol (*S*)-6.[2]



In an oven-dried reaction vial, CH_2Cl_2 solution of BCl_3 (1.00 M, 2.00 mL, 2.00 mmol) was added under nitrogen atmosphere. (*S*)-**3f** (144.2 mg, 0.40 mmol) was added to the reaction vial with stirring at room temperature. After 4 h, the volatile materials were removed under reduced pressure, and dry CH_2Cl_2 (2.50 mL) was added to the resultant product. The reaction vial was cooled to 0 °C, and benzyl azide (159.8 mg, 1.20 mmol) was added to the mixture. After stirred for 15 h at 0 °C, the reaction mixture was quenched by adding NaOH aq. (2.0 M), extracted three times with $CHCl_3$, dried over $MgSO_4$, and filtered. The crude material was then purified by flash column chromatography to obtain the corresponding amine (108.7 mg, 0.32 mmol, 80%) as a yellow oil.

A THF solution of tetrabutylanmonium fluoride (1.0 M, 2.56 mL, 2.56 mmol) was added to a solution of the amine (108.7 mg, 0.32 mmol) in THF

(4.80 mL) with stirring at room temperature. After 30 min, $KHCO_3$ (128.1 mg, 1.28 mmol), MeOH (2.50 mL) and 30% H_2O_2 (1.30 mL) were successively added to the reaction mixture. After 30 min, the reaction mixture was diluted with water, extracted with three times of $CHCl_3$, dried over $MgSO_4$, and filtered. After evaporation, the crude product was then purified by flash column chromatography to obtain the aminoalcohol (*S*)-**6** (51.1 mg, 0. 25 mmol, 77%) as a white solid. (62%, 3 steps)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 0.90 (t, *J* = 7.1 Hz, 3H), 1.21–1.59 (m, 6H), 2.65–2.73 (m, 1H), 3.32 (dd, *J* = 6.2, 11.0 Hz, 3H), 3.66 (dd, *J* = 4.0, 11.0 Hz, 1H), 3.80 (q, *J* = 13.4 Hz, 2H), 7.22–7.37 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.1 (CH_3), 23.0 (CH_2), 28.3 (CH_2), 31.3 (CH_2), 51.0 (CH_2), 58.4 (CH_3), 62.9 (CH_2), 127.3 (*C*H), 128.3 (*C*H), 128.6 (*C*H), 140.1 (*C*). HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{22}ON$, 208.16959; found, 208.16965. $[\alpha]_D^{24.7}$ +5.63 (*c* 0.8 in $CHCl_3$, 93% ee).

The ee value was determined by HPLC analysis (Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, (*S*)-**6**: t_R = 15.85 min., (*R*)-**6**: t_R = 17.19 min.).

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Chapter 4.

Copper(I)-Catalyzed Enantioselective Nucleophilic Borylation of Aldehydes

Abstract

The first catalytic enantioselective nucleophilic borylation of a C=O double bond has been achieved. A series of aldehydes reacted with a diboron reagent in the presence of a copper(I)/DTBM-SEGPHOS complex catalyst using MeOH as a proton source to give the corresponding optically active -alkoxyorganoboronate esters with excellent enantioselectivities. Furthermore, the products could be readily converted to the corresponding functionalized chiral alcohol derivatives through stereospecific C–C bond forming reactions involving the stereogenic C–B bond.

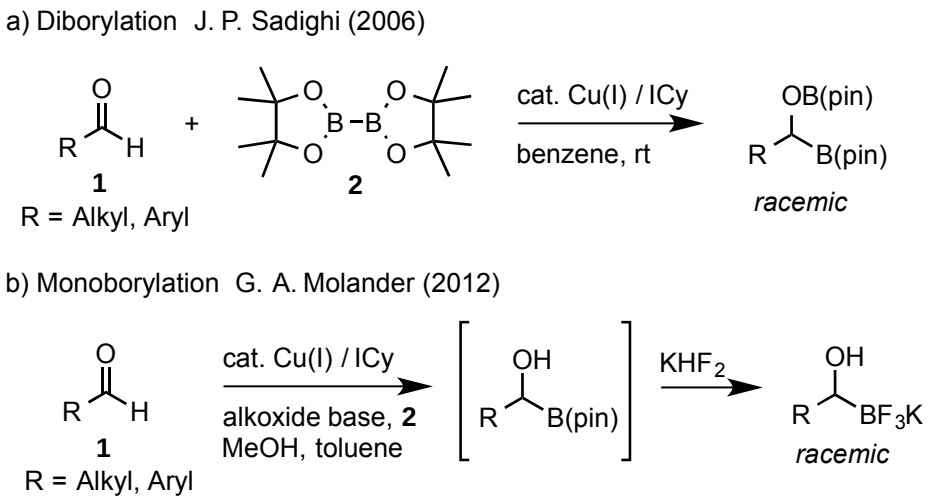
Introduction

Enantioenriched organoboronate esters are a particularly important class of chiral compounds that have attracted considerable interest from researchers working in a variety of different fields because of their broad range of synthetic and medicinal applications.[1] Significant research efforts have recently been focused on the development of catalytic enantioselective strategies for the construction of stereogenic C–B bonds.[2] In particular, copper(I)-catalyzed enantioselective borylation reactions with diboron reagents have emerged as efficient methods for the synthesis of chiral organoboronates with high enantioselectivity.[3-5] Despite this recent progress in borylation chemistry, there have been no reports in the literature pertaining to the catalytic enantioselective borylation of carbon-oxygen double bonds.[6,7] The development of a novel transformation of this type would allow for the direct synthesis of chiral α-alkoxyorganoboronate esters, which could be used as chiral building blocks in organic synthesis and medicinal chemistry.[8] Molander et al.[9] reported the successful development of a stereospecific cross-coupling reaction between chiral potassium -(benzyloxy)alkyltrifluoroborates and aryl halides. It is noteworthy, however, that this pioneering work required the synthesis of an enantiomerically enriched α-alkoxyorganotrifluoroborate through multiple

synthetic transformations as well as the addition of a stoichiometric amount of a chiral auxiliary.[10] Thus, the development of a new method for the catalytic enantioselective addition of boron nucleophiles to carbonyl compounds to give chiral -alkoxyorganoboronate esters is therefore highly beneficial.[9, 11-13]

The first of these pioneering studies towards the catalytic borylation of aldehydes was reported by Sadighi et al.[12] in 2006, where an *N*-heterocyclic carbine(NHC)/copper(I) complex was found to catalyze the diboration of both aliphatic and aromatic aldehydes (Scheme 1a). More recently, Molander et al.[9] developed a process for the copper(I)-catalyzed monoborylation of aldehydes using methanol as a proton source (Scheme 1b). Despite the considerable progress made by these researchers, their works have not yet been extended to the development of enantioselective processes via the introduction of a chiral ligand.

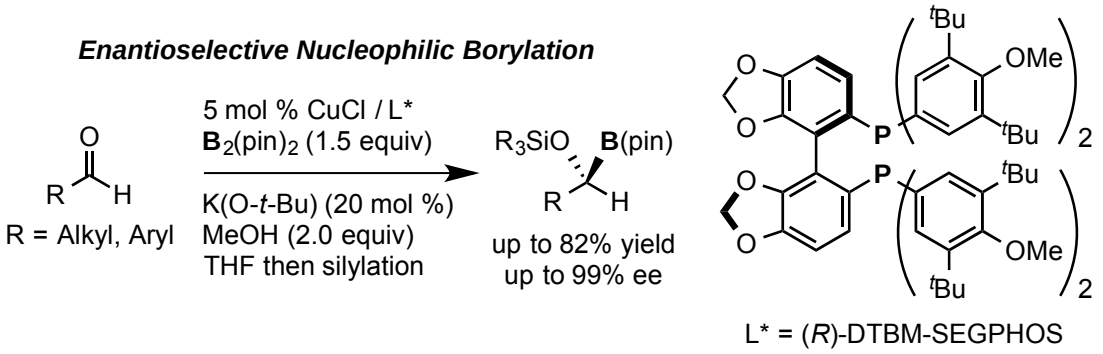
Scheme 1. Non-enantioselective Borylation of Aldehydes by Copper(I) Catalysis



Herein, the author reports the development of the first catalytic enantioselective borylation of aldehydes with a diboron compound to afford the corresponding chiral α-alkoxyorganoboronate esters using a copper(I)/DTBM-SEGPHOS complex catalyst (Scheme 2). This new reaction exhibited excellent enantioselectivities and a broad substrate scope, and the products could be converted to the corresponding enantiomerically enriched

secondary alcohol derivatives through stereospecific C–C bond forming reactions.

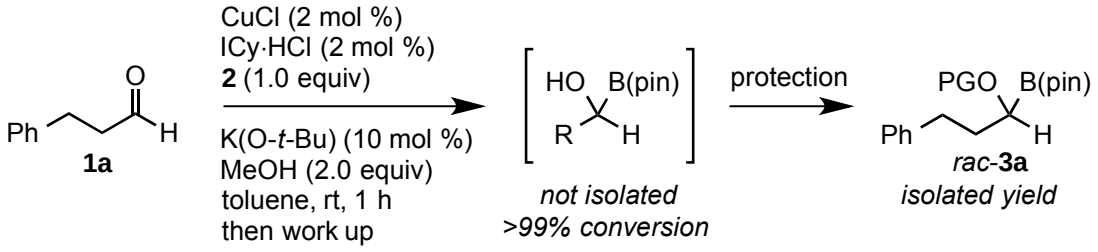
Scheme 2. The First Enantioselective Broyaltion of a C=O Double Bond



Results and Discussion

Initial efforts in this study were focused on the development of a suitable method for the purification and isolation of -hydroxyalkylboronate esters, which are generally unstable to purification by column chromatography over silica gel. Although the borylated products can be isolated by converting them to the corresponding organotrifluoroborates, it can be difficult to determine the ee values of these products by HPLC analysis.[9] With this in mind, it would be a critical requirement of any newly developed enantioselective process to incorporate an isolation procedure that would allow for HPLC analysis of the resulting products. We have attempted various etherifications of the hydroxy group in the product resulting from the borylation of aliphatic aldehyde **1a** in the presence of a copper(I)/ICy complex catalytic system, but yields were poor (Table 1, entries 1 3, <33% yields).[14] Other protection strategies, including the esterification and carbamylation under various conditions were investigated, but resulted in low isolated yields (Table 1, entries 4 7, <22% yields). Pleasingly, however, the desired product could be obtained in sufficiently good yield (Table 1, entry 8, 64% yield) when a standard silyl protection protocol was used to protect the hydroxyl group of the crude product. Furthermore, the resulting silyl ether products were suitable for HPLC analysis.[15]

Table 1. Investigation of the Protecting Group for Isolating the Aldehyde Borylation Product



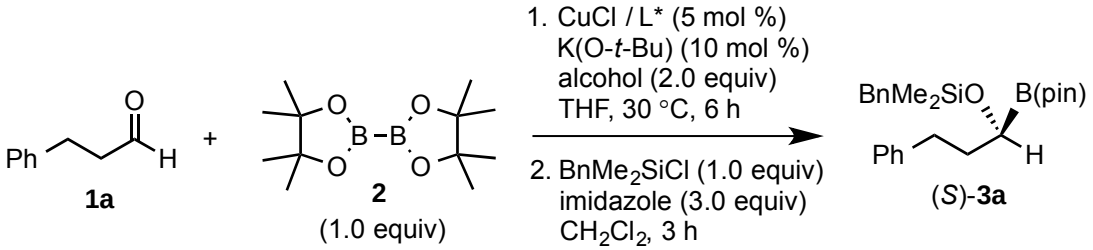
entry	PG	reaction conditions	isolated yield (%)
1	Bn-	BnBr, NaH, THF	26
2	Bn-	Benzyloxypyridinium salt, MgO	33
3	Me-	Me_3OBF_4, CH_2Cl_2	28
4	PhCO-	PhCOOH, EDC, DMAP	22
5	PhCO-	$(PhCO)_2O$, DMAP, CH_2Cl_2	20
6	PhCO-	PhCOCl, pyridine, DMAP	17
7	Me_2NCO-	Me_2NCOCl, pyridine, CH_2Cl_2	<5
8	Me_3Si-	Me_3SiCl, imidazole, CH_2Cl_2	64

With an optimized procedure in hand, the author proceeded to investigate the enantioselective borylation process using chiral bisphosphine ligands (Table 2). The reaction of aliphatic aldehyde **1a** with bis(pinacolato)diboron (**2**) (1.0 equiv) in the presence of CuCl/(*R*)-DTBM-SEGPHOS (5 mol %), K(O-*t*-Bu) (10 mol %) and MeOH (2.0 equiv), which was used as a proton source, in THF at 30 °C (Table 2) afforded the desired product (*S*)-**3a** in good yield (72%) with excellent enantioselectivity (96% ee) via the silyl protection of the crude α-hydroxyalkylboronate (Table 2, entry 1). The use of the less sterically encumbered SEGPHOS type ligands led to a significant decrease in the enantioselectivity of the reaction (Table 2, entries 2 and 3). The use of chiral phosphine ligands such as (*R*)-BINAP, (*R*,*R*)-QuinoxP* and (*R*,*R*)-BenzP* also gave poor results (Table 2, entries 4 6). The nature of the proton source was also determined to be important to the reactivity and enantioselectivity observed during the transformation (Table 2, entries 7 and 8). For example, the use of *i*-PrOH instead of MeOH resulted in a low yield (28%) and enantioselectivity (53% ee) (Table 2, entry 7). Furthermore, when the reaction was conducted without MeOH, the reaction was not completed

after longer reaction time (24 h) to afford a lower yield (34%) of the product with a lower enantioselectivity (22% ee) (Table 2, entry 8). This enantioselective borylation also proceeded with 1 mol % copper(I) catalyst and showed high enantioselectivity (96% ee), while longer reaction time was required for the completion of the reaction (Table 2, entry 9).

Next, the author proceeded to investigate the scope of enantioselective borylation using various aldehydes (Table 3). The reaction of simple aliphatic aldehydes proceeded well to give the desired products in sufficient yields with high enantioselectivities (Table 3, entries 1 5). Pleasingly, the products of the reactions involving α-branched aliphatic aldehydes could be isolated by flash column chromatography in good yields without the need for the protection of the alcohol moiety (Table 3, entries 2 and 3). It is noteworthy that this reaction exhibited good functional group compatibility, with aliphatic aldehydes bearing acetal, ester, Boc-protected amine, sulfonamide and benzyl ether groups reacting smoothly to give the corresponding chiral boronates with high enantioselectivities (Table 3, entries 6 10). Unfortunately, however, pivalaldehyde did not react under the current conditions (Table 3, entry 11). Several aromatic aldehydes were also investigated (Table 3, entries 12 14).[16] Benzaldehyde proceeded through the reaction with high enantioselectivity (90% ee) to give the desired product, albeit in a low isolated yield (i.e., 66% yield by NMR, 34% isolated yield) because of the poor stability of the product towards purification by column chromatography over silica gel (Table 3, entry 12). The application of the optimized conditions to the more sterically hindered 2-methylbenzaldehyde led to an improved chemical yield (66%), but the enantioselectivity was decreased (65% ee) (Table 2, entry 13). 2-Naphtaldehyde was also reacted with high enantioselectivity (99% ee), but resulted in a low isolated yield (22%) (Table 3, entry 14). Pleasingly, we found that the product derived from 2-naphtaldehyde could be isolated in good yield by converting the corresponding potassium α-hydroxylalkyltrifluoroborate using KHF_2 (71%).[9]

Table 2. Reaction Optimization Study



entry	chiral ligand	alcohol	NMR yield (%)	ee (%)
1	(*R*)-DTBM-SEGPHOS	MeOH	72	96
2	(*R*)-DM-SEGPHOS	MeOH	71	32
3	(*R*)-SEGPHOS	MeOH	74	24
4	(*R*)-BINAP	MeOH	66	69
5	(*R,R*)-QuinoxP*	MeOH	61	69
6	(*R,R*)-BenzP*	MeOH	68	60
7[c]	(*R*)-DTBM-SEGPHOS	*i*-PrOH	28	53
8[d]	(*R*)-DTBM-SEGPHOS	none	34	22
9[e]	(*R*)-DTBM-SEGPHOS	MeOH	65	96

[a]Conditions: CuCl (0.025 mmol), ligand (0.025 mmol), **1a** (0.5 mmol), bis(pinacolato)diboron (**2**) (0.5 mmol) and K(O-*t*-Bu) (0.05 mmol) in THF (1.0 mL). [b]The ee values for **3a** were determined by HPLC analysis. [c]The reaction time was 15 h. [d]The reaction time was 24 h. [e]The reaction was carried out with 1 mol % copper(I) catalyst and the reaction time was 24 h.

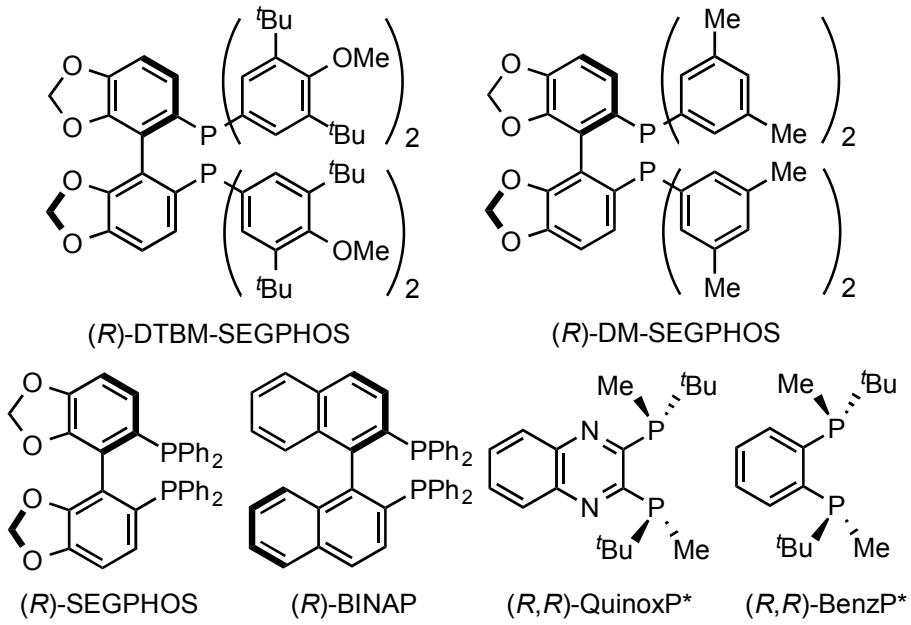
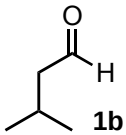
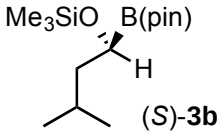
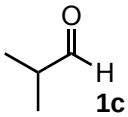
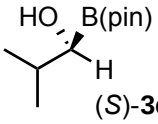
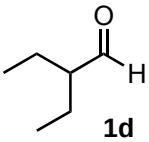
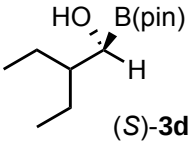
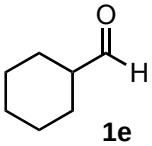
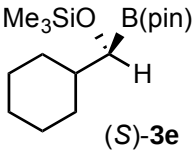
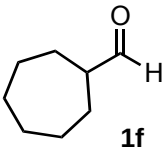
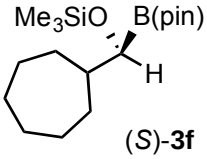
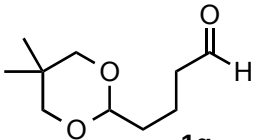
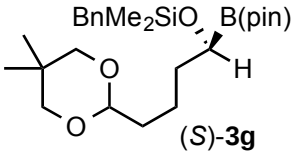
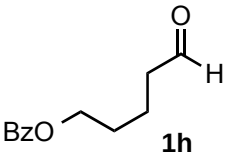
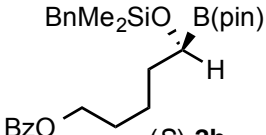
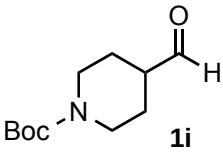
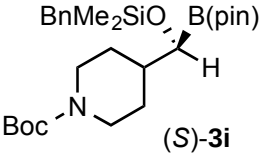
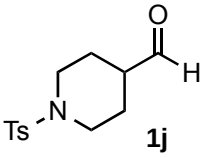
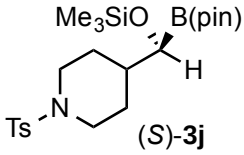
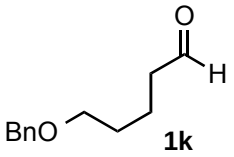
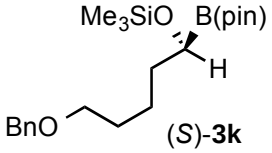
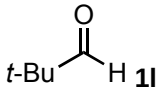
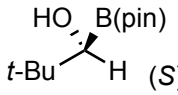
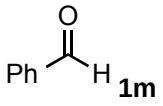
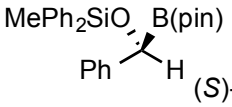
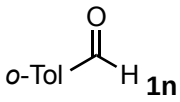
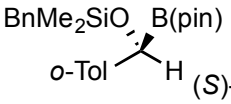
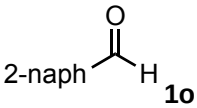
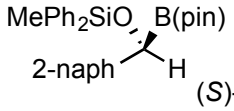


Table 3. Substrate Scope

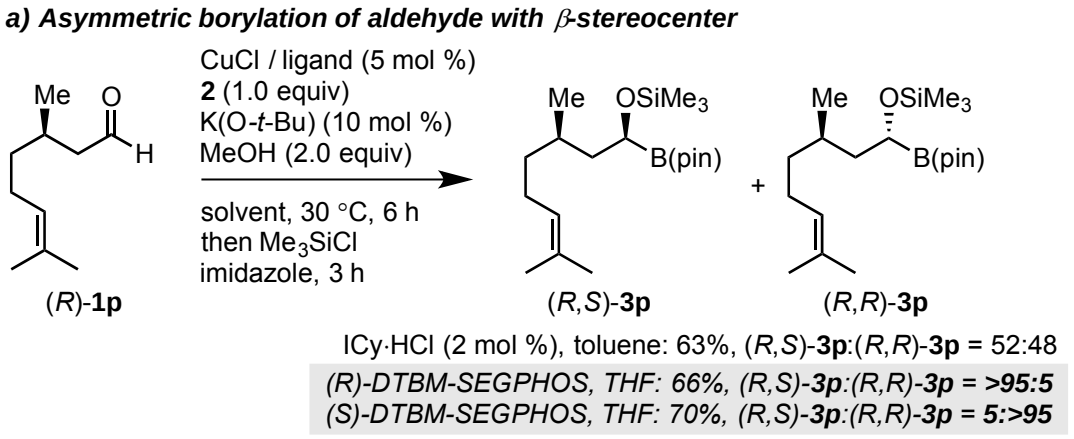
entry	substrate	product	yield (%)[b]	ee (%)[c]
1	 **1b**	 (*S*)-**3b**	51	96
2	 **1c**	 (*S*)-**3c**	77	96
3	 **1d**	 (*S*)-**3d**	82	92
4	 **1e**	 (*S*)-**3e**	61	95
5	 **1f**	 (*S*)-**3f**	84	95
6	 **1g**	 (*S*)-**3g**	66	85
7	 **1h**	 (*S*)-**3h**	69	90
8	 **1i**	 (*S*)-**3i**	81	95
9	 **1j**	 (*S*)-**3j**	52	91

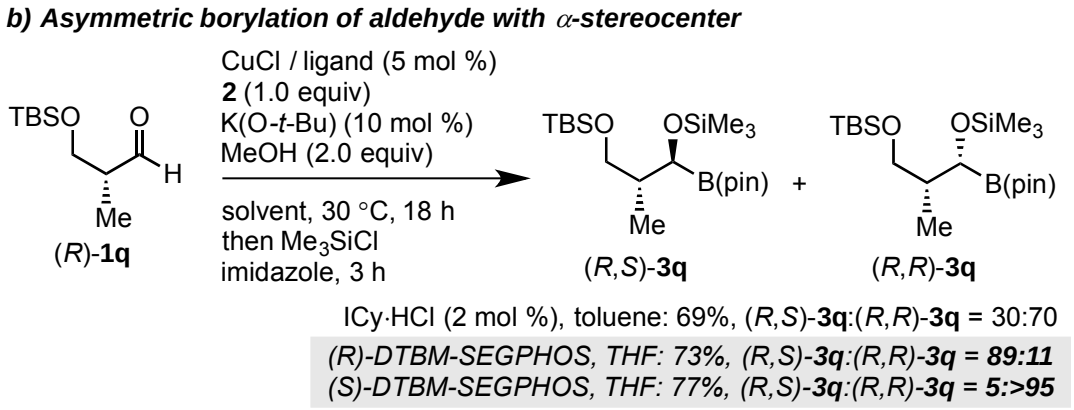
10	 **1k**	 (*S*)-**3k**	69	95
11	 **1l**	 (*S*)-**3l**	trace	–
12	 **1m**	 (*S*)-**3m**	34	90
13	 **1n**	 (*S*)-**3n**	66	65
14	 **1o**	 (*S*)-**3o**	22	99

[a]Conditions: CuCl (0.025 mmol), ligand (0.025 mmol), **1** (0.5 mmol), bis(pinacolato)diboron (**2**) (0.5 mmol) and K(O-*t*-Bu) (0.05 mmol) in THF (1.0 mL). [b]Isolated yield. [c]The ee values for **3** were determined by HPLC analysis after derivatization.

The author also tested the asymmetric borylation of chiral aldehyde substrates to ensure the extent of substrate versus catalyst control (Scheme 3). While reaction of (*R*)-citronellal [(*R*)-**1p**] led to diastereomeric mixtures (d.r. 52:48) using the ICy/CuCl achiral catalyst, excellent diastereoselectivities (d.r. >95:5) were observed when chiral DTBM-SEGPHOS ligand was used, indicating complete catalyst control (Scheme 2a). Furthermore, employing ICy as the ligand for the borylation of α chiral aldehyde (*R*)-**1q** resulted in a moderate diastereomeric ratio (d.r. 30:70) while using the ligand (*R*)- and (*S*)-DTBM-SEGPHOS provided high catalyst-controlled stereoselectivities (d.r. 89:11 and >95:5, respectively) (Scheme 2b).

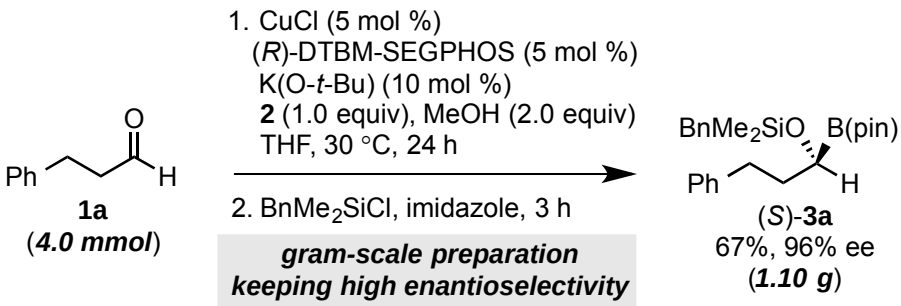
Scheme 3. Catalyst-Controlled Asymmetric Borylation of Chiral Aldehyde Substrates





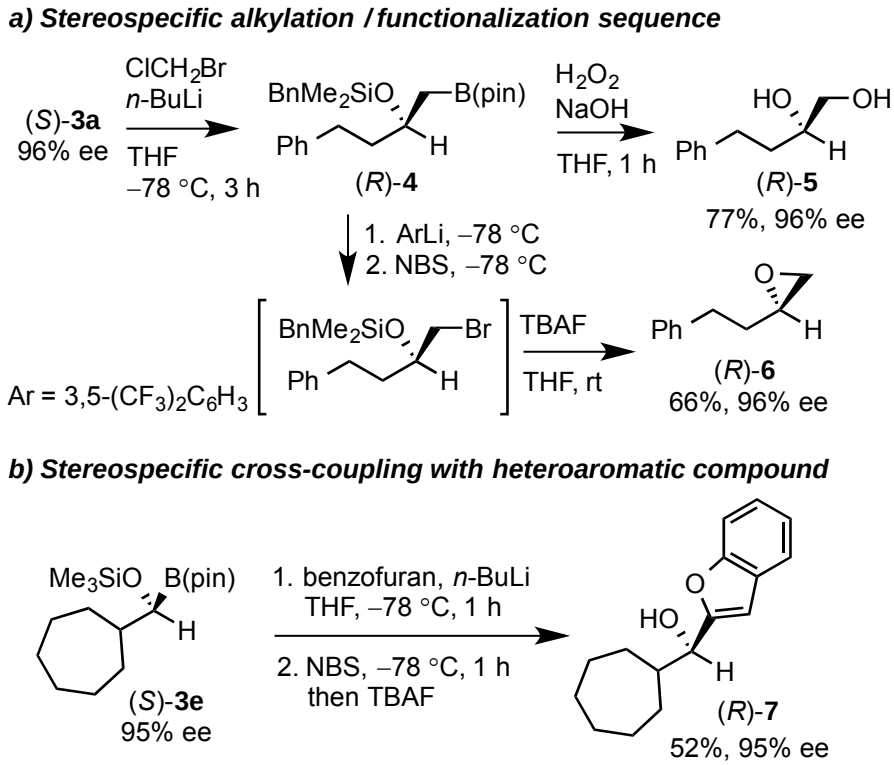
To demonstrate utility of this protocol, we investigated the gram-scale synthesis of α-alkoxyorganoboronate esters (Scheme 4). The borylation of **1a** was carried out on 4.0 mmol scale, affording the product (*S*)-**3a** in good yield with excellent enantioselectivity (67%, 96% ee).

Scheme 4. Gram-Scale Synthesis of Enantioenriched Chiral α-Alkoxyorganoboronate Esters



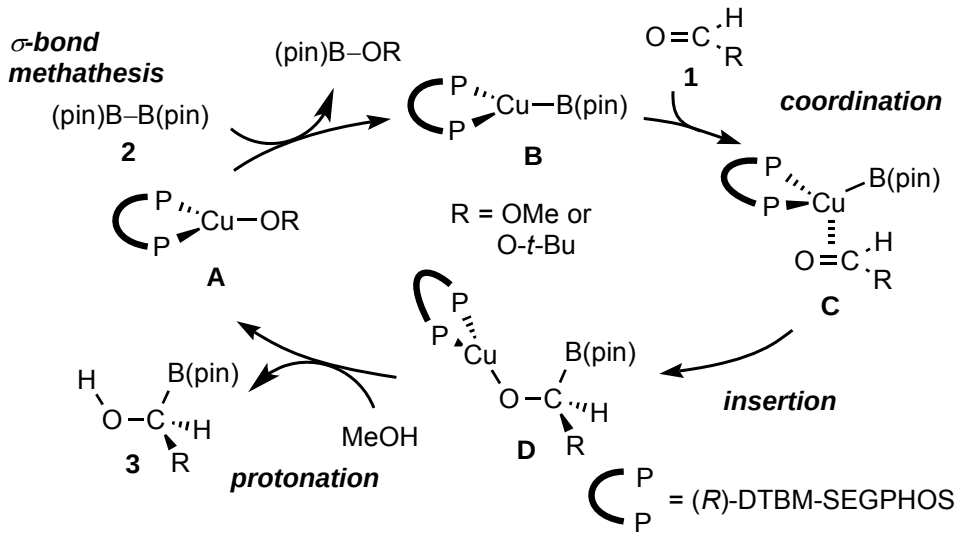
Enantioenriched α-alkoxyorganoboronate esters could potentially be used as building blocks in organic synthesis for the preparation of various functionalized chiral compounds. With this in mind, the author conducted a preliminary investigation of the stereospecific C–C bond forming reactions of the chiral boronate products using homologation methods (Scheme 4). The borylation product ((*S*)-**3a**) was subjected to a one-carbon homologation process where it was treated with a halomethyllithium reagent followed by H_2O_2 oxidation to provide the desired alkylated diol product in a completely stereospecific manner (Scheme 5).[17] Furthermore, the chiral epoxide (*R*)-**6** was successfully obtained using the same homologation strategy followed by a bromination/deprotection sequence (Scheme 5).[18] Aggarwal et al.[19] recently reported the enantiospecific coupling of optically active alkylboronates with aryllithium compounds, and this novel method was applied to the chiral boronate synthesized in the current study (Scheme 4b, eq. 8). The cross-coupling of (*S*)-**3e** with benzofuran proceeded and the subsequent deprotection of the silyl group afforded the arylated product (*R*)-**7** with excellent stereospecificity.

Scheme 5. Stereospecific C–C Bond Forming Reactions of Chiral α-Alkoxyorganoboronate Esters



The author have proposed a possible reaction mechanism for the current copper(I)-catalyzed borylation of aldehydes, which is shown in Figure 1.[20] The reaction of CuCl with the ligand and K(O-*t*-Bu) would result in the formation of copper(I) alkoxide **A**, which would initially react with diboron **2** to afford the boryl copper(I) intermediate **B**. The coordination of the aldehyde **1** to intermediate **B** would result in the formation of the π-complex **C**, which would undergo an insertion reaction to give the borylated copper(I) alkoxide **D**. The protonation of **D** would proceed in the presence of methanol to give the borylation product **3** as well as regenerating the copper(I) alkoxide A.

Figure 1. Proposed Reaction Mechanism for Copper(I)-Catalyzed Enantioselective Borylation of Aldehydes



Conclusion

In summary, the author have developed, for the first time, enantioselective nucleophilic borylation of aldehydes using a copper(I)/DTBM-SEGPHOS chiral complex catalyst to afford chiral -alkoxyorganoboronate esters with excellent enantioselectivities. The newly synthesized chiral α-alkoxyorganoboronate esters could be transformed to functionalized chiral alcohol derivatives using stereospecific C–C bond forming reactions. Recently, copper(I)-catalyzed enantioselective 1,2-silyl additions to C=O and C=N double bonds using a silylboron reagent have been reported.[20] The author believes that these studies as well as the present work on the catalytic

enantioselective 1,2-metal addition of carbonyl compounds will provide attractive umpolung pathways for the synthesis of useful enantioenriched functionalized alcohols. Further studies directed towards the elucidation of the reaction mechanism[20] and the development of methodologies for the enantioselective borylation of other carbonyl compounds such as ketones as well as imines are currently underway.

Experimental

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 (^{1}H: 400 MHz and ^{13}C: 100 MHz). Tetramethylsilane (^{1}H) and $CDCl_3$ (^{13}C) were employed as external standards, respectively. CuCl (ReagentPlus® grade, 224332-25G, ≥99%) and K(O-*t*-Bu) / THF (1.0 M, 328650-50ML) were purchased from Sigma-Aldrich Co. and used as received. Tetrachloroethane was used as an internal standard to determine NMR yields. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with 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. Elemental analyses and high-resolution mass spectra were recorded at the Center for Instrumental Analysis, Hokkaido University.

Procedure for the Copper(I)-Catalyzed Enantioselective Borylation of 1a (Table 1).

Copper chloride (2.5 mg, 0.025 mmol) and bis(pinacolato)diboron (127.0 mg, 0.50 mmol), (*R*)-DTBM-SEGPHOS (29.5 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. THF (1.0 mL) and K(O-*t*-Bu)/THF (1.0 M, 0.05 mL, 0.05 mmol) were added in the vial through the rubber septum. After **1a** (67.4 mg, 0.50 mmol) was added to the mixture at 30 °C, MeOH (40.5 μL, 1.0 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short silica

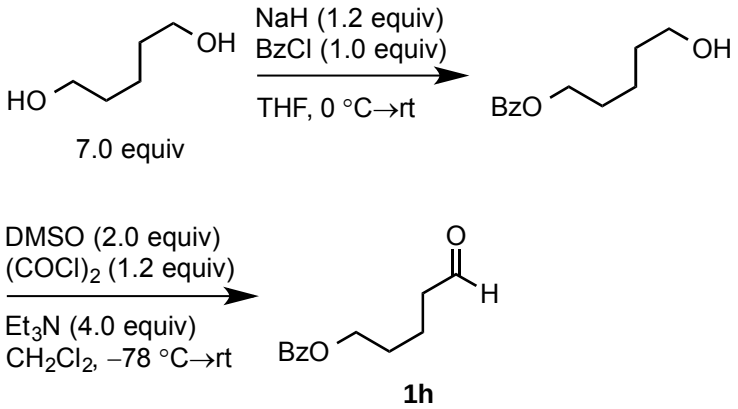
gel column eluting with Et_2O. The crude mixture was placed in a reaction vial and then diluted with CH_2Cl_2. Imidazole (102.1 mg, 1.5 mmol) was added to the solution and then $BnMe_2SiCl$ (92.4 mg, 0.50 mmol) was added dropwise. After stirred for 3 h, the mixture was passed through a short silica gel column eluting with Et_2O/CH_2Cl_2 (1:1). The crude material was purified by flash column chromatography (SiO_2, Et_2O/hexane, typically 0:100–8:92) to give the corresponding borylation product (*S*)-**3a** as a colorless oil. The flash column chromatography should be done within 5 min after the crude mixture was applied on the silica gel surface; otherwise the products are obtained in low yield. As for products containing polar functional groups, their longer retention time in the column may have resulted in decomposition of products, leading to a lower isolated yield.

The Choice of Silyl Protecting Group for Isolating the Borylation Products.

We used various silyl protecting groups (Me_3Si to $BnMe_2Si$ to Ph_2MeSi) to facilitate the isolation and the HPLC analysis. We chose the silyl protecting group with two intentions in mind. One is to enable UV detection for aldehydes without UV-detectable functional group, by attaching a detectable protecting group. The other is to ensure clean peak separation during HPLC analysis. For example, for chiral organoboronate **3a**, using the $BnMe_2Si$ group enabled better peak separation in comparison to when it was protected using other silyl groups.

The substrates for asymmetric borylation **1a** **1g** and **1l** **1n** were purchased from commercial suppliers. The received aldehydes from the suppliers were subjected to purification by distillation under reduced pressure before use.

Preparation of 5-oxopentyl benzoate (1h).[22, 23]



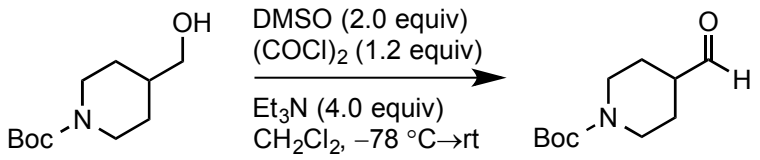
A solution of diol (7.4 mL, 70.0 mmol) in THF (18.0 mL) was added dropwise to a suspension of NaH (60 wt.%, 480.0 mg, 12.0 mmol) in THF (36.0 mL) at room temperature. Benzoyl chloride (1.20 mL, 10.0 mmol) was then added to the mixture and the reaction mixture was stirred for 5 h. The resulting suspension was diluted with diethyl ether and quenched by the addition of saturated aqueous NH_4Cl. The mixture was extracted with EtOAc three times and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc/hexane, 3:97–20:80) to afford the mono-protected product (1.624 g, 7.8 mmol, 78%) as a colorless oil.

A solution of dimethyl sulfoxide (DMSO) (425.0 μL, 6.0 mmol) in CH_2Cl_2 (2.5 mL) was added to a solution of oxalylchloride (308.7 μL, 3.6 mmol) in CH_2Cl_2 (10.0 mL) at –78 °C. The mixture was stirred for 5 min at –78 °C and a solution of diol (624.8 mg, 3.0 mmol) in CH_2Cl_2 (2.5 mL) was added dropwise. After stirring for 15 min, Et_3N (1.7 mL, 12.0 mmol) was added to the reaction mixture within 5 min and then allowed to warm to 0 °C. Aqueous $NaHCO_3$ was added to the reaction mixture after 30 min, the mixture was then extracted with CH_2Cl_2 three times and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash

chromatography (SiO_2, EtOAc/hexane, 0:100–10:90) to afford the corresponding aldehyde **1h** (532.1 mg, 2.6 mmol, 86%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.76–1.88 (m, 4H), 2.50–2.59 (m, 2H), 4.35 (t, *J* = 6.2 Hz, 2H), 7.45 (t, *J* = 7.9 Hz, 2H), 7.57 (tt, *J* = 1.5, 7.6 Hz, 1H), 8.01–8.07 (m, 2H), 9.81 (t, *J* = 1.5 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 18.8 (CH_2), 28.2 (CH_2), 43.4 (CH_2), 64.5 (CH_2), 128.5 (*C*H), 129.6 (*C*H), 130.3 (*C*), 133.0 (*C*H), 166.6 (*C*), 202.1 (*C*H). HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{15}O_3$, 207.10157; found, 207.10180.

Preparation of *tert*-butyl 4-formylpiperidine-1-carboxylate (1i).

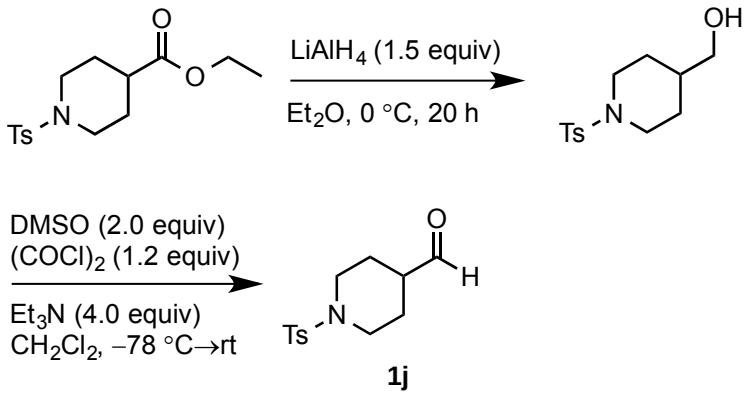


1i

The starting material was purchased from commercially suppliers. A solution of DMSO (568.0 μL, 8.0 mmol) in CH_2Cl_2 (3.5 mL) was added to a solution of oxalylchloride (411.6 μL, 8.0 mmol) in CH_2Cl_2 (13.0 mL) at –78 °C. The mixture was stirred for 5 min at –78 °C and a solution of alcohol (861.2 mg, 4.0 mmol) in CH_2Cl_2 (3.5 mL) was added dropwise. After stirring for 15 min, Et_3N (2.2 mL, 16.0 mmol) was added to the mixture within 5 min, and then the reaction mixture was allowed to warm to 0 °C. Aqueous $NaHCO_3$ was added to the mixture after 30 min and the mixture was extracted with CH_2Cl_2 three times and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc/hexane, 5:95–30:70) to afford the corresponding aldehyde **1i** (725.1 mg, 3.4 mmol, 85%) as a white solid.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.46 (s, 9H), 1.49–1.62 (m, 2H), 1.90 (br, d, *J* = 11.4 Hz, 2H), 2.42 (tt, *J* = 4.1, 10.7 Hz, 1H), 2.93 (t, *J* = 11.4 Hz, 2H), 3.99 (br, d, *J* = 8.1 Hz, 2H), 9.67 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.5 (CH_2), 27.8 (CH_3), 42.5 (br, CH_2), 47.2 (*C*H), 78.8 (*C*), 153.9 (*C*), 202.2 (*C*H). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{11}H_{19}NO_3$, 213.13591; found, 213.13649.

Preparation of *N*-tosylpiperidine-4-carbaldehyde (1j).



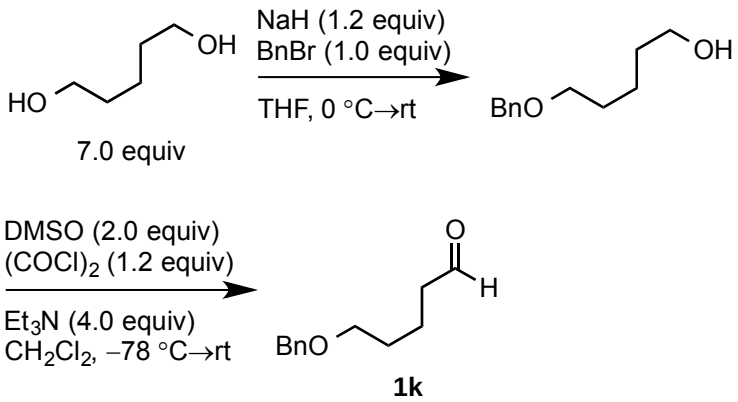
The starting material was obtained from the corresponding amine through the standard tosyl protection. A solution of the ethyl ester (7.785 g, 25.0 mmol) in Et_2O (25.0 mL) was added dropwise to a slurry of $LiAlH_4$ (1.423 g, 37.5 mmol) in Et_2O (25.0 mL) at 0 °C. After stirred for 20 min, the reaction 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 solvents were removed by evaporation under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc/CH_2Cl_2, 0:100–5:95) to afford the corresponding alcohol (6.061 g, 22.5 mmol, 90%) as a white solid.

A solution of DMSO (427.9 μL, 6.0 mmol) in CH_2Cl_2 (2.6 mL) was added to a solution of oxalylchloride (308.8 μL, 3.6 mmol) in CH_2Cl_2 (10.0 mL) at –78 °C. The mixture was stirred for 5 min at –78 °C and a solution of the alcohol (808.0 g, 3.0 mmol) in CH_2Cl_2 (2.6 mL) was added dropwise. After stirring for 15 min, Et_3N (1.7 mL, 12.0 mmol) was added within 5 min and the reaction mixture was allowed to warm to 0 °C. Aqueous $NaHCO_3$ was then added after 30 min and the mixture was extracted with CH_2Cl_2 three times and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc/hexane, 2:98–10:90) to afford the corresponding aldehyde **1j** (649.6 mg, 2.4 mmol, 81%) as a white solid.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.72–1.84 (m, 2H), 1.97 (q, *J* = 4.2 Hz, 1H), 2.01 (q, *J* = 4.0 Hz, 1H), 2.23 (dq, *J* = 4.8, 14.7 Hz, 1H), 2.44 (s, 3H), 2.56–2.66 (m, 2H), 3.52 (dt, *J* = 4.4, 12.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 9.60 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 21.4 (CH_3), 24.6 (CH_2), 45.0

(CH_2), 46.6 (CH), 127.5 (CH), 129.6 (CH), 132.8 (*C*), 143.6 (*C*), 202.3 (CH). HRMS–EI (*m*/*z*): $[M+H]^+$ calcd for $C_{13}H_{18}NO_3S$, 268.10019; found, 268.10057.

Preparation of 5-(benzyloxy)pentanal (1k).



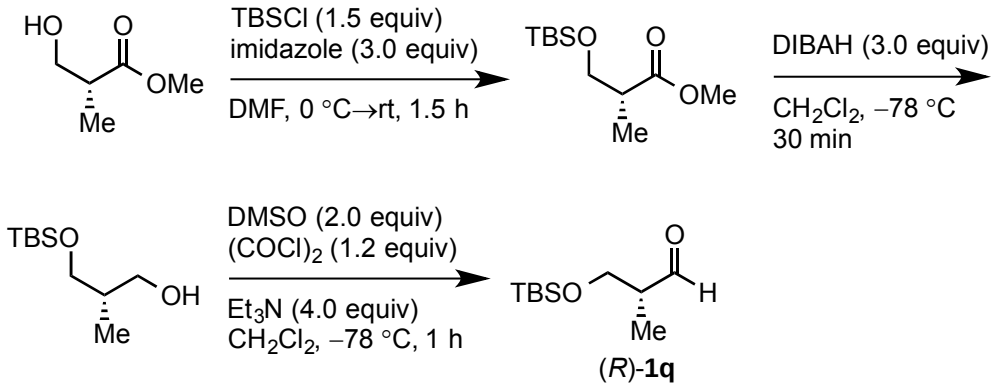
A solution of diol (7.4 mL, 70.0 mmol) in THF (18.0 mL) was added to a suspension of NaH (60 wt.%, 480.0 mg, 12.0 mmol) in THF (36.0 mL) at room temperature. Benzyl bromide (1.2 mL, 10.0 mmol) was then added and the reaction mixture was stirred for 5 h. The resulting suspension was diluted with ether and quenched with saturated aqueous NH_4Cl. The mixture was extracted with EtOAc three times and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc/hexane, 0:100–40:60) to afford the mono-protected product (1.789 g, 9.2 mmol, 92%) as a colorless oil.

A solution of DMSO (1.28 mL, 18.0 mmol) in CH_2Cl_2 (8.0 mL) was added to a solution of oxalylchloride (926.2 μL, 10.8 mmol) in CH_2Cl_2 (32.0 mL) at –78 °C. The mixture was stirred for 5 min at –78 °C and a solution of diol (1.75 g, 9.0 mmol) in CH_2Cl_2 (8.0 mL) was added dropwise. After stirring for 15 min, Et_3N (5.0 mL, 36.0 mmol) was added within 5 min and the reaction mixture was allowed to warm to 0 °C. Aqueous $NaHCO_3$ was then added after 30 min and the mixture was extracted with CH_2Cl_2 three times and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc/hexane, 0:100–10:90) to afford the corresponding aldehyde **1k** (1.52 g, 7.9 mmol, 88%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.57–1.80 (m, 4H), 2.46 (dt, *J* = 1.7, 7.3 Hz, 2H), 3.49 (t, *J* = 6.2 Hz, 2H), 4.50 (s, 2H), 7.26–7.38 (m, 5H), 9.76 (t, *J* = 1.8 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 18.9 (CH_2), 29.1 (CH_2), 43.5 (CH_2), 69.7 (CH_2), 72.9 (CH_2), 127.56 (CH), 127.62 (CH), 128.4 (CH), 138.4 (*C*), 202.5 (CH).

HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{16}O_2$, 192.11503; found, 192.11410.

Preparation of (*R*)-3-[(*tert*-butyldimethylsilyl)oxy]-2-methylpropanal [(*R*)-1q].[24]



TBS chloride (2.26 g, 15.0 mmol) was added to a cooled (0 ℃) solution of methyl (*R*)- hydroxyisobutyrate (1.18 g, 10.0 mmol) and imidazole (2.04 g, 30.0 mmol) in dry DMF (15.0 mL) under nitrogen atmosphere. After stirring for 2 h at room temperature, water was then added and the mixture was extracted with CH_2Cl_2 three times and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc/hexane, 0:100–10:90) to afford the corresponding silyl ether (2.32 g, 10.0 mmol, >99%) as a colorless oil.

DIBAL-H (30.0 mL, 30.0 mmol, 1.0 M hexane, 3.0 equiv) was added to a cooled (78 ℃) solution of protected ester (2.32g, 10 mmol) in dry CH_2Cl_2 (40.0 mL) under nitrogen atmosphere. After stirring for 30 min, water and small amount of aqueous NaOH (2.5 M) were added and the mixture was filtered through Celite. The resultant reaction mixture was then dried over MgSO4, filtered and concentrated under reduced pressure to afford the corresponding diol (1.70 g, 8.3 mmol, 83%) as a colorless oil.

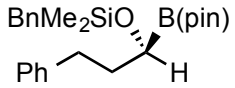
A solution of DMSO (1.14 mL, 16.0 mmol) in CH_2Cl_2 (7.0 mL) was added to a solution of oxalyl chloride (827.0 μL, 9.6 mmol) in CH_2Cl_2 (25.0 mL) at –78 °C. The mixture was stirred for 5 min at –78 °C and a solution of the alcohol (1.64 g, 8.0 mmol) in CH_2Cl_2 (7.0 mL) was added dropwise. After stirring for 15 min, Et_3N (4.5 mL, 32.0 mmol) was added and the reaction mixture was stirred for 1 h at –78 °C. Aqueous $NaHCO_3$ was then added at

0 °C and the mixture was extracted with CH_2Cl_2 three times and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, EtOAc/hexane, 0:100–10:90) to afford the corresponding aldehyde (*R*)-**1q** (1.02 g, 5.04 mmol, 63%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.055 (s, 6H), 0.88 (s, 9H), 1.09 (d, *J* = 7.0 Hz, 3H), 2.49–2.58 (m, 1H), 3.81 (dd, *J* = 6.4, 10.5 Hz, 1H), 3.85 (dd, *J* = 5.3, 10.4 Hz, 1H), 9.74 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –5.62 (CH_3), –5.59 (CH_3), 10.2 (CH_3), 18.1 (*C*), 25.7 (CH_3), 48.7 (*C*H), 63.4 (CH_2), 204.5 (*C*H). HRMS–EI (*m*/*z*): [M CH_3]$^+$ calcd for $C_9H_{19}O_2Si$, 187.11543; found, 187.11512. $[\alpha]_D^{23.4}$ –53.65 (*c* 1.0 in $CHCl_3$).

Borylation Product Characterization

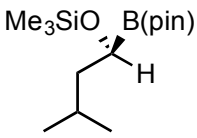
(*S*)-Benzyldimethyl[3-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) propoxy]silane [(*S*)-3a].



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

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.070 (s, 3H), 0.085 (s, 3H), 1.26 (s, 6H), 1.27 (s, 6H), 1.80–1.97 (m, 2H), 2.19 (d, *J* = 14.3 Hz, 1H), 2.25 (d, *J* = 13.9 Hz, 1H), 2.57–2.67 (m, 1H), 2.69–2.80 (m, 1H), 3.58 (dd, *J* = 5.5, 8.1 Hz, 1H), 7.04–7.10 (m, 2H), 7.14–7.31 (m, 8H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –2.14 (CH_3), –2.00 (CH_3), 24.5 (CH_3), 25.0 (CH_3), 26.9 (CH_2), 32.9 (CH_2), 36.3 (CH_2), 83.9 (*C*), 124.0 (*C*H), 125.6 (*C*H), 128.1 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 128.5 (*C*H), 139.5 (*C*), 142.5 (*C*). HRMS–ESI (*m*/*z*): [M+Na]$^+$ calcd for $C_{24}H_{35}O_3BNaSi$, 432.23770; found, 432.23764. $[\alpha]_D^{20.9}$ –1.50 (*c* 1.0 in $CHCl_3$, 96% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, *S* isomer: t_R = 10.89 min., *R* isomer: t_R = 16.55 min.

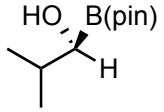
(*S*)-Trimethyl[3-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy]silane [(*S*)-3b].



(*S*)-**3b**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.10 (s, 9H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 1.25 (s, 6H), 1.26 (s, 6H), 1.54–1.62 (m, 2H), 1.72–1.84 (m, 1H), 3.54 (dd, *J* = 4.4, 10.6 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –0.063 (CH_3), 21.5 (CH_3), 23.5 (CH_3), 24.2 (*C*H), 24.5 (CH_3), 24.9 (CH_3), 42.9 (CH_2), 58.5 (br, B–*C*H), 83.6 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{14}H_{31}O_3BNaSi$, 308.20640; found, 308.20645. $[\alpha]_D^{19.4}$ +10.83 (*c* 0.9 in $CHCl_3$, 96% ee). The ee value was determined by HPLC analysis of the corresponding ester after homologation, deprotection of silyl ether using TBAF and subsequent esterification with *p*-nitorobenzoyl chloride of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, *S* isomer: t_R = 13.93 min., *R* isomer: t_R = 17.35 min.

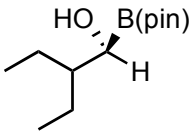
(*S*)-2-Methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propan-1-ol [(*S*)-3c].



(*S*)-**3c**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.96 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.3 Hz, 3H), 1.28 (s, 12H), 1.84–1.97 (m, 1H), 3.38 (t, *J* = 4.0 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 18.5 (CH_3), 19.3 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 32.2 (*C*H), 66.3 (br, B–*C*H), 84.0 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{10}H_{21}O_3BNa$, 222.15123; found, 222.15142. $[\alpha]_D^{26.6}$ –8.43 (*c* 1.6 in $CHCl_3$, 96% ee). The ee value was determined by HPLC analysis of the corresponding ester after standard silyl protection, homologation, followed by deprotection of silyl ether using TBAF and subsequent esterification with p-nitorobenzoyl chloride of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® IC-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, *S* isomer: t_R = 26.75 min., *R* isomer: t_R = 32.11 min.

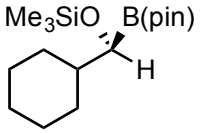
(*S*)-2-Ethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-ol [(*S*)-3d].



(*S*)-**3d**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.90–0.95 (m, 6H) 1.28 (s, 12H), 1.31–1.50 (m, 5H), 3.66 (br, s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 12.0 (CH_3), 12.2 (CH_3), 23.3 (CH_2), 23.6 (CH_2), 24.7 (CH_3), 24.8 (CH_3), 45.7 (*C*H), 62.1 (br, B–*C*H), 84.1 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{12}H_{25}O_3BNa$, 250.18253; found, 250.18187. $[\alpha]_D^{20.5}$ –5.75 (*c* 1.0 in $CHCl_3$, 93% ee). The ee value was determined by HPLC analysis of the corresponding ester after standard silyl protection, homologation, followed by deprotection of silyl ether using TBAF and subsequent esterification with p-nitorobenzoyl chloride of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, *S* isomer: t_R = 13.41 min., *R* isomer: t_R = 15.64 min.

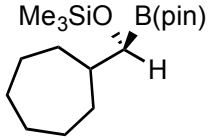
(*S*)-[Cyclohexyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methoxy]trimethylsilane [(*S*)-3e].



(*S*)-**3e**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.086 (s, 9H), 0.95–1.25 (m, 4H), 1.26 (s, 6H), 1.27 (s, 6H), 1.47–1.83 (m, 7H), 3.23 (d, *J* = 7.0 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –0.14 (CH_3), 24.5 (CH_3), 24.9 (CH_3), 26.2 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 41.8 (*C*H), 66.0 (br, B–*C*H), 83.5 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{33}O_3BNaSi$, 334.22205; found, 334.22222. $[\alpha]_D^{21.6}$ +3.72 (*c* 1.1 in $CHCl_3$, 95% ee). The ee value was determined by HPLC analysis of the corresponding ester after homologation, deprotection of silyl ether using TBAF and subsequent esterification with p-nitorobenzoyl chloride of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, *S* isomer: t_R = 14.57 min., *R* isomer: t_R = 16.16 min.

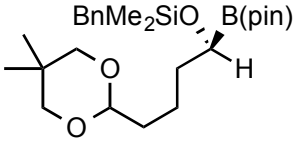
(*S*)-[Cycloheptyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methoxy]trimethylsilane [(S)-3f].



(*S*)-**3f**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.089 (s, 9H), 1.15–1.81 (m, 13H), 1.26 (s, 6H), 1.27 (s, 6H), 3.23 (d, *J* = 6.9 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –0.034 (CH_3), 24.5 (CH_3), 24.9 (CH_3), 26.7 (CH_2), 26.8 (CH_2), 28.51 (CH_2), 28.53 (CH_2), 30.5 (CH_2), 31.3 (CH_2), 43.3 (*C*H), 66.0 (br, B–*C*H), 83.5 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{35}O_3BNaSi$, 348.23770; found, 348.23784. $[\alpha]_D^{19.3}$ +6.81 (*c* 1.1 in $CHCl_3$, 95% ee). The ee value was determined by HPLC analysis of the corresponding ester after homologation, deprotection of silyl ether using TBAF and subsequent esterification with p-nitorobenzoyl chloride of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, *S* isomer: t_R = 23.75 min., *R* isomer: t_R = 29.17 min.

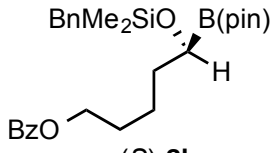
(*S*)-Benzyl[4-(5,5-dimethyl-1,3-dioxan-2-yl)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy]dimethylsilane [(*S*)-3g].



(*S*)-**3g**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.057 (s, 3H), 0.065 (s, 3H), 0.71 (s, 3H), 1.18 (s, 3H), 1.26 (s, 6H), 1.27 (s, 6H), 1.38–1.70 (m, 6H), 2.17 (d, *J* = 14.3 Hz, 1H), 2.22 (d, *J* = 13.9 Hz, 1H), 3.41 (d, *J* = 10.6 Hz, 2H), 3.51 (dd, *J* = 5.3, 7.9 Hz, 1H), 3.59 (d, *J* = 11.4 Hz, 2H), 3.60 (s, 1H), 4.39 (t, *J* = 5.1 Hz, 1H), 7.02–7.09 (m, 3H), 7.16–7.23 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –2.23 (CH_3), –2.15 (CH_3), 16.4 (CH_2), 20.9 (CH_2), 21.8 (CH_3), 23.0 (CH_3), 24.5 (CH_3), 24.9 (CH_3), 26.8 (CH_2), 30.1 (*C*), 33.9 (CH_2), 34.7 (CH_2), 61.0 (br, B–*C*H), 77.1 (CH_2), 83.7 (*C*), 102.1 (*C*H), 123.9 (*C*H), 128.0 (*C*H), 128.3 (*C*H), 139.5 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{25}H_{43}O_5BNaSi$, 484.29013; found, 484.29005. $[\alpha]_D^{19.6}$ +25.50 (*c* 1.1 in $CHCl_3$, 85% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, *S* isomer: t_R = 14.80 min., *R* isomer: t_R = 19.29 min.

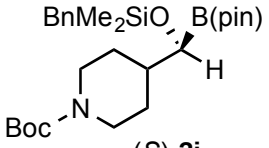
(*S*)-5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-[(trimethylsilyl)oxy]pentyl benzoate [(*S*)-3h].



(*S*)-**3h**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.010 (s, 9H), 1.24 (s, 6H), 1.25 (s, 6H), 1.43–1.56 (m, 1H), 1.57–1.71 (m, 3H), 1.73–1.85 (m, 2H), 3.48–3.52 (m, 1H), 4.32 (t, *J* = 6.8 Hz, 2H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.52–7.57 (m, 1H), 8.01–8.06 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –0.11 (CH_3), 23.0 (CH_2), 24.4 (CH_3), 24.9 (CH_3), 28.7 (CH_2), 33.7 (CH_2), 61.0 (br, B–CH), 65.0 (CH_2), 83.7 (*C*), 128.2 (CH), 129.5 (CH), 130.5 (*C*), 132.7 (CH), 166.6 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{35}O_5BNaSi$, 428.22753; found, 428.22745. $[\alpha]_D^{22.0}$ +18.25 (*c* 1.0 in $CHCl_3$, 90% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, *R* isomer: t_R = 13.67 min., *S* isomer: t_R = 14.36 min.

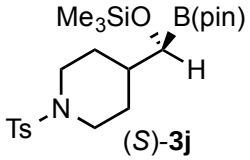
***tert*-Butyl (*S*)-4-{[(benzyldimethylsilyl)oxy][4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl]methyl}piperidine-1-carboxylate [(*S*)-3i].**



(*S*)-**3i**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.036 (s, 3H), 0.058 (s, 3H), 1.21–1.29 (m, 1H), 1.26 (s, 6H), 1.27 (s, 6H), 1.46 (s, 9H), 1.56 (d, *J* = 13.2 Hz, 1H), 1.61–1.72 (m, 3H), 2.16 (d, *J* = 13.9 Hz, 1H), 2.22 (d, *J* = 14.3 Hz, 1H), 2.65 (br, s, 2H), 3.31 (d, *J* = 6.6 Hz, 1H), 4.11 (br, s, 2H), 7.02–7.09 (m, 3H), 7.19 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –2.34 (CH_3), –2.07 (CH_3), 24.6 (CH_3), 25.0 (CH_3), 26.8 (CH_2), 28.4 (CH_3), 28.6 (CH_2), 28.7 (CH_2), 40.4 (CH), 44.0 (br, N–CH_2), 65.0 (br, B–CH), 79.1 (*C*), 83.8 (*C*), 124.0 (CH), 128.1 (CH), 128.4 (CH), 139.3 (*C*), 154.8 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{26}H_{44}O_5NBNaSi$, 511.30103; found, 511.30131. $[\alpha]_D^{20.4}$ +19.45 (*c* 1.1 in $CHCl_3$, 95% ee). Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 0.25/99.75, 0.5 mL/min, 40 °C, *R* isomer: t_R = 59.12 min., *S* isomer: t_R = 60.72 min.

(*S*)-4-{[4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl][(trimethylsilyl)oxy]methyl}-1-tosylpiperidine [(*S*)-3j].

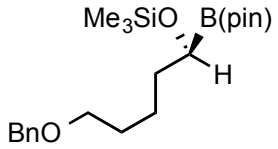


(*S*)-**3j**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.060 (s, 9H), 1.23 (s, 6H), 1.24 (s, 6H), 1.39–

1.51 (m, 3H), 1.60–1.68 (m, 1H), 1.73–1.82 (m, 1H), 2.13–2.26 (m, 2H), 2.43 (s, 3H), 3.23 (d, J = 5.1 Hz, 1H), 3.77–3.87 (m, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.4, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –0.21 (CH_3), 21.4 (CH_3), 24.5 (CH_3), 24.9 (CH_3), 28.0 (CH_2), 28.2 (CH_2), 39.4 (*C*H), 46.3 (*C*H), 46.5 (*C*H), 64.3 (br, B–*C*H), 83.8 (*C*), 127.6 (*C*H), 129.5 (*C*H), 133.1 (*C*), 143.2 (*C*). HRMS–ESI (*m*/*z*): [M+Na]$^+$ calcd for $C_{22}H_{38}O_5NBNaSSi$, 489.22615; found, 489.22590. $[\alpha]_D^{20.3}$ +34.96 (*c* 1.5 in $CHCl_3$, 92% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, *S* isomer: t_R = 21.72 min., *R* isomer: t_R = 23.96 min.

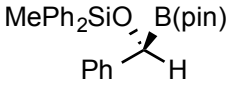
(*S*)-{[5-(Benzyloxy)-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl]oxy}trimethylsilane [(*S*)-3k].



(*S*)-**3k**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.094 (s, 9H), 1.24 (s, 6H), 1.25 (s, 6H), 1.33–1.69 (m, 6H), 3.43–3.51 (m, 3H), 4.49 (s, 2H), 7.24–7.35 (m, 5H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –0.091 (CH_3), 23.1 (CH_2), 24.5 (CH_3), 24.9 (CH_3), 29.7 (CH_2), 33.9 (CH_2), 61.0 (br, B–*C*H), 70.4 (CH_2), 72.8 (CH_2), 83.6 (*C*), 127.4 (*C*H), 127.5 (*C*H), 128.3 (*C*H), 138.7 (*C*). HRMS–ESI (*m*/*z*): [M+Na]$^+$ calcd for $C_{21}H_{37}O_4BNaSi$, 414.24827; found, 414.24834. $[\alpha]_D^{19.3}$ +4.00 (*c* 1.0 in $CHCl_3$, 95% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.1/99.9, 0.5 mL/min, 40 °C, *R* isomer: t_R = 19.12 min., *S* isomer: t_R = 20.00 min.

(*S*)-Methyldiphenyl[phenyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methoxy]silane [(*S*)-3m].

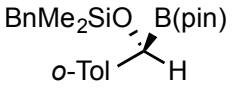


(*S*)-**3m**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.61 (s, 3H), 1.12 (s, 12H), 4.76 (s, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.23–7.43 (m, 10H), 7.55–7.65 (m, 4H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –2.49 (CH_3), 24.3 (CH_3), 24.6 (CH_3), 64.3 (br, B–*C*H), 84.0 (*C*), 125.7 (*C*H), 126.2 (*C*H), 127.66 (*C*H), 127.69 (*C*H), 128.1 (*C*H), 129.6 (*C*H), 134.5 (*C*H), 134.6 (*C*H), 136.2 (*C*), 136.3 (*C*), 141.8 (*C*). HRMS–ESI (*m*/*z*): [M+Na]$^+$ calcd for $C_{26}H_{31}O_3BNaSi$, 452.20640; found, 452.20649. $[\alpha]_D^{26.5}$ –10.00 (*c* 1.4 in $CHCl_3$, 90% ee). Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 0.1/99.9, 0.5 mL/min,

40 °C, *R* isomer: t_R = 11.03 min., *S* isomer: t_R = 11.64 min.

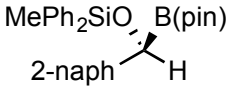
(*S*)-Benzyldimethyl[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)(*o*-tolyl)methoxy]silane [(*S*)-3n].



(*S*)-**3n**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.021 (s, 3H), 0.039 (s, 3H), 1.18 (s, 6H), 1.20 (s, 6H), 2.15 (d, *J* = 13.9 Hz, 1H), 2.20 (d, *J* = 13.9 Hz, 1H), 2.28 (s, 3H), 4.71 (s, 1H), 6.98–7.21 (m, 8H), 7.46 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –2.26 (CH_3), –1.93 (CH_3), 19.4 (CH_3), 24.4 (CH_3), 24.6 (CH_3), 27.0 (CH_2), 62.3 (br, B–*C*H), 83.8 (*C*), 123.9 (*C*H), 125.8 (*C*H), 126.1 (*C*H), 126.6 (*C*H), 128.1 (*C*H), 128.3 (*C*H), 129.8 (*C*H), 134.1 (*C*), 139.3 (*C*), 140.5 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{23}H_{33}O_3BNaSi$, 418.22205; found, 418.22239. $[\alpha]_D^{26.5}$ –16.44 (*c* 0.9 in $CHCl_3$, 65% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, *R* isomer: t_R = 11.27 min., *S* isomer: t_R = 12.05 min.

(*S*)-Methyl[naphthalen-2-yl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methoxy]diphenylsilane [(S)-3o].

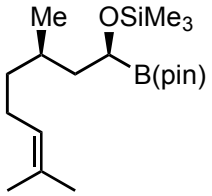


(*S*)-**3o**

(*S*)-**3o** contained inseparable some impurities.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.64 (s, 3H), 1.10 (s, 6H), 1.12 (s, 6H), 4.91 (s, 1H), 7.28–7.49 (m, 9H), 7.56–7.67 (m, 4H), 7.74–7.84 (m, 4H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –2.46 (CH_3), 24.3 (CH_3), 24.6 (CH_3), 65.0 (br, B–*C*H), 84.0 (*C*), 123.9 (*C*H), 124.5 (*C*H), 125.1 (*C*H), 125.7 (*C*H), 127.5 (*C*H), 127.6 (*C*H), 127.68 (*C*H), 127.71 (*C*H), 127.9 (*C*H), 129.7 (*C*H), 132.3 (*C*), 133.5 (*C*), 134.6 (*C*H) 136.1 (*C*), 136.2 (*C*), 139.5 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{30}H_{33}O_3BNaSi$, 502.22205; found, 502.22264. $[\alpha]_D^{23.5}$ –53.15 (*c* 1.0 in $CHCl_3$, 99% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.1/99.9, 0.5 mL/min, 40 °C, *R* isomer: t_R = 17.21 min., *S* isomer: t_R = 18.41 min.

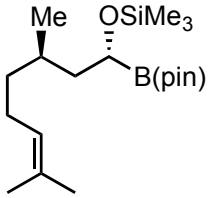
{[(1*S*,3*R*)-3,7-Dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-6-en-1-yl]oxy}trimethylsilane [(*R*,*S*)-3p].



(*R*,*S*)-**3p**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.098 (s, 9H), 0.86 (d, *J* = 6.6 Hz, 3H), 1.15–1.21 (m, 1H), 1.25 (s, 6H), 1.26 (s, 6H), 1.26–1.36 (m, 1H), 1.59 (s, 3H), 1.63–1.71 (m, 3H), 1.67 (s, 3H), 1.97 (q, *J* = 7.8 Hz, 2H), 3.56 (dd, *J* = 4.0, 10.6 Hz, 1H), 5.10 (m, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –0.053 (CH_3), 17.6 (CH_3), 18.7 (CH_3), 24.5 (CH_3), 24.9 (CH_3), 25.56 (CH_2), 25.64 (CH_3), 28.6 (*C*H), 37.9 (CH_2), 41.1 (CH_2), 58.5 (br, B–*C*H), 83.6 (*C*), 125.0 (*C*H), 130.8 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{39}O_3BSi$, 354.27615; found, 354.27559. $[\alpha]_D^{25.5}$ +26.3 (*c* 1.0 in $CHCl_3$).

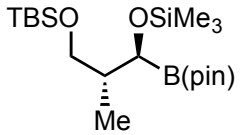
{[(1*R*,3*R*)-3,7-Dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-6-en-1-yl]oxy}trimethylsilane [(*R*,*R*)-3p].



(*R*,*R*)-**3p**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.010 (s, 9H), 0.91 (d, *J* = 6.9 Hz, 3H), 1.01–1.11 (m, 1H), 1.24 (s, 6H), 1.25 (s, 6H), 1.36–1.45 (m, 1H), 1.48 (t, *J* = 7.1 Hz, 2H), 1.56–1.59 (m, 1H), 1.59 (s, 3H), 1.67 (s, 3H), 1.88–2.06 (m, 2H), 3.56 (t, *J* = 7.7 Hz, 1H), 5.10 (m, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –0.072 (CH_3), 17.5 (CH_3), 20.3 (CH_3), 24.5 (CH_3), 24.8 (CH_3), 25.4 (CH_2), 25.6 (CH_3), 28.9 (*C*H), 36.4 (CH_2), 41.6 (CH_2), 58.5 (br, B–*C*H), 83.5 (*C*), 124.9 (*C*H), 130.8 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{39}O_3BSi$, 354.27615; found, 354.27550. $[\alpha]_D^{25.3}$ –22.90 (*c* 1.0 in $CHCl_3$).

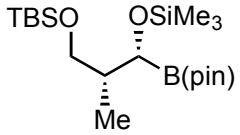
(4*S*,5*R*)-2,2,5,8,8,9,9-Heptamethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,7-dioxa-2,8-disiladecane [(*R*,*S*)-3q].



(*R*,*S*)-**3q**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.032 (s, 6H), 0.093 (s, 9H), 0.89 (s, 9H), 0.90 (d, *J* = 7.0 Hz, 3H), 1.26 (s, 6H), 1.27 (s, 6H), 1.83 1.92 (m, 1H), 3.41 (d, *J* = 7.7 Hz, 1H), 3.50 (dd, *J* = 7.1, 10.1 Hz, 1H), 3.64 (dd, *J* = 4.4, 9.9 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –5.40 (CH_3), –5.31 (CH_3), 0.053 (CH_3), 13.8 (CH_3), 18.3 (*C*), 24.6 (CH_3), 25.0 (CH_3), 26.0 (CH_3), 39.9 (*C*H), 62.0 (br, B–*C*H), 64.8 (CH_2), 83.6 (*C*). HRMS–EI (*m*/*z*): [M CH_3]$^+$ calcd for $C_{18}H_{40}O_4BSi_2$, 387.25582; found, 387.25516. $[\alpha]_D^{24.9}$ +12.63 (*c* 1.2 in $CHCl_3$).

(4*R*,5*R*)-2,2,5,8,8,9,9-Heptamethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,7-dioxa-2,8-disiladecane [(*R*,*R*)-3q].



(*R*,*R*)-**3q**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.034 (s, 3H), 0.037 (s, 3H), 0.089 (s, 9H), 0.89 (s, 9H), 0.92 (d, *J* = 7.3 Hz, 3H), 1.25 (s, 6H), 1.27 (s, 6H), 1.77 1.87 (m, 1H), 3.34 (dd, *J* = 7.7, 9.9 Hz, 1H), 3.60 3.66 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): –5.32 (CH_3), 0.072 (CH_3), 13.1 (CH_3), 18.3 (*C*), 24.4 (CH_3), 25.1 (CH_3), 26.0 (CH_3), 39.9 (*C*H), 65.2 (CH_2), 83.6 (*C*). HRMS–EI (*m*/*z*): [M CH_3]$^+$ calcd for $C_{18}H_{40}O_4BSi_2$, 387.25582; found, 387.25483. $[\alpha]_D^{24.6}$ –6.32 (*c* 1.1 in $CHCl_3$).

Borylation Product Functionalization Procedure

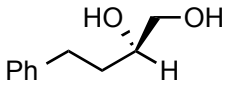
Procedure for the Synthesis of Chiral Diol (*R*)-5 through the One-Carbon Homologation Following Oxidation of (*S*)-3a.

The one-carbon homologation was performed according to the literature procedure.[25] In an oven-dried reaction vial, (*S*)-**3a** (82.1 mg, 0.20 mmol) and bromochloromethane (51.8 mg, 0.40 mmol) were dissolved in dry THF (2.5 mL) in nitrogen atmosphere. After the mixture was cooled to –78 °C, *n*-BuLi in hexane (1.55 M, 193.5 μL, 0.30 mmol) was added dropwise. The mixture was stirred at –78 °C for 10 min, and then stirred at room temperature for 2 h. The reaction mixture was quenched by the addition of aqueous NH_4Cl,

extracted three times with Et_2O, dried over $MgSO_4$, and filtered. The resulting product **4** was used in the next reaction without further purification.

The boronate **4** was dissolved in THF (1.0 mL) and NaOH aq. (3.0 M, 1.0 mL), and the reaction mixture was cooled to 0 °C. Into the mixture, H_2O_2 aq. (30%, 0.50 mL) was then added dropwise, and the resultant mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of aqueous $Na_2S_2O_3$, extracted three times with EtOAc, dried over $MgSO_4$, and filtered. The crude material was purified by flash column chromatography (SiO_2, EtOAc/hexane, 30:70–70:30) to give the corresponding diol (*R*)-**5** (25.6 mg, 0.15 mmol, 77%) as a colorless oil.

(*R*)-4-Phenylbutane-1,2-diol [(*R*)-5].



(*R*)-**5**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.68–1.83 (m, 2H), 2.19 (br, s, 1H), 2.39 (br, s, 1H), 2.65–2.73 (m, 1H), 2.77–2.85 (m, 1H), 3.46 (dd, *J* = 7.9, 11.2 Hz, 1H), 3.65 (dd, *J* = 2.6, 11.4 Hz, 1H), 3.69–3.78 (m, 1H), 7.17–7.32 (m, 5H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 31.7 (CH_2), 34.6 (CH_2), 66.7 (CH_2), 71.5 (*C*H), 125.9 (*C*H), 128.35 (*C*H), 128.40 (*C*H), 141.6 (*C*). HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{10}H_{14}O_2Na$, 189.08890; found, 189.08892. $[\alpha]_D^{19.3}$ +7.42 (*c* 1.0 in $CHCl_3$, 96% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, *R* isomer: t_R = 26.85 min., *S* isomer: t_R = 35.33 min.

The absolute configuration of borylation product (*S*)-**3a** was determined by comparison of the optical rotation of the diol (*R*)-**5** and the literature value for (*S*)-**5** **[**$[\alpha]_D^{20}$ 16.24 (*c* 1.1 in $CHCl_3$)].[26]

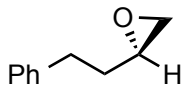
Procedure for the Synthesis of Chiral Epoxide (*R*)-6 through the One-Carbon Homologation Following Bromination/Deprotection Sequence of (*S*)-3a.

The one-carbon homologation was performed according to the procedure described above. The sequential bromination was performed according to the literature procedure with slight modification.[27] *n*-BuLi in hexane (1.55 M, 150.0 μL, 0.24 mmol) was added to a solution of 1-bromo-3,5-bis(trifluoromethyl)benzene (42.0 μL, 0.24 mmol) in THF (2.0

mL) at –78 °C. The mixture was stirred for 1 h at –78 °C before a solution of boronate **4** (0.20 mmol) in THF (1.0 mL) was added dropwise. The reaction mixture was stirred for 30 min at –78 °C to give the ate-complex solution. A solution of *N*-bromosuccinimide (NBS) (42.8 mg, 0.24 mmol) in THF (2.0 mL) was then added dropwise, and the mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of aqueous $Na_2S_2O_3$. The mixture was then extracted three times with Et_2O, dried over $MgSO_4$, and filtered. The obtained crude halohydrin was used in next step without further purification.

Tetrabutylammonium fluoride (TBAF) in THF (1.0 M, 400.0 μL, 0.40 mmol) was added to a solution of the halohydrin in THF (1.0 mL) at room temperature. After stirred for 2 h, the mixture was passed through a short silica gel column eluting with Et_2O. The crude material was purified by flash column chromatography (SiO_2, Et_2O/Hex, 0:100–5:95) to give the desired chiral epoxide (*R*)-**6** as a colorless oil (19.6 mg, 0.13 mmol, 66%).

(*R*)-2-Phenethyloxirane [(*R*)-6].



(*R*)-**6**

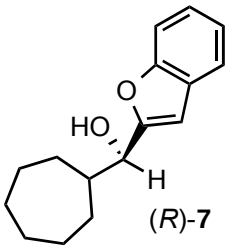
^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.77–1.94 (m, 2H), 2.47 (dd, *J* = 2.8, 5.0 Hz, 1H), 2.70–2.88 (m, 3H), 2.92–2.99 (m, 1H), 7.16–7.34 (m, 5H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 32.2 (CH_2), 34.3 (CH_2), 47.2 (CH_2), 51.8 (CH), 126.0 (CH), 128.3 (CH), 128.4 (CH), 141.2 (C). HRMS–ESI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_{12}O$, 148.08881; found, 148.08932. $[\alpha]_D^{20.3}$ +2.50 (*c* 1.8 in $CHCl_3$, 96% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, *R* isomer: t_R = 20.36 min., *S* isomer: t_R = 28.00 min.

Procedure for the Synthesis of Arylated Product (*R*)-7 through the Stereospecific Cross-Coupling of (*S*)-3h with Benzofuran.

The stereospecific cross-coupling was performed according to the literature procedure.[28] A solution of benzofuran (28.3 mg, 0.24 mmol) in THF (0.80 mL) was cooled to –78 °C and treated with *n*-BuLi in hexane (1.55 M, 155.0 μL 0.24 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was then cooled to –78 °C and the boronate (*S*)-**3h** (65.3 mg, 0.20 mmol) was added as a solution in THF (0.40 mL) and

the reaction stirred at the same temperature for 1 h. A solution of NBS (42.7 mg, 0.24 mmol) in THF (0.80 mL) was then added dropwise to the mixture. After 1 h at –78 °C, $Na_2S_2O_3$ aq. was added and the reaction mixture was allowed to warm to room temperature. The mixture was extracted three times with Et_2O, dried over $MgSO_4$, and filtered. The resulting crude product was used in the next reaction without further purification. The crude material was dissolved in THF (1.0 mL) and a THF solution of TBAF (1.0 M, 0.40 mL) was added to the mixture. After stirred for 2 h, the mixture was passed through a short silica gel column eluting with EtOAc. The crude material was purified by flash column chromatography (SiO_2, EtOAc/hexane, 2:98–15:85) to give the arylated product (*R*)-**7** (25.4 mg, 0.10 mmol, 52%) as a colorless oil.

(*R*)-Benzofuran-2-yl(cycloheptyl)methanol [(*R*)-7].



(*R*)-**7**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.19–1.76 (m, 10H), 1.84–1.93 (m, 1H), 1.99 (t, *J* = 5.1 Hz, 1H), 2.03–2.14 (m, 1H), 4.62 (t, *J* = 6.0 Hz, 1H), 6.60 (s, 1H), 7.16–7.28 (m, 2H), 7.41–7.47 (m, 1H), 7.50–7.55 (m, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 26.6 (CH_2), 26.7 (CH_2), 28.3 (CH_2), 28.5 (CH_2), 29.1 (CH_2), 44.1 (*C*H), 73.3 (*C*H), 103.3 (*C*H), 111.2 (*C*H), 120.9 (*C*H), 122.7 (*C*H), 123.9 (*C*H), 128.1 (*C*), 154.6 (*C*), 159.0 (*C*). HRMS–EI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{20}O_2$, 244.14633; found, 244.14537. $[\alpha]_D^{20.9}$ +23.62 (*c* 0.8 in $CHCl_3$, 95% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 3/97, 0.5 mL/min, 40 °C, *R* isomer: t_R = 25.68 min., *S* isomer: t_R = 28.92 min.

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Chapter 5.

Computational Insight into the Enantioselective Borylation of Aldehydes Catalyzed by Chiral Bisphosphine Copper(I) Complexes

Abstract

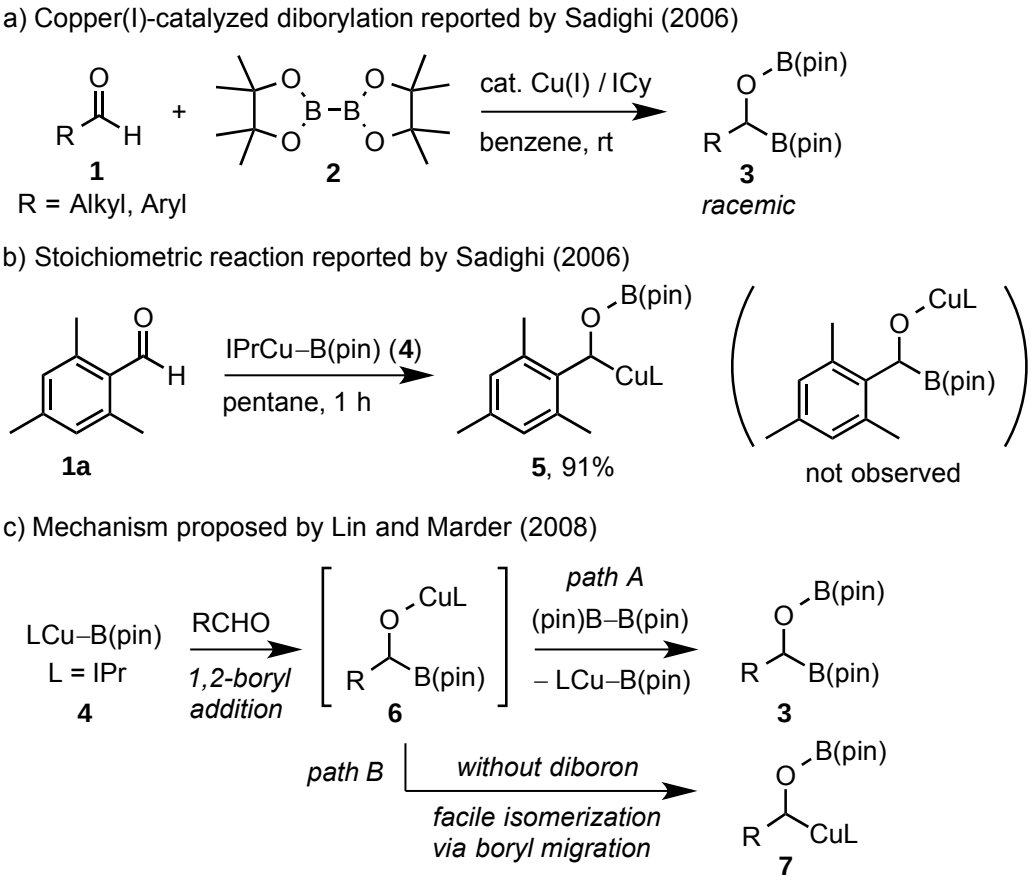
Density functional theory calculations were performed to validate the proposed reaction mechanism for the enantioselective nucleophilic borylation of a polarized C=O double bond in the presence of diphosphine/borylcopper(I) complexes. Consequently, the author successfully elucidated the origin for the regioselectivity and the mechanism for the enantioselectivity of the reaction. The author also obtained theoretical explanations for the fact that the presence of a proton source gave a higher reactivity and a better enantioselectivity in the borylation reaction of aldehydes with a copper(I)/(*R*)-DTBM-SEGPHOS complex catalyst. This study is particularly valuable toward the development and design of novel enantioselective borylation reactions with polarized carbon-heteroatom double bonds.

Introduction

Organoboron compounds have attracted significant attention due to their broad range of synthetic and medicinal applications.[1] Synthetic strategies that utilize metal-catalyzed borylation strategies have recently made significant contributions toward the efficient preparation of various organoboron compounds. Copper(I)-catalyzed reactions are a particularly powerful tool for the umpolung nucleophilic addition of a boryl group to various electrophiles such as aldehydes.[2-6] The study that originally pioneered the catalytic borylation of a polarized C=O double bond was reported by Sadighi et al. in 2006. They discovered that an *N*-heterocyclic carbine(NHC)/copper(I) complex could catalyze the diboration of both aliphatic and aromatic aldehydes **1** with a diboron reagent **2** (Scheme 1a).[3] Molander et al. later reported on the copper(I)-catalyzed monoborylation of aldehydes with the addition of methanol as a proton source to give -hydroxyalkylboron compounds.[4] In a study on the diboration of aldehydes, it was discovered that the borylation of mesitaldehyde (**1a**) in the presence of a stoichiometric amount of (IPr)Cu-B(pin) [IPr = 1,3,-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] **4** gave a compound,

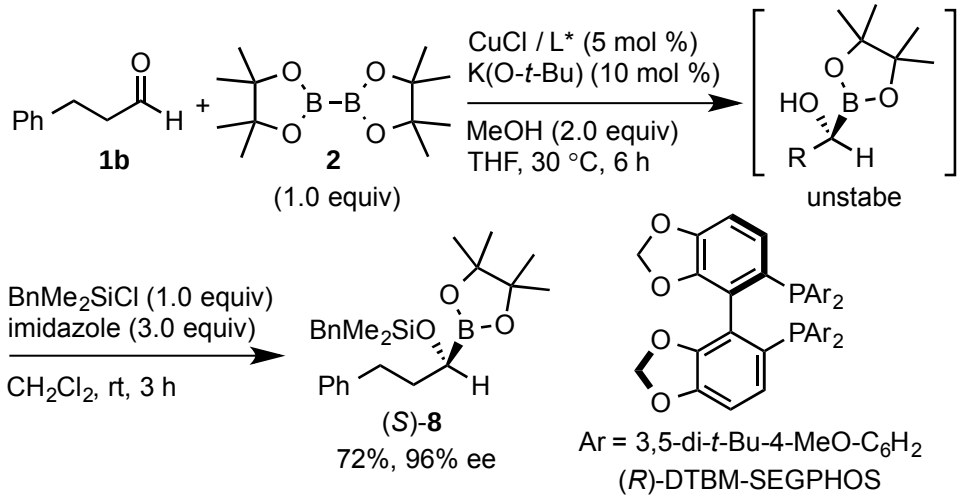
(IPr)Cu-CHAr[OB(pin)] (Ar = 2,4,6-$Me_3C_6H_2$) **5** that contained a Cu C σ bond (Scheme 1b).[3] This result was particularly intriguing because it suggested that the B(pin) ligand most likely acted as a boryl nucleophile to form the C B and Cu O bonds. Lin and Marder et al. then reported on a theoretical study regarding the mechanism of aldehyde insertion chemistry using density functional theory (DFT) calculations (Scheme 1c).[5] They demonstrated that diboration proceeds through the 1,2-addition of the borylcopper(I) complex to a C=O double bond to form intermediate **6** with a Cu O C B linkage. This is followed by a metathesis reaction with an additional diboron compound **3** (path A, Scheme 1c). In the absence of the additional diboron reagent, the isomerization of the insertion intermediate **6** generates a more thermodynamically stable isomer **7**. This compound contains a Cu C O B linkage due to a boryl migration (path B, Scheme 1c).

Scheme 1. (a) The First Catalytic Borylation of Aldehydes. (b) Stoichiometric Borylation of Mesitaldehyde. (c) Proposed Mechanism based on DFT calculation.



The author reported on the copper(I)-catalyzed enantioselective nucleophilic borylation of aliphatic and aromatic aldehydes (Scheme 2).[6] Aliphatic aldehyde **1b** was reacted with bis(pinacolato)diboron (**2**) (1.0 equiv) in the presence of CuCl/(*R*)-DTBM-SEGPHOS (5 mol %), K(O-*t*-Bu) (10 mol %), and a proton source, MeOH (2.0 equiv) in THF at 30 °C to afford the desired product (*S*)-**8** in a relatively high yield (72%). This reaction also gave an excellent enantioselectivity (96% ee) after the crude -hydroxyalkylboronate was protected by a silyl group. It was not possible to obtain an enantioenriched product from the nucleophilic borylation of a polarized C=O double bond prior to this discovery.[7-10]

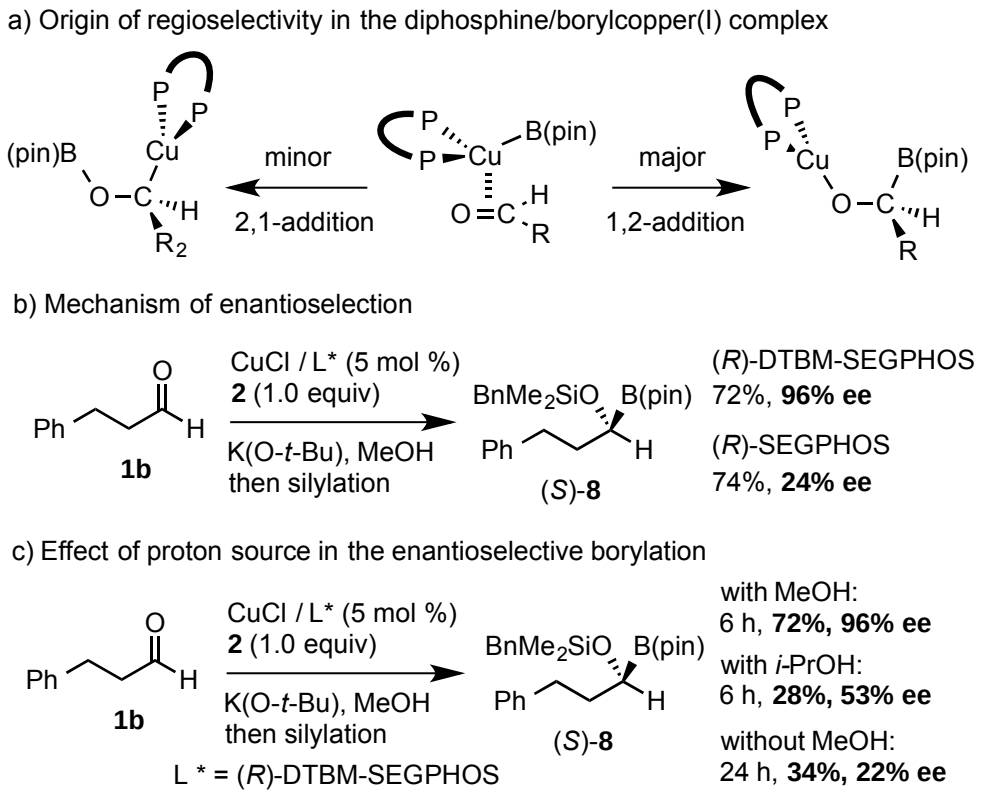
Scheme 2. Enantioselective Borylation of Aldehydes in the presence of Chiral DTBM-SEGPHOS/Copper(I) Complex Catalysis



The mechanistic study of the NHC-borylcopper(I) catalytic system by Lin and Marder revealed a pathway that consists of a 1,2-boryl addition (**4**→**6**), diboration (**6**→**3**), and isomerization (**6**→**7**).[5] However, Scheme 3 illustrates several additional points that need to be addressed in the particular case of an asymmetric carbonyl borylation with a chiral diphosphine ligand. The regioselectivity for the addition of a diphosphine-borylcopper(I) complex to a polarized C=O double bond (1,2-addition vs 2,1-addition) in the first step needs to be further investigated (Scheme 3a). Although similar theoretical studies on the NHC-borylcopper(I) complex have already been reported by Lin and Marder, the differences in the reactivity of the diphosphine- and NHC-complex is yet to be fully explained. The mechanism for the enantioselective formation of products in the reaction between the borylcopper(I)/(*R*)-DTBM-SEGPHOS complex and the aldehydes will also be discussed (Scheme 3b). This particular enantioselectivity is only attributed to the (*R*)-DTBM-SEGPHOS ligand since similar chiral ligands such as (*R*)-SEGPHOS have given poor experimental results. In addition, our previous study showed that the presence of a proton source was critical to the experimental outcome of the reaction (Scheme 3c). Although the proton source does not participate in the borylation step, the yields and ee values were significantly lowered in the presence of *i*-PrOH or in the absence of MeOH. An investigation of the effects of a proton source in these reactions has never been reported. To fill these gaps in knowledge (outlined in Scheme

3), we decided to further elucidate the detailed reaction mechanism for the chiral diphosphine/copper(I)-catalyzed enantioselective borylation of a polarized C=O double bond using DFT calculations.

Scheme 3. Factors That Were Not Fully Addressed in Previous Studies



Results and Discussion

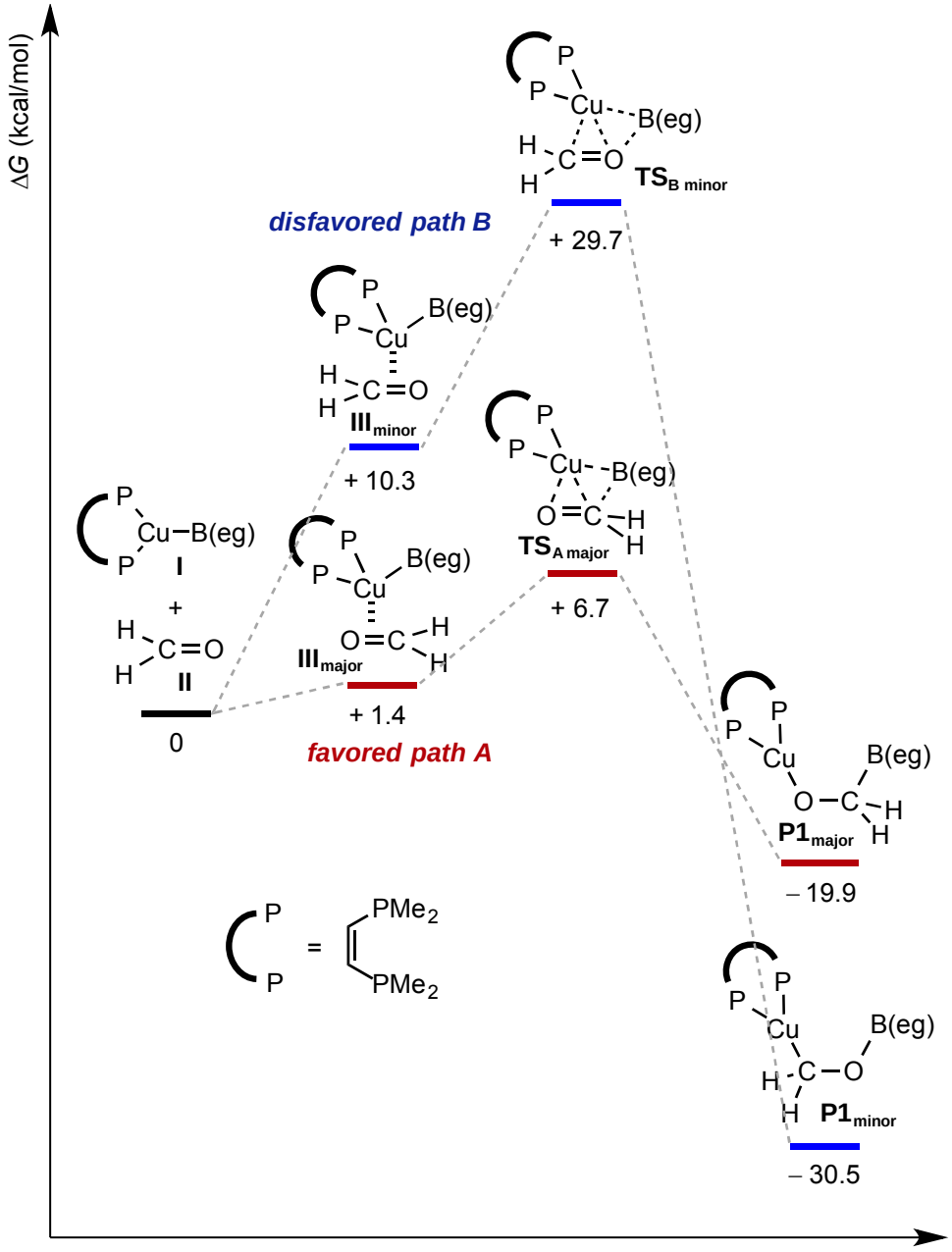
All calculations were performed with a Gaussian 09W (revision C.01) program package.[11] Geometry optimizations were performed using B3PW91/cc-pVDZ in the gas-phase. The molecular orbitals were drawn with a GaussView 5.0 program. The transition states (TS) were confirmed based on the presence of one imaginary frequency at their normal vibrational modes. The intermediates (I), reactant complexes (RC), and products were confirmed as local minima based on all of the positive frequencies. The intrinsic reaction coordinate (IRC) was calculated for the transition states to confirm that the structures were indeed connected by two relevant minimas.

In addition, the energy profiles were derived from the free energies of formation at 298.15 K.

Investigation on the Origin of Regioselectivity

To reveal the origins for the regioselectivity of the diphosphine/borylcopper(I) complex, we carried out the DFT calculation by employing an simplified model, achiral borylcopper(I)/$Me_2PCH{=}CHPMe_2$ model complex with the substrate, formaldehyde (Figure 1). The two regioisomeric pathways for the insertion of borylcopper(I) into formaldehyde were investigated. The free energy of activation for the disfavored path B (**TS**$_{\mathbf{B\ minor}}$) was higher than path A (**TS**$_{\mathbf{A\ major}}$) by +23.0 kcal/mol. Furthermore, the π-complex, **III**$_{\mathbf{minor}}$, in path B was significantly destabilized by +8.9 kcal/mol in comparison to **III**$_{\mathbf{major}}$ in path A. However, the addition product, **P1**$_{\mathbf{minor}}$, was stabilized in path B by 10.6 kcal/mol compared to **P1**$_{\mathbf{major}}$ in path A. These results indicate that the diphosphine/copper(I)-catalyzed borylation of aldehydes proceeds under a kinetically controlled mechanism (path A), which can lead to the 1,2-boryl addition product, LCu-OCH_2-B($O_2C_2H_4$) (**P1**$_{\mathbf{major}}$). Thus, the author found that the regioselectivity trends for the diphosphine-borylcopper(I) complex were similar to those for the NHC complex catalyst studied by Lin and Marder.[5]

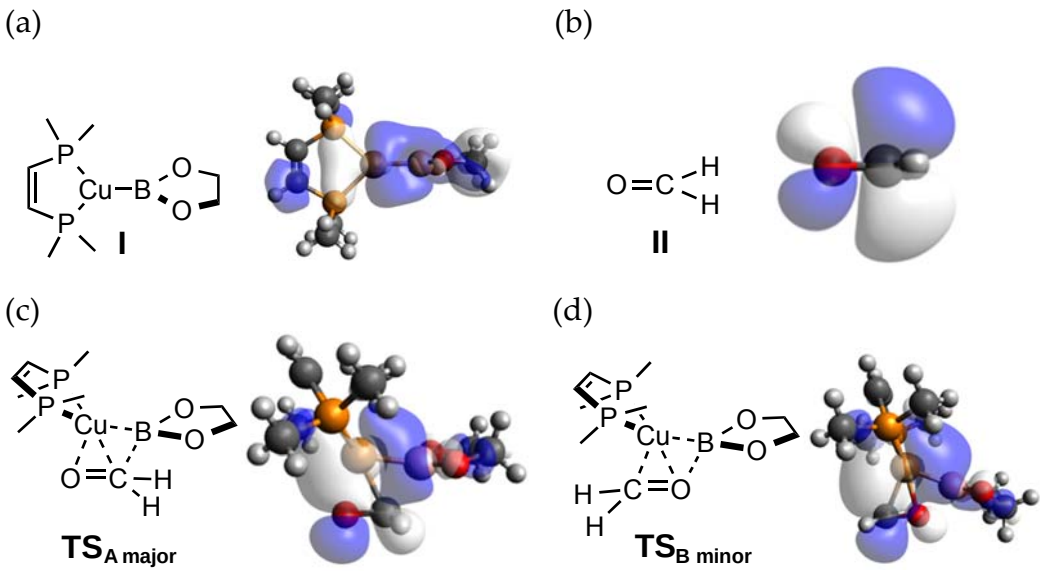
Figure 1. DFT Calculation (B3PW91/cc-pVDZ) of the Aldehyde Addition Step in the Diphosphine/copper(I) Catalyzed Borylation Reaction. Gibbs Free Energy Values Relative to the Starting Model Compounds, **I** and **II**, are Shown in kcal/mol at 298 K and 1.0 atm in the Gas Phase.



HOMO-LUMO orbital analysis gave an explanation for the large difference in the activation energy between **TS**$_{\text{A major}}$ and **TS**$_{\text{B minor}}$ (Figure 2). The result shows that the HOMO orbitals of the borylcopper(I) complex **I** are primarily located in the Cu–B σ bond, which imparts a nucleophilic character to complex **I** (Figure 2a). The contribution of the carbon 2p orbital to the LUMO orbital of complex **I** is significantly greater than the contribution of the oxygen 2p orbital in formaldehyde **II** (Figure 2b). Thus, **P1**$_{\text{major}}$ is favored

since the activation barrier for **TS**$_{\text{A major}}$ is smaller than **TS**$_{\text{B minor}}$. This complex is more stabilized due to the larger orbital overlap between the HOMO of borylcopper(I) and the LUMO of the C=O double bond in the transition state (Figure 2c and d).[12,13]

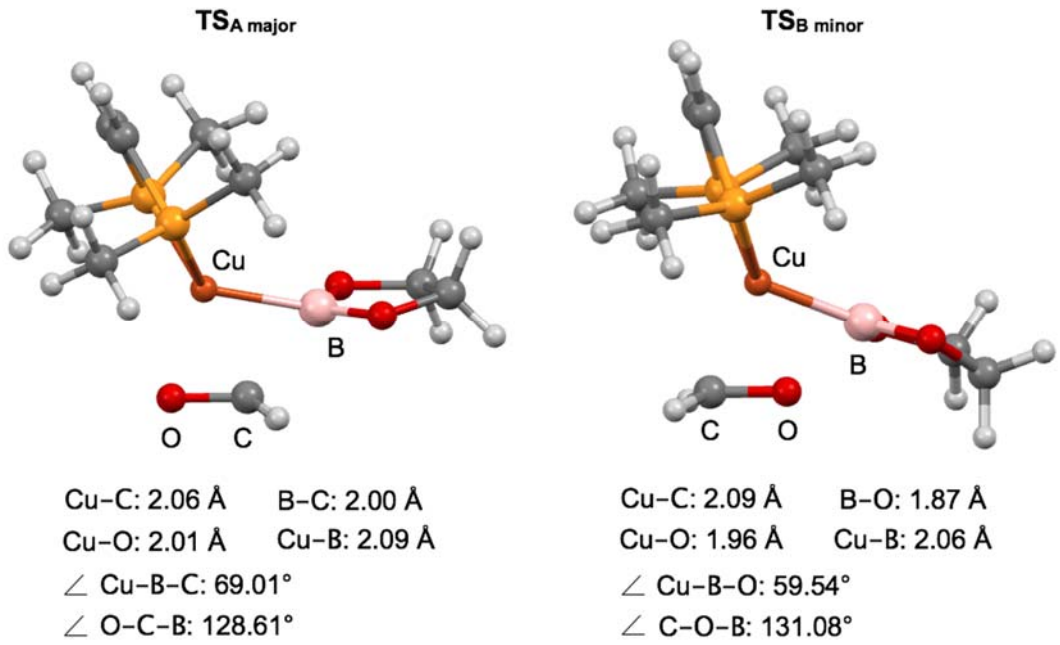
***Figure* 2.** (a) HOMO of Borylcopper(I) Complex **I**. (b) LUMO of Formaldehyde **II**. (c) HOMO of TS$_{\text{A major}}$. (d) HOMO of TS$_{\text{B minor}}$.



The structural parameters for the **TS**$_{\text{A major}}$ and **TS**$_{\text{B minor}}$ transition states are shown in Figure 3. The lengths of both the Cu–O and B–C bonds in the more favorable **TS**$_{\text{A major}}$ pathway are relatively short (2.01 and 2.00 Å, respectively).[14] This indicates that there is reasonable strength of interaction between borylcopper(I) and the substrate. In contrast, **TS**$_{\text{B minor}}$ has a noticeably shorter distance between the boron atom and the carbonyl oxygen (1.87 Å) and a relatively longer distance between the copper center and the carbonyl carbon (2.09 Å). Because the copper center has weaker interaction with the substrate than **TS**$_{\text{A major}}$, the insertion of the complex is disfavored. In addition, the bond angle (Cu B O) for **TS**$_{\text{B minor}}$ (59.54) is significantly smaller than **TS**$_{\text{A major}}$ (69.01), which is most likely observed because of the strong interaction between boron and the carbonyl oxygen. This structure strain causes significant destabilization of the complex due to the distortion of the **TS**$_{\text{B minor}}$ structure. These structural features are all consistent with the

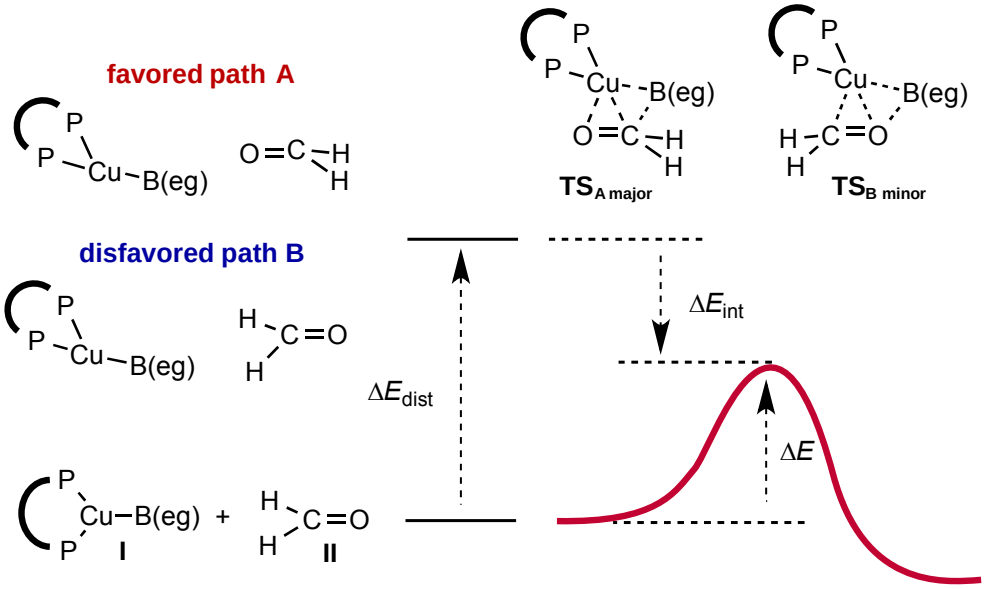
regioselectivity trends observed in the HOMO-LUMO orbital analysis.

Figure 3. Calculations of the Selected Bond Lengths and Angles for $TS_{A\ major}$ and $TS_{B\ minor}$

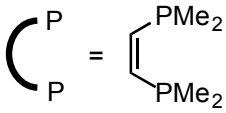


The author have conducted activation strain model (ASM) analysis to obtain deeper understanding on the regioselectivity issue (Table 1).[15] The energies to deform the isolated reactants to the transition geometry (E_{dist}) and the energy of interaction between these deformed reactants are summarized as shown below. The deformation energy of favored 1,2-addition pathway A (30.58 kcal/mol) is larger than that of disfavored 2,1-addition pathway B (24.66 kcal/mol). The interaction energy (E_{int}) of 1,2-addition pathway (–23.04 kcal/mol) is significantly larger than that of 2,1-addition pathway (–9.43 kcal/mol, respectively). This analysis indicates that the lower activation barrier of the 1,2-addition pathway compared to 2,1-addition pathway is attributable to the efficient interaction between borylcopper(I) complex and formaldehyde in the 1,2-addition pathway to stabilize the transition state. This explanation agrees with the result of the HOMO-LUMO orbital analysis shown in Figure 2.

Table 1. ASM Analysis (B3PW91/cc-pVDZ) for the Addition Transition States. Electronic Energies Relative to the Starting Model Compounds, I and II, are Shown in kcal/mol at 298 K and 1.0 atm in the Gas Phase



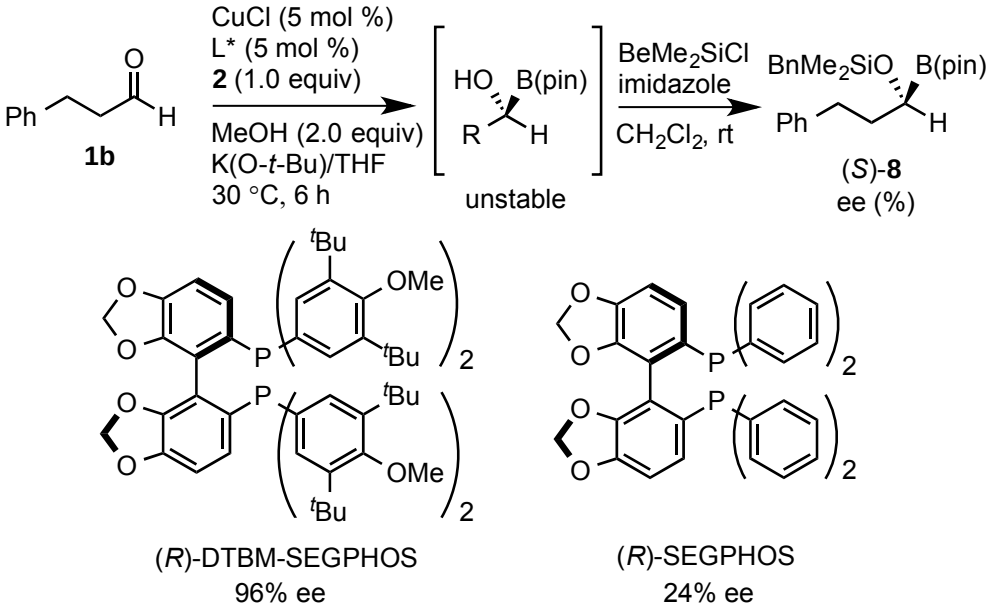
reaction path	ΔE	ΔE_{dist}	ΔE_{int}
favored path A	7.54	30.58	–23.04
disfavored path B	15.28	24.66	–9.43



Investigation on the Mechanism for Enantioselectivity.

The author previously reported that a high enantioselectivity was obtained (96% ee) for the borylation of an aliphatic aldehyde **1b** with a (*R*)-DTBM-SEGPHOS chiral ligand. In contrast, the less sterically encumbered (*R*)-SEGPHOS ligand gave a significant decrease in the enantioselectivity (24% ee) of the reaction (Scheme 4).

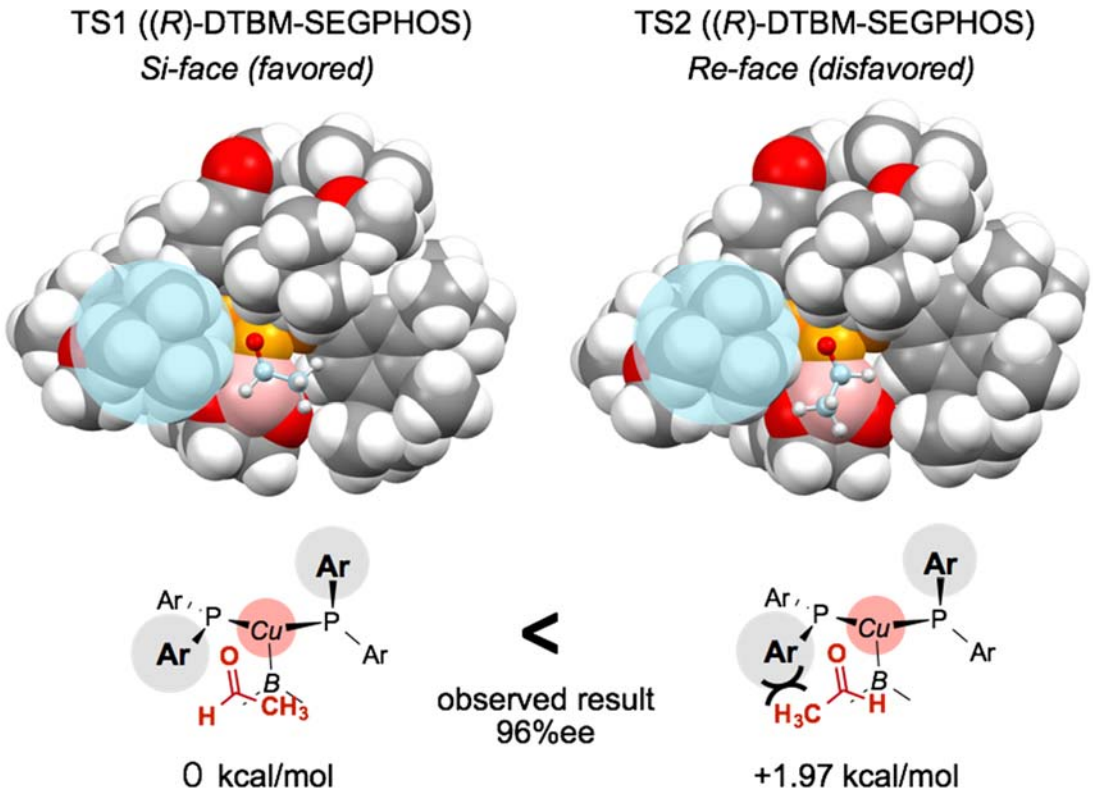
Scheme 4. Comparison of Enantioselectivities in the Borylation of Aldehydes with SEGPHOS-Type Chiral Ligands



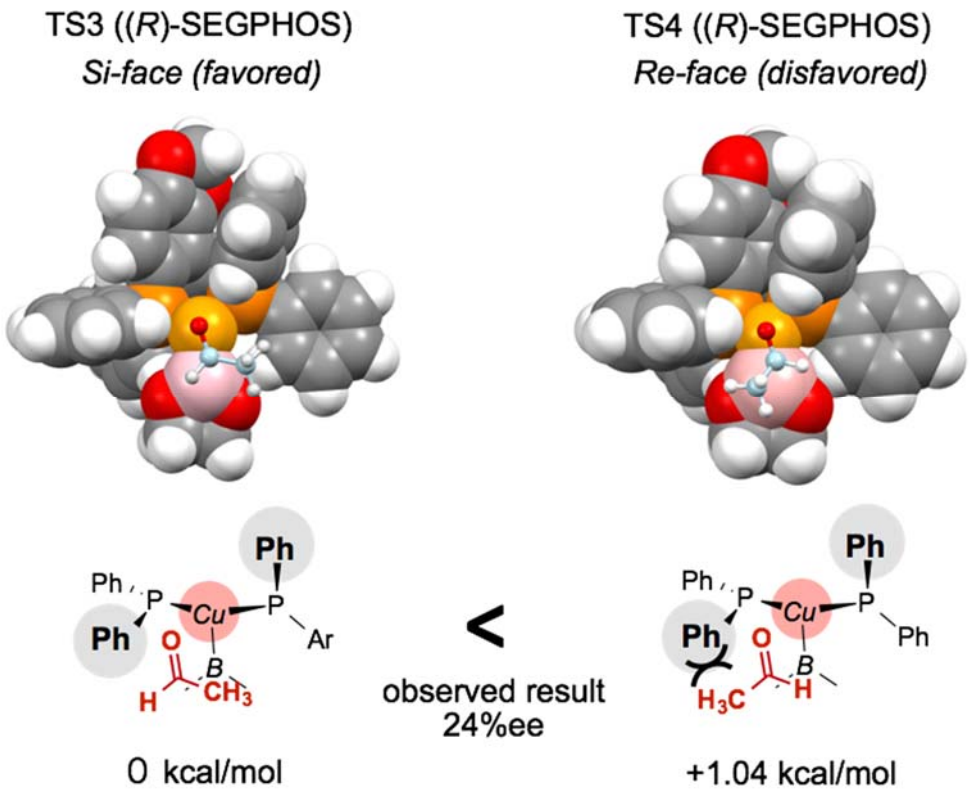
DFT calculations (B3PW91) were used to explain the substituent effects of SEGPHOS-type ligands for the enantioselective borylation of aldehydes (Figure 4). The results showed that the activation barrier for the *Re*-face addition of (*R*)-DTBM-SEGPHOS/borylcopper(I) to acetaldehyde in the transition state **TS2** was higher than the *Si*-face addition for the transition state **TS1** by +1.97 kcal/mol. In the case of a *Si*-face attack, the transition state **TS1** is free from steric congestion between the *t*-Bu group on the ligand (displayed in blue on Figure 4a) and the acetaldehyde substituent. This produces an (*S*)-isomer as a major enantiomer, which agrees with the observed absolute configuration of the borylated product. In contrast, the unfavored transition state **TS2** is destabilized because the substituent on acetaldehyde is sterically hindered by one of the *t*-Bu groups on the ligand. This results in a higher activation barrier for **TS2**. The author also performed similar calculations with the less sterically hindered (*R*)-SEGPHOS ligand. As previously mentioned, this ligand gave a poor enantioselectivity for the borylation of the aliphatic aldehyde **1b** (Figure 4b). The disfavored transition state **TS4** is destabilized less than **TS2** because the acetaldehyde substituent is relatively far from the phenyl groups on the ligand. Thus, the energy difference between **TS3** and **TS4** is smaller than that between **TS1** and **TS2**. This indicates that enantioselectivity is largely controlled by the steric effects between the *t*-Bu group on the ligand and the substituent on the aldehyde.

Figure 4. DFT Calculations (B3PW91/cc-pVDZ) of the Transition States for the (*R*)-DTBM-SEGPHOS and (*R*)-SEGPHOS/Copper(I)-Catalyzed Enantioselective Borylation of Acetaldehyde. Relative *G* Values (kcal/mol) were Obtained at 298 K and 1.0 atm in the Gas Phase.

(a)



(b)

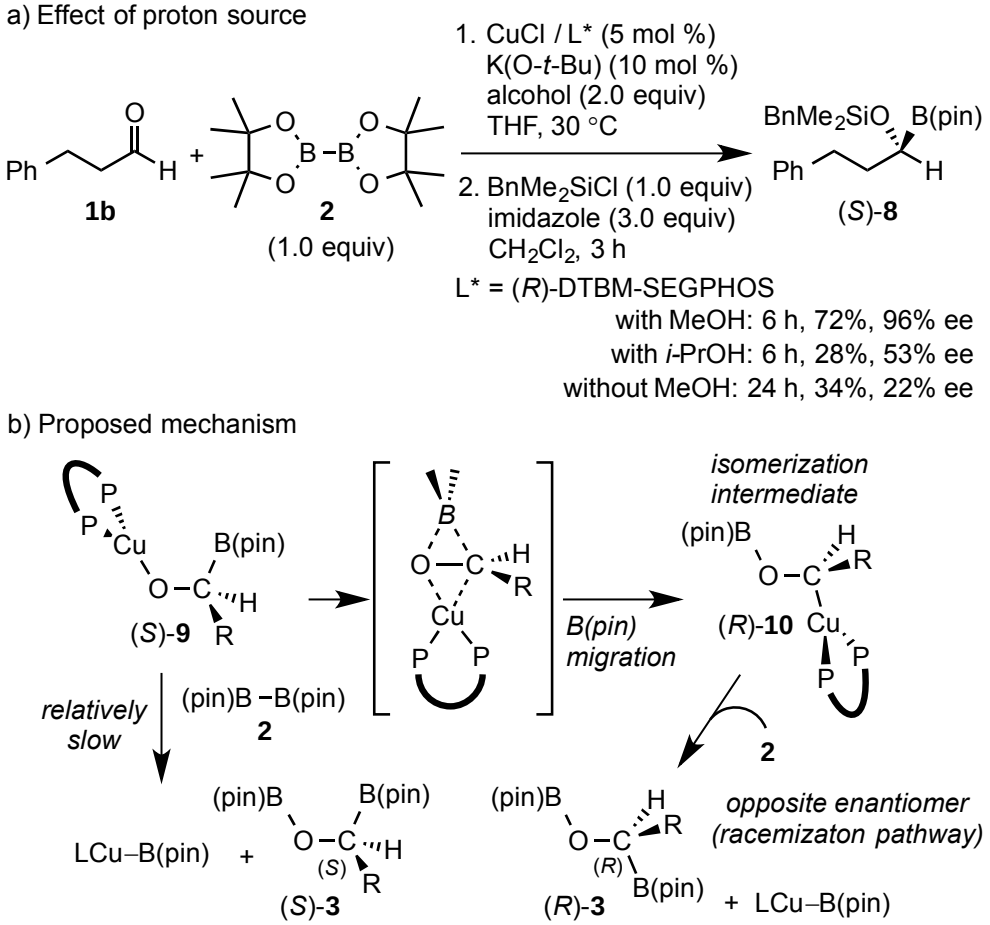


Investigation on the Effect of a Proton Source in the Enantioselective Borylation of Aldehydes

In the previous study, the author found that a proton source has a great impact on the reactivity and enantioselectivity of the copper(I)-catalyzed borylation of a C=O double bond.[15] The use of *i*-PrOH instead of MeOH resulted in a low yield (28%) and enantioselectivity (53% ee) (Scheme 5a). A reaction in the absence of MeOH did not reach completion of the reaction even with a longer reaction time (24 h). The product with a lower yield (34%) and a lower enantioselectivity (22% ee) (Scheme 5a) was thus obtained. The proposed reaction mechanism for the reaction in the absence of a proton source was shown in Scheme 5b. The author speculates that the reaction of the addition intermediate (*S*)-**9** with the diboron compound **2** to give the borylated product (*S*)-**3** would be slow due to the significant steric interaction between the bulky (*S*)-**9** complex and the B(pin) group in **2**.[17,18] The isomerization from (*S*)-**9** to a more thermodynamically stable intermediate (*R*)-**10** would also proceed. A further reaction with **2** gives the

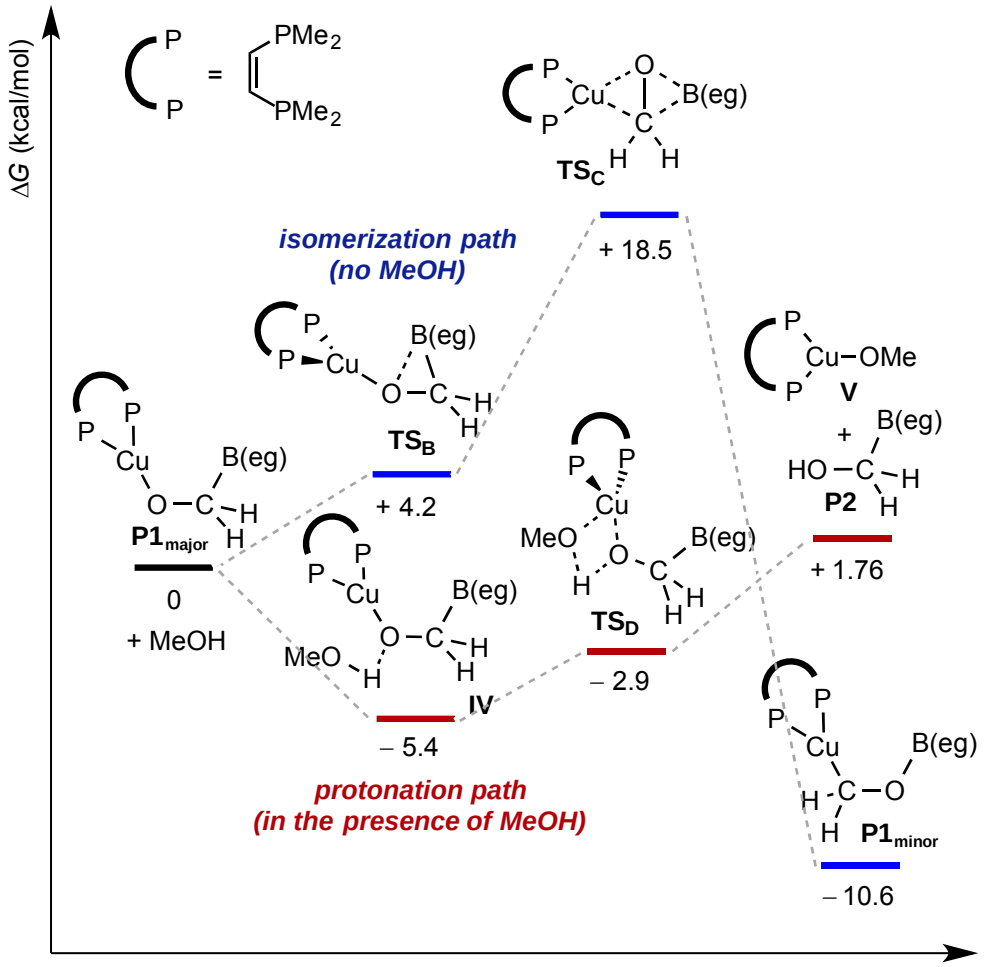
opposite enantiomer (*R*)-**3** through the net stereoinversion reaction in terms of the C–B bond.[17] As for the use of sterically hindered *i*-PrOH, the relatively slow protonation of intermediate (*S*)-**9** could lead to the isomerization of (*S*)-**9** to (*R*)-**10**, which decreases the enantiomeric excess of the borylation product.[19]

Scheme 5. Impact of the Proton Source on the Copper(I)-Catalyzed Enantioselective Borylation of Aldehydes



To confirm the isomerization pathway, the author performed a DFT calculation (B3PW91/cc-pVDZ) using a borylcopper(I)/$Me_2PCH{=}CHPMe_2$ model complex and the model substrate, formaldehyde (Figure 5, isomerization path). The result showed that the activation energy required for isomerization was 18.5 kcal/mol, which was a reasonable value in light of the current reaction conditions. The isomerization of (*S*)-**9** explains why racemized products can be observed after the reaction.

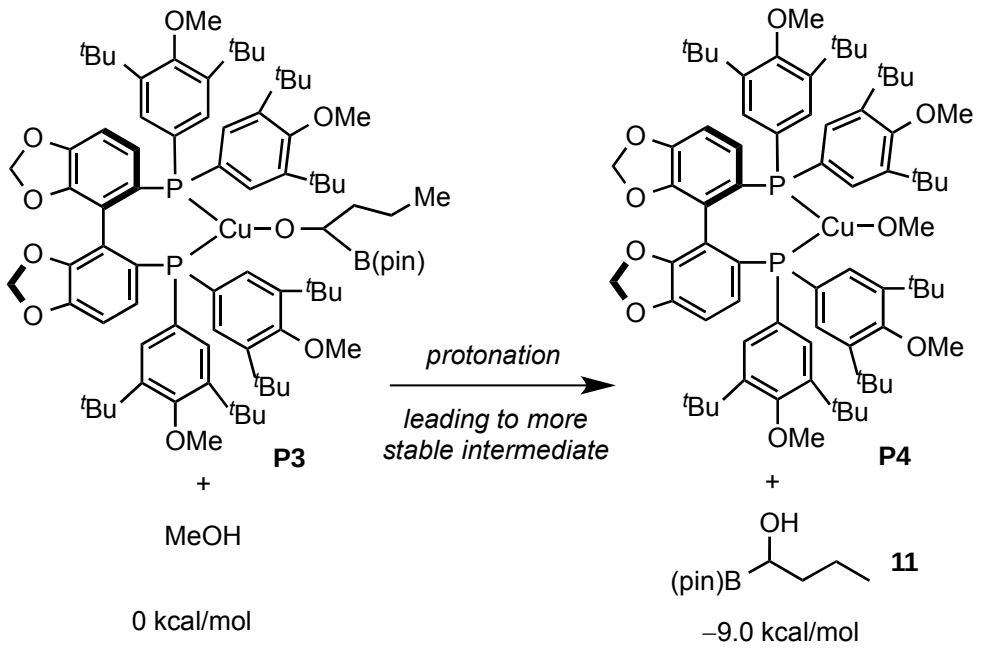
Figure 5. DFT calculations (B3PW91/cc-pVDZ) of the isomerization pathway and the protonation pathway with MeOH. Gibbs free energy values relative to $P1_{major}$ are shown in kcal/mol at 298 K and 1.0 atm in the gas phase for the isomerization step. Gibbs free energy values relative to the total energy of $P1_{major}$ and MeOH are shown in kcal/mol at 298 K and 1.0 atm in the gas phase for the protonation step.



The author also found that the activation barrier for the protonation of the addition complex **P1**$_{major}$ by MeOH was relatively low [ΔG (**TS**$_D$ **IV**) = +2.5 kcal/mol]. This indicates that the isomerization pathway can be suppressed by facile protonation in the presence of MeOH (Figure 5, protonation path). However, the free energy of the protonation product **P2** is higher than **P1**$_{major}$,

which is most likely due to the use of a small model complex **I** and aldehyde **II**. The author then performed a DFT calculation on the protonation step by using the sterically bulky ligand, (*R*)-DTBM-SEGPHOS, and the substrate, butyl aldehyde (Scheme 6). Although the transition state between the addition complex **P3** and L*CuOMe **P4** could not be determined, the activation energy for the protonation step would be very low as shown in Figure 5. The author found that the total energy for the intermediate **P3** and MeOH was higher than LCuOMe and the protonation product **P4**. This is most likely observed because of the larger steric congestion in **P3** than in **P4**. This result suggests that the steric effects of the ligand can facilitate the protonation process in a thermodynamically controlled reaction to suppress side reactions such as isomerization. The subsequent reaction of **P4** with diboron is much faster than the reaction of **P3** with diboron to regenerate LCuB(pin).[17] Thus, the product is obtained with a higher yield and enantioselectivity in an (*R*)-DTBM-SEGPHOS/copper(I)-catalyzed borylation with a proton source.

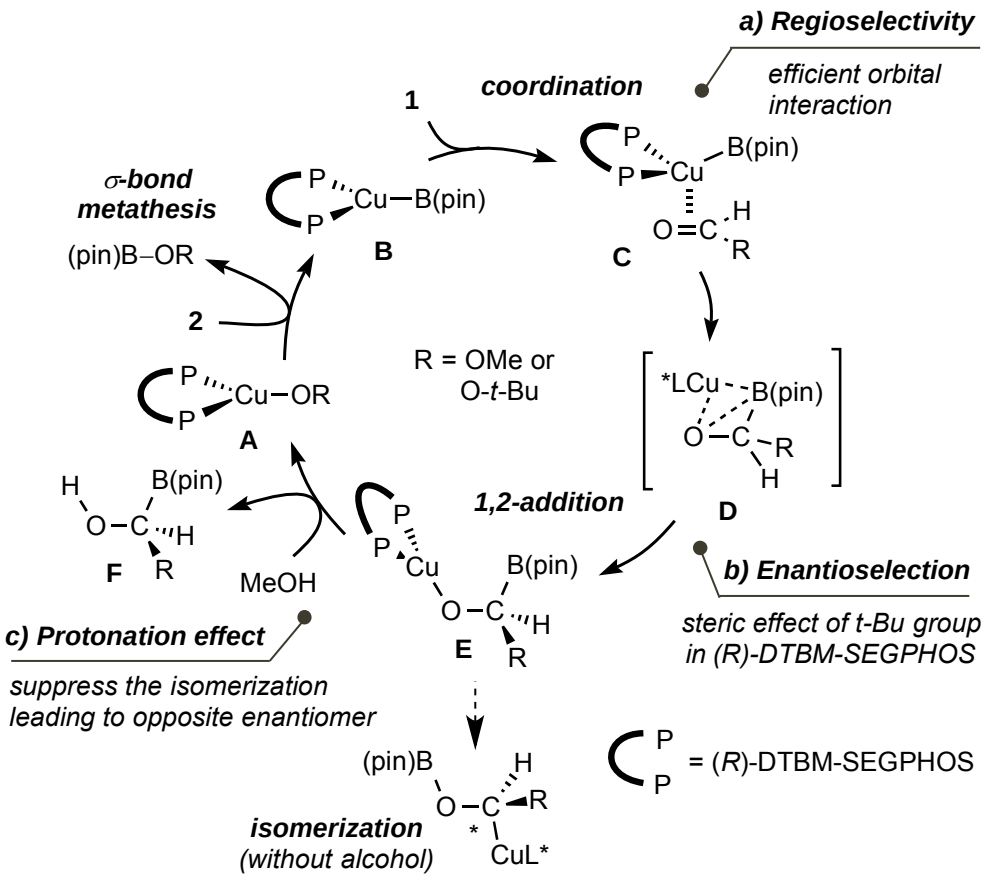
Scheme 6. DFT Calculation (B3PW91/cc-pVDZ) of the Protonation Step using a (*R*)-DTBM-SEGPHOS Complex



Conclusion

In this study, the author successfully elucidated the origin for the regioselectivity, the mechanism for the enantioselectivity, and the effect of a proton source in the copper(I)-catalyzed nucleophilic borylation of a polarized C=O double bond. Scheme 7 shows the proposed catalytic cycle based on these theoretical investigations. The borylcopper(I) active species **B**, which was generated through the reaction of copper(I) alkoxide **A** and a diboron reagent **2**, reacts with aldehydes to form the coordinated complex **C**. A 1,2-addition reaction then occurs to generate the boryl addition complex **E**. Analysis of the HOMO-LUMO orbitals revealed that the orbital interactions between borylcopper(I) and the C=O double bond in the 1,2-addition transition state were stronger than a 2,1-addition transition state that facilitates the formation of LCu-OCHR-B(pin) **E** (Scheme 7a). A borylcopper(I)/(*R*)-DTBM-SEGPHOS complex and the substrate, acetaldehyde, were used in the enantioselectivity model. It was discovered that the steric hindrance between the *t*-Bu group on the ligand and the substituent on acetaldehyde in the transition state **D** largely influences the enantioselectivity of the reaction (Scheme 7b). The author also found that rapid protonation of the sterically hindered LCu-OCHR-B(pin) **E** intermediate with MeOH under a thermodynamically controlled reaction provided the product **F** and copper(I) alkoxide **A**. The presence of MeOH suppresses an isomerization pathway that causes a decrease in the enantioselectivity of the generated products (Scheme 7c). Although the metathesis reaction between **E** and a diboron reagent can still generate the product, addition of MeOH causes a faster protonation of **E** to provide the product and the copper(I) alkoxide **A**. This theoretical study on the mechanism for the enantioselective borylation of a polarized carbon-heteroatom bond will be valuable for the further development and rational design of novel copper(I)-catalyzed nucleophilic borylation reactions.

Scheme 7. Proposed Catalytic Cycle based on Our Current Theoretical Study

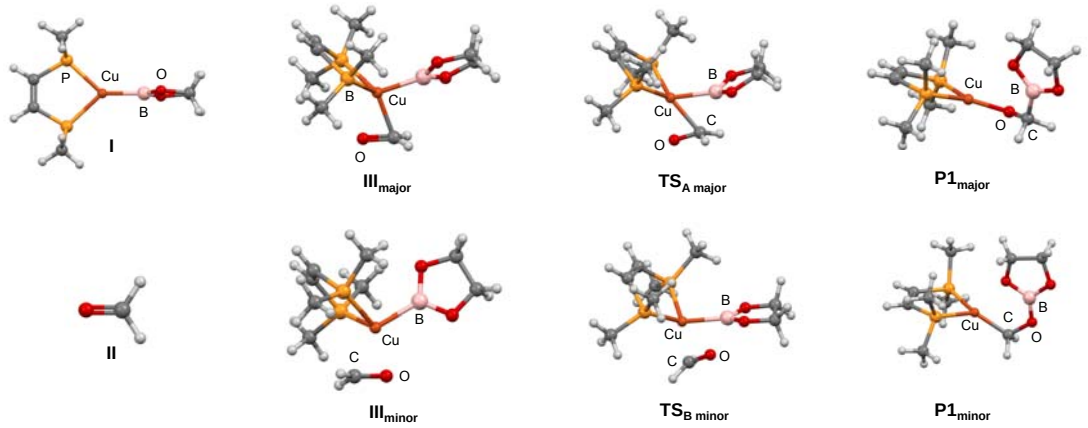


Details of DFT Calculations

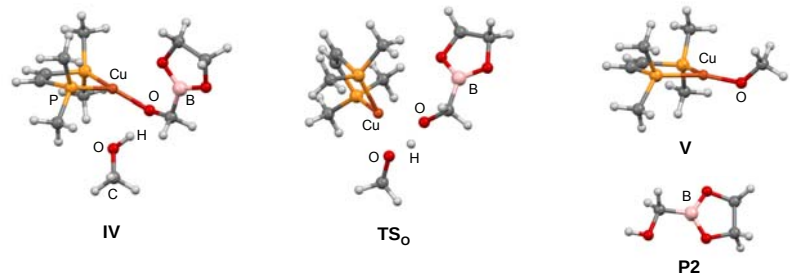
All calculations were performed using the Gaussian 09W (revision C.01) program package.[20] Geometry optimizations and transition states (TS) calculations were performed with B3PW91/cc-pVDZ in the gas-phase. Molecular structures were drawn using the Mercury 3.5 program.[21] Frequency calculations were conducted on gas-phase optimized geometries to check the all the stationary points as either minima or transition states.

Optimized Structures, Calculated Energies, and Thermochemical Parameters

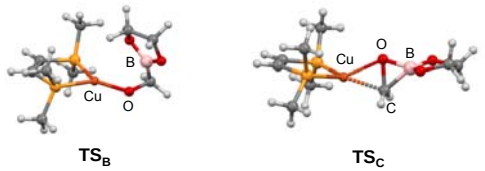
a) Aldehyde addition step



b) Protonation path



c) Isomerization path



d) Protonation step using (*R*)-DTBM-SEGPHOS complex

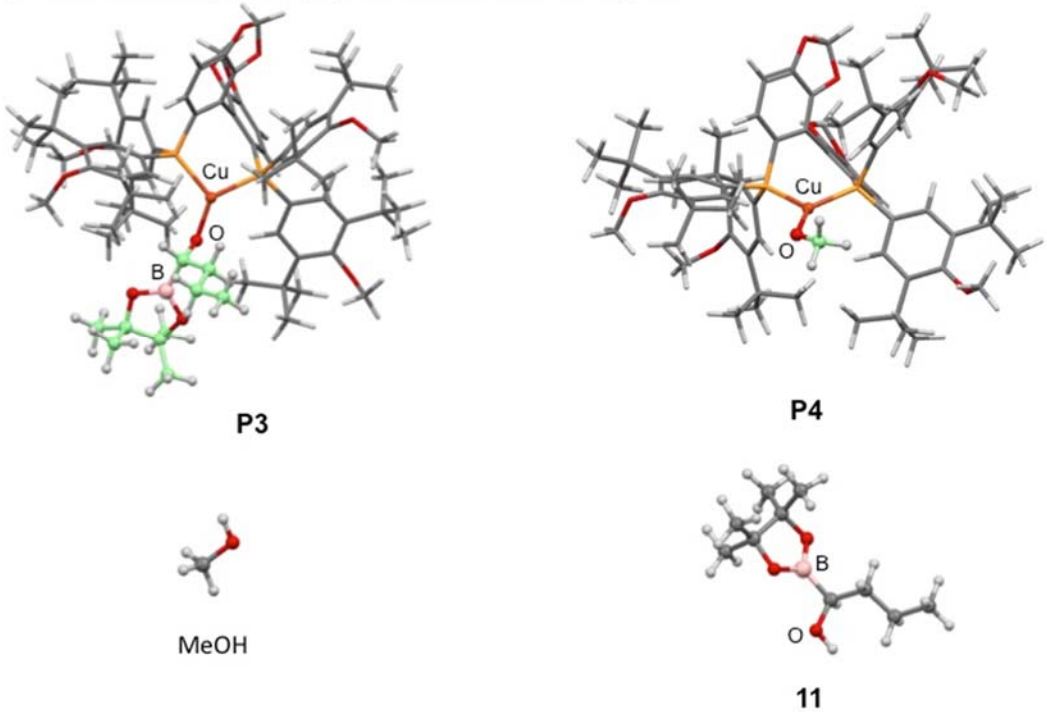


Figure S1. Optimized Structures for Aldehyde Addition Step (a), Protonation Step (b), Isomerization Step (c), and Protonation Step using (*R*)-DTBM-SEGPHOS Complex (d).

Table S1. Calculated Energies and Thermochemical Parameters of the Optimized Structures

	E / Hartree	*H* / Hartree	*S* / Hartree	G^a / kcal mol^{-1}
Aldehyde addition step				
I	-2813.883360	-2813.862939	-2813.861994	-1765771.928
II	-114.436103	-114.433234	-114.432289	-71822.92826
III$_{major}$	-2928.336108	-2928.312845	-2928.311901	-1837593.495
TS$_{A\ major}$	-2928.330286	-2928.308188	-2928.307244	-1837588.14
P1$_{major}$	-2928.369879	-2928.347228	-2928.346284	-1837614.791
III$_{minor}$	-2928.323026	-2928.299793	-2928.298849	-1837584.54
TS$_{B\ minor}$	-2928.293971	-2928.271905	-2928.270961	-1837565.161
P1$_{minor}$	-2928.386599	-2928.363996	-2928.363052	-1837625.34
Enantioselection				
TS1	-6209.916750	-6209.814302	-6209.813358	-3896870.421
TS2	-6209.913372	-6209.811084	-6209.810140	-3896868.455
TS3	-4495.456261	-4495.408645	-4495.407701	-2820994.423
TS4	-4495.454868	-4495.407339	-4495.406395	-2820993.378
Protonation path				
IV	-3044.024403	-3043.997283	-3043.996339	-1910193.847
TS$_D$	-3044.024571	-3043.998553	-3043.997609	-1910191.345
P2	-368.896500	-368.889054	-368.888110	-231506.8552
V	-2675.098743	-2675.080983	-2675.080038	-1678679.817
Isomerization path				
TS$_B$	-2928.364644	-2928.342609	-2928.341665	-1837610.545
TS$_C$	-2928.341745	-2928.319601	-2928.318656	-1837596.292
Protonation step using (*R*)-DTBM-SEGPHOS complex				
P3	-6445.610318	-6445.499212	-6445.498268	-4044777.93
MeOH	-115.630729	-115.627420	-115.626476	-72573.64486
P4	-5917.417646	-5917.320356	-5917.319411	-3713322.531
11	-643.830915	-643.814144	-643.813200	-404038.0495

[a]Relative *G* values (kcal mol^{-1}) at 298 K, 1.0 atm, gas phase.

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(18) The author have experimentally observed that the reaction rate of the DTBM-SEGPHOS/copper(I)-catalyzed borylation without MeOH is slower than that of the protonation reaction with MeOH, as aldehyde substrate **1b** still remained (23% recovery of **1b**) even after 24 h while full conversion of **1b** was observed within 6 h in the reaction with MeOH. In the absence of MeOH, the product is produced by both the metathesis of (*S*)-**9** and B2pin2 and the isomerization [(*S*)-**9** to (*R*)-**10** to (*R*)-**3**]. These results suggest that the metathesis of (*S*)-**9** and B2pin2 is much slower than the protonation pathway in the presence of MeOH. The isomerization was reported to proceed easily (ref. 3) and the calculate activation energy (18.5 kcal/mol) is roughly comparable the reaction rate in the absence of MeOH. These results suggest that the isomerization pathway is comparable to the metathesis pathway, contributing the low ees of the product.
(19) The author cannot completely exclude the possibility that an alcohol molecule would be involved in the addition transition state at this stage. However, it is unlikely that the coordination of an alcohol to the copper(I) center because the copper(I) intermediate in the transition state is coordinatively saturated 18-electron complex. In addition, the author have confirmed that the borylation of **1b** using a polar solvent such as DMI to check the polarity effect of an alcohol on the enantioselectivity resulted in no reaction. Thus, we argued that the significant alcohol effect is attributable to the facile protonation of (*S*)-**9** to suppress the isomerization-induced racemization.
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Chapter 6.

Copper(I)-Catalyzed Enantioselective Borylative Dearomatization of Indoles

Abstract

The first enantioselective borylative dearomatization of a heteroaromatic compound has been achieved using a copper(I) catalyst and a diboron reagent. This reaction involves the unprecedented regio- and enantioselective addition of borylcopper(I) active species to indole-2-carboxylates, followed by the diastereoselective protonation of the resulting copper(I) enolate to give the corresponding chiral indolines bearing consecutive stereogenic centers.

Introduction

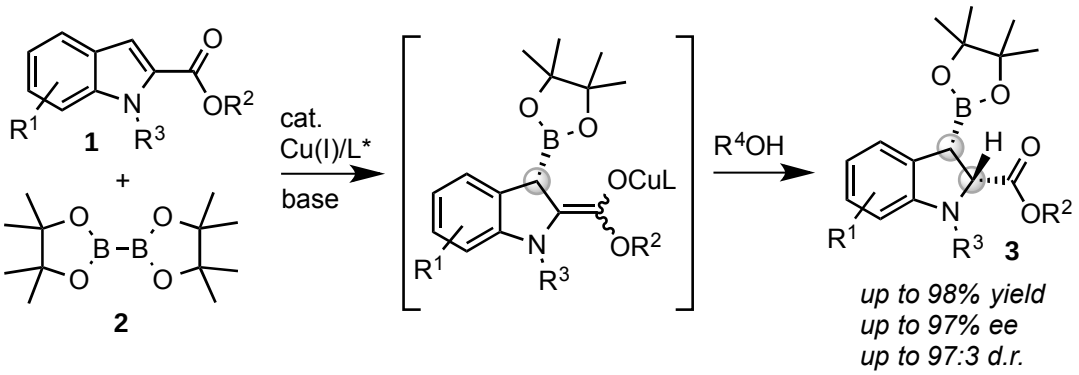
Aromatic compounds are ubiquitous in nature and readily available as synthetic materials. The enantioselective dearomatization reactions of heteroaromatic compounds are very powerful transformations because they can be used to provide direct access to a wide variety of chiral-saturated heterocycles, which are important components of pharmaceutical drugs and bioactive molecules.[1] The development of new methods for the formation of consecutive stereogenic centers via the stereoselective dearomatization of multi-substituted aromatic compounds would also have important practical implications for the synthesis of natural products.[2]

Enantioenriched organoboron compounds are recognized as useful chiral building blocks in synthetic chemistry because they can be readily applied to the stereospecific functionalization of stereogenic C–B bonds.[3] Considerable research efforts have recently been devoted to the development of new methods for the metal-catalyzed enantioselective hydro- and protoboration reactions of prochiral C=C double bonds.[4,5] Despite significant progress in this area, there have been no reports pertaining to the development of C–B bond-forming dearomatization reactions. The lack of research in this area is most likely caused by the high energy barrier encountered during the dearomatization process.[1] The development of an enantioselective C–B bond-forming dearomatization reaction would provide an attractive and complementary approach for the synthesis of complex, functionalized cyclic molecules in combination with the stereospecific transformation of a stereogenic C–B bond.

Ohmura et al.[6] and Weetman et al.[7] independently reported the results of their pioneering studies towards the development of a borylative dearomatization reaction, where pyridines were subjected to a dearomative hydroboration reaction with pinacolborane in the presence of Rh(I) and Mg(II) catalysts. In 2014, Marks et al.[8] reported the development of a similar reaction using La(III) as a catalyst. However, the authors of these studies were only able to demonstrate non-enantioselective N B bond-forming dearomatization reactions.[9,10]

Herein, we report for the first time the development of a copper(I)-catalyzed reaction for the highly regio-, diastereo- and enantioselective C–B bond-forming dearomatization of heteroaromatic compounds (Scheme 1). This reaction involves the unprecedented enantioselective addition of an active borylcopper(I) species to an indole-2-carboxylate **1**, followed by the diastereoselective protonation of the resulting copper(I) enolate to give the corresponding enantioenriched chiral indoline derivative **3** with excellent diastereo- and enantioselectivities. The stereospecific oxidation of the chiral 3-borylindoline product **3** has also been demonstrated.

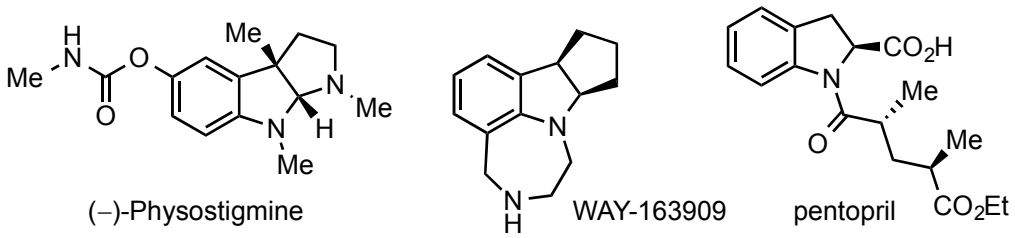
Scheme 1. Copper(I)-Catalyzed Enantioselective C–B Bond Forming Dearomatization of Indoles



During the last decade, our group has been involved in the development of new methods for the copper(I)-catalyzed enantioselective borylation of prochiral alkenes.[11] The results of the related research in this field revealed that electron-deficient substrates with low LUMO levels tend to react efficiently with active borylcopper(I) species.[12] Based on these results, it was

envisaged that heteroaromatic systems bearing an electron-withdrawing group could also react with a borylcopper(I) complex in a process involving the formation of a stereogenic C–B bond. With this in mind, a readily available indole-2-carboxylate derivative was selected as a model substrate to investigate the optimum reaction conditions for the enantioselective borylative dearomatization of this substrate using a chiral copper(I) catalyst. This reaction would allow for the synthesis of chiral indolines containing consecutive stereogenic centers at their 2- and 3-positions. Chiral indolines can be found in a wide variety of naturally occurring bioactive compounds and the synthesis of these compounds has consequently attracted considerable interest from researchers working in a number of different fields (Figure 1).[13,14] The development of an enantioselective dearomative borylation reaction for indoles would therefore provide an interesting and efficient approach to this class of enantioenriched heterocycles.

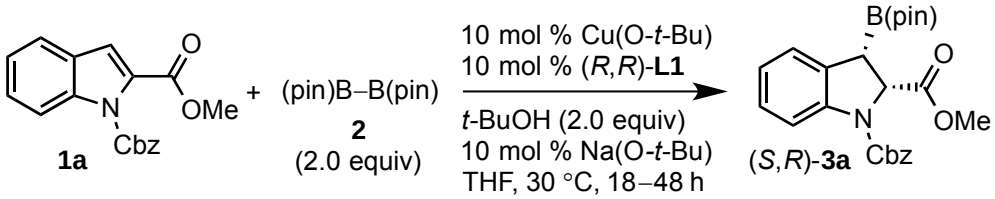
Figure 1. Chiral Indoline-Based Bioactive Molecules



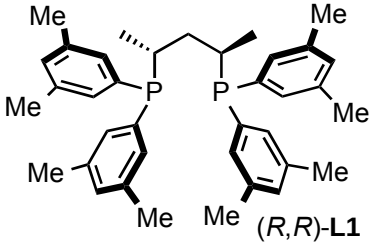
Results and Discussion

The results of an extensive series of optimization experiments revealed that the reaction of carboxybenzyl (Cbz)-protected methyl indole-2-carboxylate (**1a**) with bis(pinacolato)diboron (**2**) (2.0 equiv) in the presence of Cu(O-*t*-Bu)/(*R*,*R*)-**L1** (10 mol %), Na(O-*t*-Bu) (10 mol %) and *t*-BuOH (2.0 equiv), which was used as a proton source, in THF at 30 °C afforded the desired dearomatization product (*S*,*R*)-**3a** in high yield (98%), with excellent diastereo- and enantioselectivities (d.r. 97:3, 93% ee) (Table 1, entry 1).[15] Notably, no product was observed when the reaction was conducted in the absence of Cu(O-*t*-Bu) or ligand **L1** (Table 1, entries 2 and 3). A lower yield (74%) of the dearomatization product **3a** was obtained when Na(O-*t*-Bu) was omitted from the reaction (Table 1, entry 4), although the omission of *t*-BuOH led to a significant decrease in the yield and stereoselectivity of the product (33%, d.r. 76:24, 74% ee) (Table 1, entry 5). The use of the less sterically hindered (*R*,*R*)-BDPP ligand **L2** led to a lower enantioselectivity (74% ee) (Table 1, entry 6). Several other chiral bisphosphine ligands were also tested in the reaction, including (*R*,*R*)-QuinoxP* **L3**, (*R*,*R*)-BenzP* **L4** and (*R*,*R*)-Me-Duphos **L5**, but they all showed poor stereoselectivities (Table 1, entries 7 9). No reaction was observed when the monophosphine-type chiral ligand (*R*)-MOP **L6** was used in the reaction (Table 1, entry 10). A decrease in the loading of the catalyst to 5 mol % did not lead to an erosion in the enantioselectivity (93% ee), although slight decreases were observed in the product yield (76%) and diastereoselectivity (d.r. 92:8) (Table 1, entry 11). The bulkiness of the alcohol was only found to affect the diastereoselectivity of this reaction, because the use of MeOH provided moderate diastereoselectivity (d.r. 75:25, Table1, entry 12).

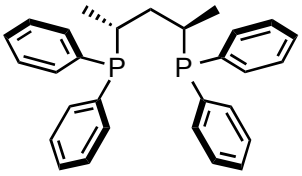
Table 1. Optimization Study



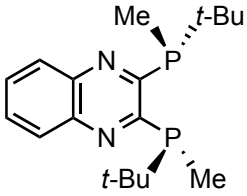
entry	conditions	yield (%)	d.r.	ee (%)
1	standard conditions	98	97:3	93
2	no Cu(O-*t*-Bu)	<5	–	–
3	no (*R,R*)-**L1**	<5	–	–
4	no Na(O-*t*-Bu)	74	89:11	93
5	no *t*-BuOH	33	76:24	74
6	(*R,R*)-**L2** instead of (*R,R*)-**L1**	98	89:11	74
7	(*R,R*)-**L3** instead of (*R,R*)-**L1**	93	90:10	27
8	(*R,R*)-**L4** instead of (*R,R*)-**L1**	77	91:9	61
9	(*R,R*)-**L5** instead of (*R,R*)-**L1**	71	97:3	37
10	(*R,R*)-**L6** instead of (*R,R*)-**L1**	<5	–	–
11	5 mol % of Cu(O-*t*-Bu)/(*R,R*)-**L1**	76	92:8	93
12	MeOH instead of *t*-BuOH	94	75:25	94



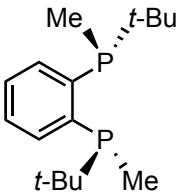
(*R,R*)-**L1**



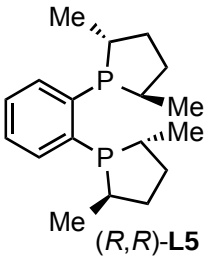
(*R,R*)-**L2**



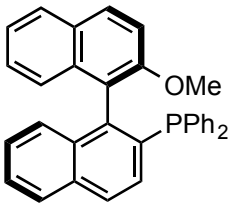
(*R,R*)-**L3**



(*R,R*)-**L4**



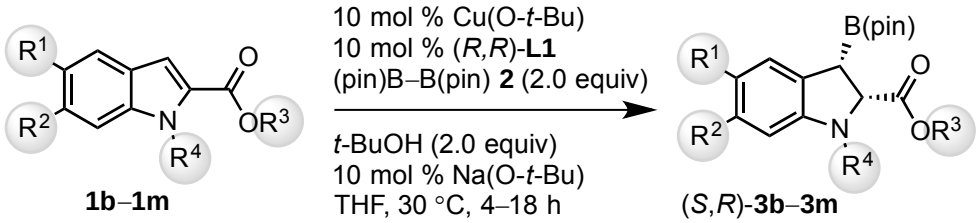
(*R,R*)-**L5**

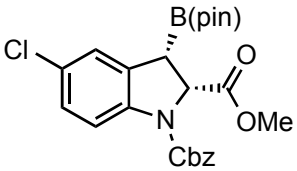


(*R*)-**L6**

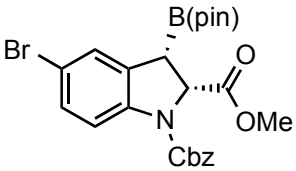
With an optimized procedure in hand, we proceeded to investigate the scope of the reaction using a variety of indole substrates (Table 2). The introduction of an electron-withdrawing or electron-donating functional group at the 5-position of the indole was well tolerated, with the borylation reaction affording consistently excellent selectivities (**3b e**). Indoles bearing a bromo, methoxy or phenyl substituent at their 6-position also reacted with high levels of stereoselectivity (**3f h**). The borylation of an indole bearing an ethyl ester group (**3i**) proceeded with high enantioselectivity (95% ee), but with a lower product yield (52%). The borylation of an indole bearing a bulky isopropyl ester group (**1j**) failed to provide any of the desired product (*S*,*R*)-**3j** under the optimized conditions. Fortunately, the replacement of (*R*,*R*)-**L1** with (*R*,*R*)-**L2** allowed for the borylation of **1j** to proceed in good yield (88% NMR) and excellent stereoselectivity (d.r. 95:5, 90% ee). We subsequently proceeded to investigate the scope of the protecting group on the indole. The borylation of *tert*-butyloxycarbonyl (Boc)-protected indole **1k** provided the expected product (*S*,*R*)-**3k** with the highest enantioselectivity (98% ee) observed in the current study, although the yield was significantly decreased (22% NMR). The replacement of (*R*,*R*)-**L1** with the less sterically hindered (*R*,*R*)-**L2** led to a significant improvement in the yield (98% NMR) with good stereoselectivity (d.r. 93:7, 86% ee). Unfortunately, the application of the optimized conditions to a fluorenylmethyloxycarbonyl (Fmoc)-protected indole group failed to provide any of the desired product, presumably because of the reaction of the acidic proton of the Fmoc group with Na(O-*t*-Bu), which resulted in the formation of a complex mixture. We also found that Me-protected indoles were not applicable to this protocol.

Table 2. Substraate Scope

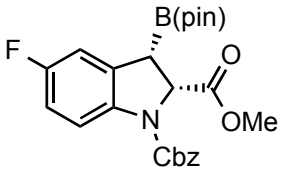




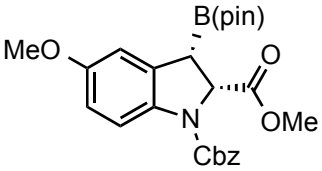
(*S*,*R*)-**3b**
64% (93%)
d.r. 93:7, 95% ee



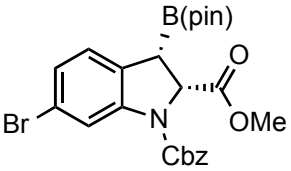
(*S*,*R*)-**3c**
74% (96%)
d.r. 97:3, 92% ee



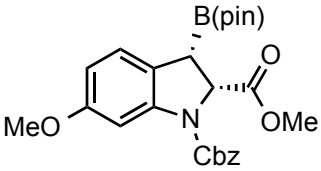
(*S*,*R*)-**3d**
74% (93%)
d.r. 97:3, 95% ee



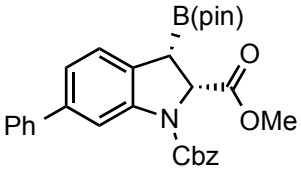
(*S*,*R*)-**3e**
74% (99%)
d.r. 97:3, 97% ee



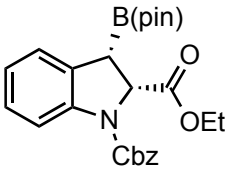
(*S*,*R*)-**3f**
62% (99%)
d.r. 93:7, 86% ee



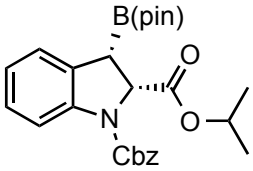
(*S*,*R*)-**3g**
76% (88%)
d.r. 94:6, 93% ee



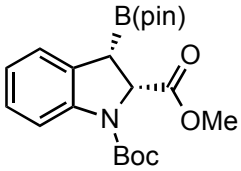
(*S*,*R*)-**3h**
71% (82%)
d.r. 83:17, 89% ee



(*S*,*R*)-**3i**
52% (55%)
d.r. 86:14, 95% ee

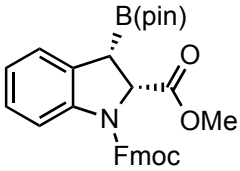


(*S*,*R*)-**3j**[c]
67% (88%)
d.r. 95:5, 90% ee

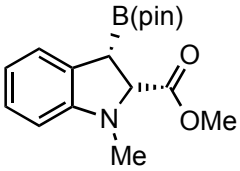


(*S*,*R*)-**3k**
ligand: (*R*,*R*)-**L1**
13% (22%)
d.r. 94:6, 98% ee

ligand: (*R*,*R*)-**L2**
95% (98%)
d.r. 93:7, 86% ee



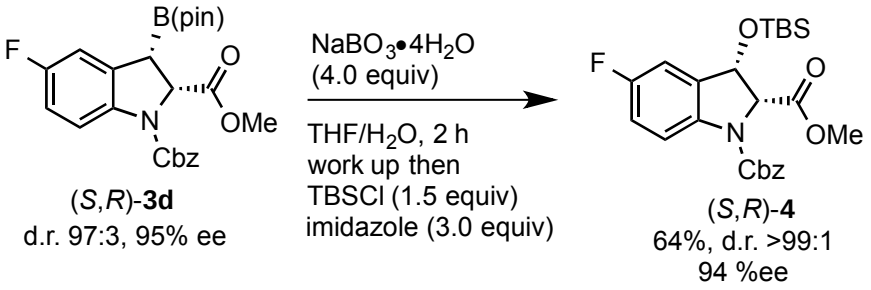
(*S*,*R*)-**3l**
complex mixture
(<5%)



(*S*,*R*)-**3m**
no product
(<5%)

The chiral borylation product (*S,R*)-**3d** generated in this study was subjected to an oxidation reaction, where it was treated with $NaBO_3$ followed by a silyl protection reaction to give the desired chiral 1,2-aminoalcohol (*S,R*)-**4** in a highly stereoselective manner (d.r. >99:1, 94% ee, Scheme 2). It is noteworthy that it would not be possible to synthesize this product using existing dearomative oxidation methods.[16]

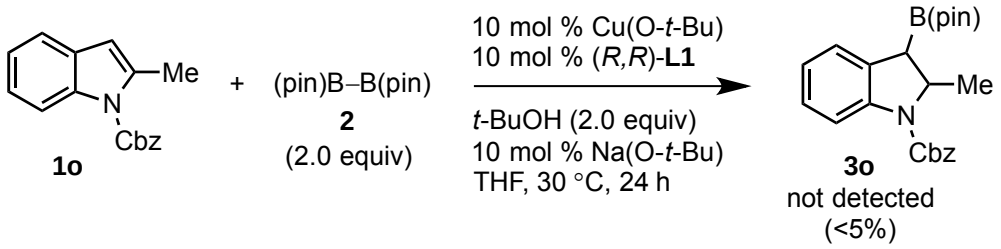
Scheme 2. Stereospecific Oxidation



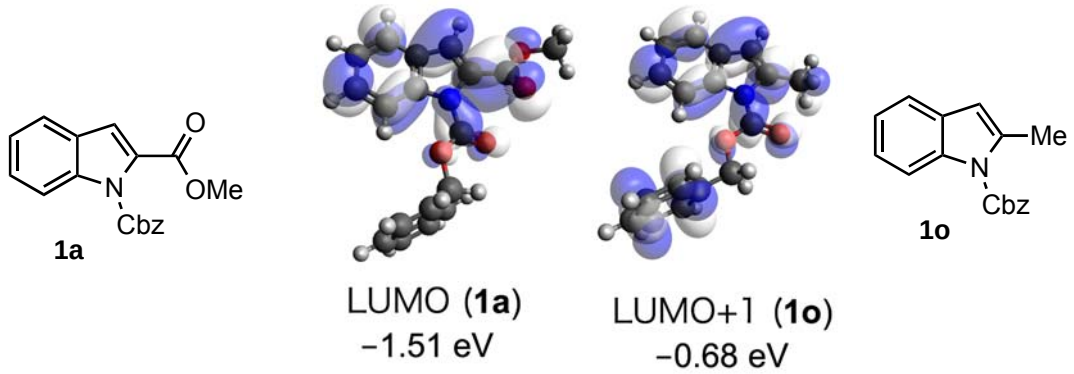
The enantioselective borylation of the 2-methyl indole that does not contain an ester group (**1o**) resulted in no reaction (Scheme 3a).[17] Preliminary density functional theory (DFT) calculation (B3PW91/cc-pVDZ) was used to explain the effect of substituents at the 2-position in the substrate (Scheme 3b).[18] The results show that the LUMO level of **1a** (–1.51 eV) was considerably lower than the LUMO+1 level of **1o** (–0.68 eV), which is localized in the reactive site, indicating that the electron-withdrawing ester moiety would facilitate the addition of borylcopper(I) intermediate to the indoles.

Scheme 3. a) Borylation of 2-Me-Indoles with Copper(I) Catalysis. (b) The Reactive Vacant Orbital Levels of **1a** and **1o** (B3PW91/cc-pVDZ).

a)

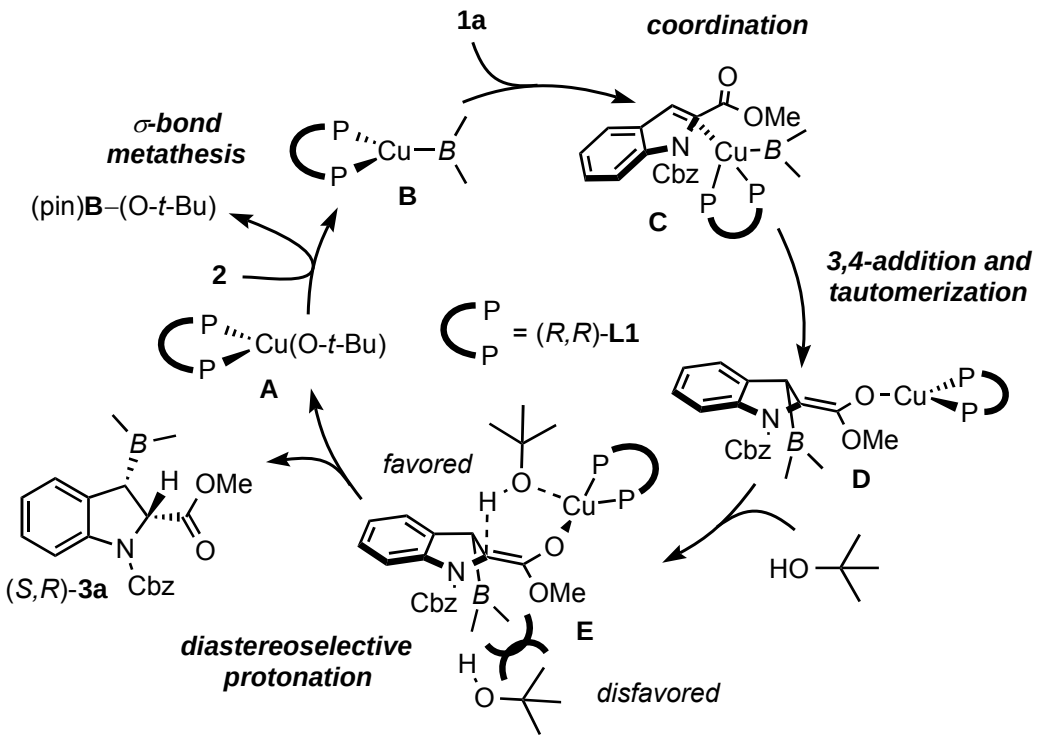


b)



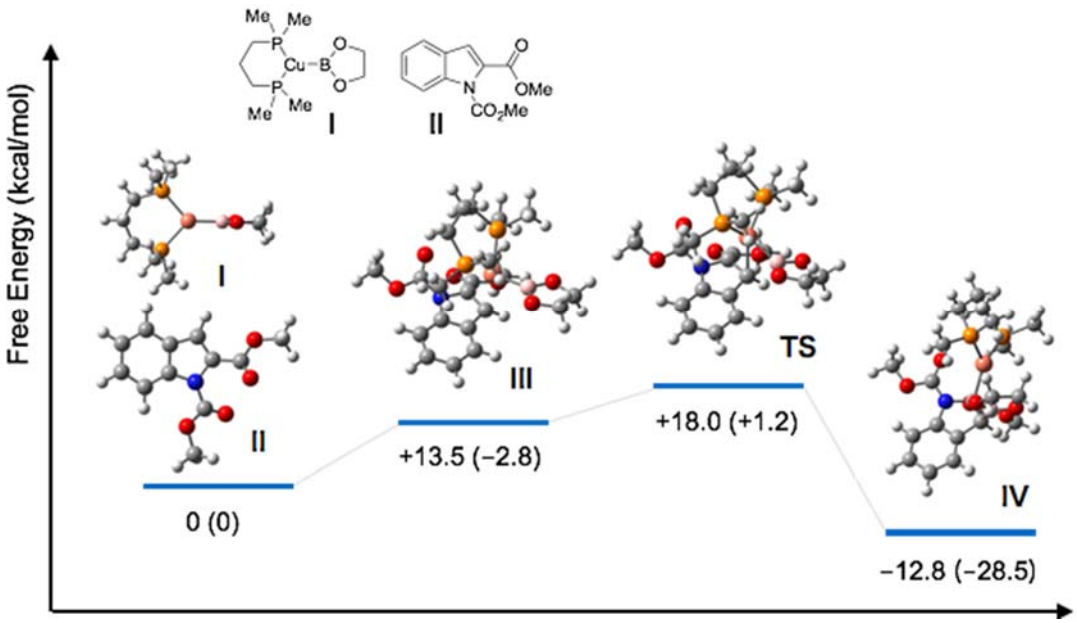
A mechanism was proposed for the current copper(I)-catalyzed dearomative borylation of indoles (Figure 2). Cu(O-*t*-Bu) **A** would initially react with diboron reagent **2** to form the borylcopper(I) **B**. The coordination of indole **1a** to the copper center would result in the formation of -complex **C**. The subsequent 3,4-addition of **B** into **1a** would give the copper(I) *C*-enolate and then transform to the *O*-enolate **D** with concomitant formation of a stereogenic C B bond.[18] After the formation of **D**, the bulky *t*-BuOH additive would access **D** from the opposite side of the pinacolate boryl group to avoid steric congestion between the B(pin) and *t*-Bu groups. The subsequent diastereoselective protonation of **D** would proceed via a six-membered ring transition state **E** to provide the dearomatization product (*S*,*R*)-**3a** and the Cu(O-*t*-Bu) precatalyst **A**.

Figure 2. Proposed Reaction Mechanism



A preliminary DFT calculation (B3PW91/cc-pVDZ) was performed to elucidate the mechanism of the dearomatization step in this reaction (Figure 3).[18] The results showed that the activation energy for the addition of borylcopper(I) **I** to indole **II** to furnish the copper(I) *C*-enolate **IV** was +18.0 kcal/mol, which was in agreement with the proposed pathway (Figure 2).[18]

Figure 3. DFT Calculation on the Dearomatiztion Step



Conclusion

In summary, we have developed the first enantioselective C–B bond-forming dearomatization of heteroaromatic compound using a chiral bisphosphine-copper(I) complex catalyst and a diboron reagent. This reaction involved the unprecedented enantioselective dearomative addition of borylcopper(I) to methyl indole-2-carboxylate with concomitant formation of a stereogenic C–B bond, followed by the diastereoselective protonation of the copper(I) enolate intermediate to deliver the enantioenriched chiral indoline bearing consecutive stereogenic centers with excellent regio-, diastereo- and enantioselectivities. The newly synthesized chiral 3-borylindoline derivative was successfully transformed to the corresponding chiral 1,2-aminoalcohol with high stereospecificity via the oxidation of the C–B bond. The key to the success of this novel dearomative borylation was the introduction of an electron-withdrawing ester group at the 2-position of the indole, which effectively promoted the addition of the active borylcopper(I) species to the

indole ring. It is envisaged that the results of this study will provide further opportunities for the development of novel stereoselective dearomative borylation reactions involving a wide variety of aromatic compounds, such as pyrroles, furans and polyaromatic hydrocarbons. Advances in this area would therefore allow for the efficient synthesis of complex saturated heterocyclic compounds with potentially interesting biological activities.

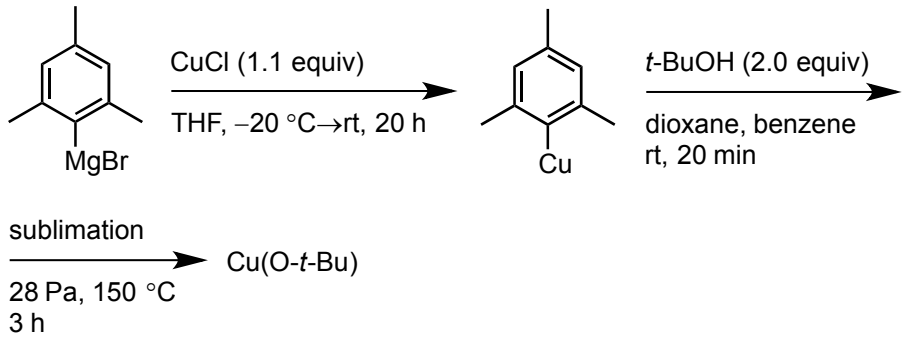
Experimental

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 4Å). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^{1}H: 400 MHz and ^{13}C: 100 MHz). Tetramethylsilane (^{1}H) and $CDCl_3$ (^{13}C) were employed as external standards, respectively. CuCl (ReagentPlus® grade, 224332-25G, ≥99%) was purchased from Sigma-Aldrich Co. and used as received. 2-Phenylethyl chloride was used as an internal standard to determine NMR yields. 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 was recorded at the Center for Instrumental Analysis, Hokkaido University.

General Experimental Procedures

Preparation of Cu(O-*t*-Bu)[19]



All operations were conducted under argon or nitrogen atmosphere. An oven-dried Schlenk flask was charged with CuCl (2.6 g, 26.6 mmol) in an argon-filled glovebox. The flask was capped with a rubber septum and removed from the glovebox. After dry THF (10.0 mL) was added, the suspension was cooled to −20 °C and a THF solution of 2-mesitylmagnesium bromide (0.86 M, 28.1 mL, 24.2 mmol) was added via a syringe. After 15 min, the reaction mixture was allowed to warm to room temperature, and stirred

overnight. Dry 1,4-dioxane (15.0 mL) was added to the reaction mixture and stirred for 15 min and then allowed to stand without stirring. The resultant supernatant layer was transferred via cannula to a separate oven-dried Schlenk flask through a filter funnel under nitrogen atmosphere. The precipitated salt was washed with dry benzene. *t*-BuOH (4.6 mL, 48.8 mmol) was then added to the residual solution. After stirring for 20 min, the solvents were removed in vacuo. The reaction vessel was transferred into a glove box and then the crude product was transferred from the Schlenk flask to a sublimation apparatus. The sublimation apparatus was removed from the glovebox. The crude product was purified by sublimation (bath temp. 150 °C, 28 Pa) to afford Cu(O-*t*-Bu) (0.59 g, 4.3 mmol, 18%). Cu(O-*t*-Bu) is very sensitive to air and moisture and should be stored and treated in a glove box.

Preparation of chiral ligands

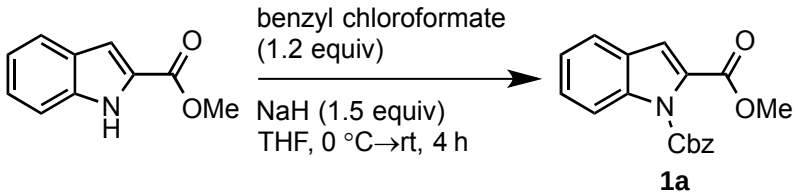
(*R*,*R*)-**L1** was synthesized according to the literature procedure.[20] Other chiral ligands were obtained from commercial suppliers without further purification.

Procedure for the copper(I)-catalyzed enantioselective borylative dearomatization of 1a (Table 1).

1a (155.7 mg, 0.50 mmol) and bis(pinacolato)diboron (253.2 mg, 1.0 mmol), (*R*,*R*)-3,5-xyl-BDPP (27.7 mg, 0.050 mmol) were placed in an oven-dried reaction vial. After the vial was placed in a glove box, Cu(O-*t*-Bu) (6.8 mg, 0.050 mmol) and Na(O-*t*-Bu) (4.8 mg, 0.050 mmol) were placed in the vial. After being sealed with a screw cap containing a teflon-coated rubber septum, the vial was removed in a glove box connected to a nitrogen line through a needle. THF (1.0 mL) was added to the mixture through the rubber septum at 30 °C. Then *t*-BuOH (94.9 μL, 1.0 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short silica gel column eluting with Et_2O/Hexane (80:20). The crude mixture was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, typically 4:96–10:90) to give the corresponding borylation product (*S*,*R*)-**3a** as a colorless oil.

Substrate Preparation

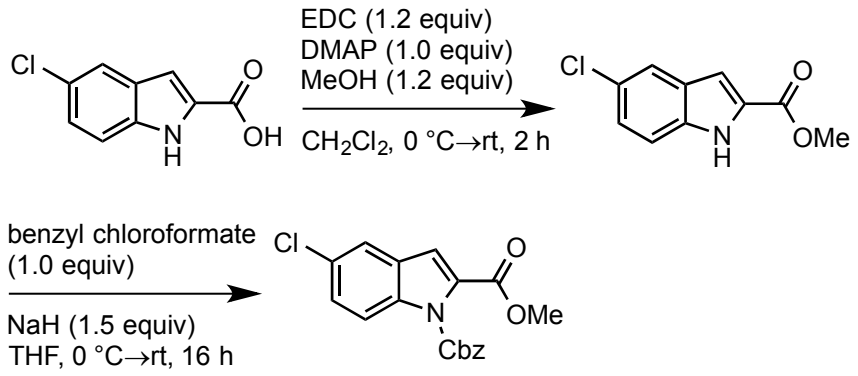
Preparation of 1-benzyl 2-methyl 1*H*-indole-1,2-dicarboxylate (1a).



The Cbz-protection was performed according to the literature procedure.[21] In a 50 mL round bottomed flask, NaH (180.0 mg, 60% dispersion in paraffin liquid, 4.5 mmol) was dissolved in dry THF (6.0 mL) and the mixture was cooled to 0 °C under nitrogen atmosphere. Methyl indole-2-carboxylate (524.0 mg, 3.0 mmol) was added in three separate times. Benzyl chloroformate (513.9 L, 3.6 mmol) was then added dropwise. After stirred for 4 h at room temperature, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2 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 (SiO_2, ethyl acetate/hexane, 3:97–10:90) to obtain **1a** (659.4 mg, 2.1 mmol, 71%) as a white solid.

^{1}H NMR (392 MHz, $CDCl_3$,): 3.73 (s, 3H), 5.42 (s, 2H), 7.13 (s, 1H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.32 7.49 (m, 6H), 7.60 (d, *J* = 7.9 Hz, 1H), 8.08 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 52.3 (CH_3), 69.6 (CH_2), 115.0 (*C*H), 115.6 (*C*H), 122.2 (*C*H), 123.6 (*C*H), 127.0 (*C*H), 127.6 (*C*), 128.6 (*C*H), 128.7 (*C*H), 128.8 (*C*), 130.3 (*C*), 134.4 (*C*), 137.6 (*C*), 150.6 (*C*), 162.1 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{15}O_4NNa$, 332.08933; found, 332.08934.

Preparation of methyl-1-benzyloxycabonyl-5-chloro-indole-2-carboxylate (1b).



1b

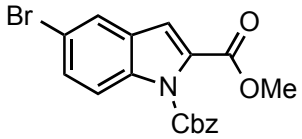
The condensation was performed according to the literature procedure.[22] In a vacuum dried 100 mL round bottomed flask, 5-chloro-indole-2-carboxylate (980.2 mg, 5.0 mmol) and 4-dimethylaminopyridine (DMAP) (612.9 mg, 5.0 mmol), methanol (242.8 L, 6.0 mmol) were dissolved in dry CH_2Cl_2 (20.0 mL), and the reaction mixture was cooled to 0 °C under nitrogen atmosphere. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (1.15 g, 6.0 mmol) was then added to the mixture. After stirred for 2 h at room temperature, the reaction mixture was quenched by addition of HCl aq. (1.0 N) and extracted with CH_2Cl_2 three times. The combined organic layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the corresponding methyl ester (801.1 mg, 3.8 mmol, 76%) as a white solid.

In a 50 mL round bottomed flask, NaH (231.9 mg, 60% dispersion in paraffin liquid, 5.8 mmol) was dissolved in dry THF (8.0 mL) and the mixture was cooled to 0 °C. The methyl ester (801.1 mg, 3.8 mmol) was added in three separate times. Benzyl chloroformate (545.3 L, 3.8 mmol) was then added dropwise. After stirred for 16 h at room temperature, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2 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 (SiO_2, ethyl acetate/hexane, 4:96–7:93) to obtain **1b** (715.3 mg, 2.1 mmol, 54%) as a white solid.

^{1}H NMR (392 MHz, $CDCl_3$,): 3.72 (s, 3H), 5.41 (s, 2H), 7.04 (s, 1H), 7.26 (s, 1H), 7.33 7.49 (m, 5H), 7.58 (d, J = 2.2 Hz, 1H), 8.02 (d, J = 9.0 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 52.5 (CH_3), 69.9 (CH_2), 114.3 (CH), 116.2 (CH),

121.6 (*C*), 127.3 (*C*), 128.75 (*C*H), 128.84 (*C*H), 128.95 (*C*H), 129.3 (*C*), 131.5 (*C*), 134.2 (*C*), 135.8 (*C*), 150.3 (*C*), 161.9 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{14}O_4NClNa$, 366.05036; found, 366.05086.

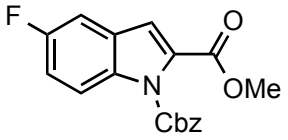
Preparation of 1-benzyl 2-methyl 5-bromo-1*H*-indole-1,2-dicarboxylate (1c).



1c

1c was prepared from the corresponding indole-2-carboxylic acid according to the procedure described above. ^{1}H NMR (392 MHz, $CDCl_3$,): 3.72 (s, 3H), 5.41 (s, 2H), 7.04 (s, 1H), 7.35 7.54 (m, 6H), 7.74 (d, *J* = 1.8 Hz, 1H), 7.96 (d, *J* = 9.0 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 52.5 (CH_3), 69.9 (CH_2), 114.1 (*C*H), 116.5 (*C*H), 116.9 (*C*), 124.7 (*C*H), 128.7 (*C*H), 128.8 (*C*H), 128.9 (*C*H), 129.2 (*C*), 129.9 (*C*H), 131.3 (*C*), 134.1 (*C*), 136.1 (*C*), 150.3 (*C*), 161.8 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{14}O_4NBrNa$, 409.99984; found, 410.00044.

Preparation of 1-benzyl 2-methyl 5-fluoro-1*H*-indole-1,2-dicarboxylate (1d).

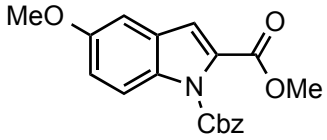


1d

1d was prepared from the corresponding indole-2-carboxylic acid according to the procedure described above. ^{1}H NMR (392 MHz, $CDCl_3$,): 3.73 (s, 3H), 5.42 (s, 2H), 7.07 (d, *J* = 0.7 Hz, 1H), 7.15 (td, *J* = 2.6, 9.1 Hz, 1H), 7.26 (dd, *J* = 2.5, 8.1 Hz, 1H), 7.36 7.49 (m, 5H), 8.05 (q, *J* = 4.5 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 52.4 (CH_3), 69.8 (CH_2), 107.3 (*C* F, d, *J* = 23.5 Hz, *C*H), 114.7 (*C* F, d, *J* = 3.8 Hz, *C*H), 115.0 (*C* F, d, *J* = 25.4 Hz, *C*H), 116.2 (*C* F, d, *J* = 8.5 Hz, *C*H), 128.3 (*C* F, d, *J* = 10.3 Hz, *C*), 128.7 (*C*H), 128.8 (*C*H), 128.8 (*C*H), 131.7 (*C*), 133.8 (*C*), 134.2 (*C*), 150.3 (*C*), 159.4 (*C* F, d, *J* = 240.5 Hz, *C*), 161.9 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{14}O_4NFNa$, 350.07991; found, 350.08011.

Preparation of 1-benzyl 2-methyl 5-methoxy-1*H*-indole-1,2-dicarboxylate

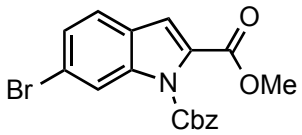
(1e).



1e

1e was prepared from the corresponding indole-2-carboxylic acid according to the procedure described above. ^{1}H NMR (392 MHz, $CDCl_3$,): 3.73 (s, 3H), 3.86 (s, 3H), 5.41 (s, 2H), 7.00 7.08 (m, 3H), 7.35 7.50 (m, 5H), 7.95 8.01 (m, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 52.3 (CH_3), 55.6 (CH_3), 69.5 (CH_2), 103.7 (*C*H), 115.4 (*C*H), 115.9 (*C*H), 116.5 (*C*H), 128.3 (*C*), 128.6 (*C*H), 128.7 (*C*H), 130.7 (*C*), 132.3 (*C*), 134.4 (*C*), 150.6 (*C*), 156.4 (*C*), 162.1 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{17}O_5NNa$, 362.09989; found, 362.10004.

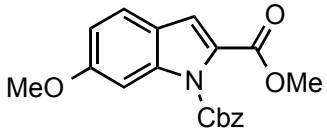
Preparation of 1-benzyl 2-methyl 6-bromo-1*H*-indole-1,2-dicarboxylate (1f).



1f

1f was prepared from the corresponding indole-2-carboxylic acid according to the procedure described above. ^{1}H NMR (392 MHz, $CDCl_3$,): 3.72 (s, 3H), 5.42 (s, 2H), 7.08 (s, 1H), 7.36 7.50 (m, 7H), 8.30 (t, J = 0.9 Hz, 1H). ^{13}C NMR (98.5 MHz, $CDCl_3$,): 52.3 (CH_3), 69.9 (CH_2), 115.0 (*C*H), 118.1 (*C*H), 120.8 (*C*H), 123.2 (*C*H), 126.3 (*C*), 127.0 (*C*H), 128.6 (*C*H), 128.7 (*C*H), 128.8 (*C*H), 130.5 (*C*), 134.1 (*C*), 138.0 (*C*), 150.1 (*C*), 161.7 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{14}O_4NBrNa$, 409.99984; found, 410.00007.

Preparation of 1-benzyl 2-methyl 6-methoxy-1*H*-indole-1,2-dicarboxylate (1g).

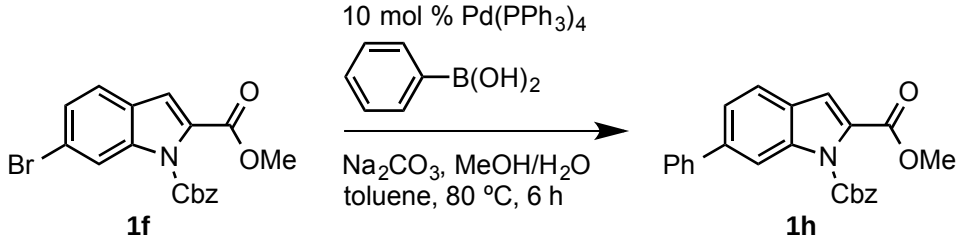


1g

1g was prepared from the corresponding indole-2-carboxylic acid according to the procedure described above. ^{1}H NMR (392 MHz, $CDCl_3$,): 3.73 (s, 3H), 3.79 (s, 3H), 5.41 (s, 2H), 6.89 (dd, J = 2.2, 8.6 Hz, 1H), 7.12 (s, 1H),

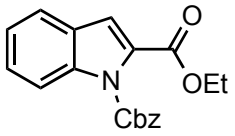
7.33 7.50 (m, 6H), 7.57 (d, J = 2.2 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 52.1 (CH_3), 55.5 (CH_3), 69.6 (CH_2), 98.1 (*C*H), 113.9 (*C*H), 116.7 (*C*H), 121.1 (*C*), 122.9 (*C*H), 128.7 (*C*H), 128.78 (*C*H), 128.79 (*C*H), 128.9 (*C*), 134.5 (*C*), 139.3 (*C*), 150.9 (*C*), 159.9 (*C*), 161.9 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{17}O_5NNa$, 362.09989; found, 362.09976.

Preparation of 1-benzyl 2-methyl 6-phenyl-1*H*-indole-1,2-dicarboxylate (1h).



$Pd(PPh_3)_4$ (231.1 mg, 0.20 mmol) and phenyl boronic acid (487.7 mg, 4.0 mmol) and Na_2CO_3 (424.0 mg, 4.0 mmol) and **1f** (776.4 mg, 2.0 mmol) was placed in a round bottom flask. Dry toluene (6.0 mL) and a mixture solvent of MeOH/H_2O (1:1, 4.0 mL) were added to the flask at room temperature. The reaction mixture was stirred at 80 ºC for 6 h. After the reaction mixture was cooled to room temperature, the mixture was quenched by saturated $NaHCO_3$ aq. and extracted with EtOAc three times. The combined organic layer was then dried over $MgSO_4$. The crude material was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 0:100–10:90) and gel permeation chromatography (eluent: $CHCl_3$) to give the corresponding coupling product **1h** (358.1 mg, 0.93 mmol, 46%) as a green colored oil. ^{1}H NMR (395 MHz, $CDCl_3$, δ): 3.76 (s, 3H), 5.43 (s, 2H), 7.16 (d, J = 0.79 Hz, 1 H), 7.33–7.66 (m, 12 H), 8.30 (t, J = 0.99 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 52.2 (CH_3), 69.7 (CH_2), 113.4 (*C*H), 115.6 (*C*H), 122.4 (*C*H), 123.1 (*C*H), 126.7 (*C*) 127.29 (*C*H), 127.33 (*C*H), 128.6 (*C*H), 128.7 (*C*H), 128.75 (*C*H), 128.78 (*C*H), 130.6 (*C*), 134.3 (*C*), 138.2 (*C*), 140.3 (*C*), 140.9 (*C*), 150.5 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{24}H_{19}O_4NNa$, 408.12063; found, 408.12064.

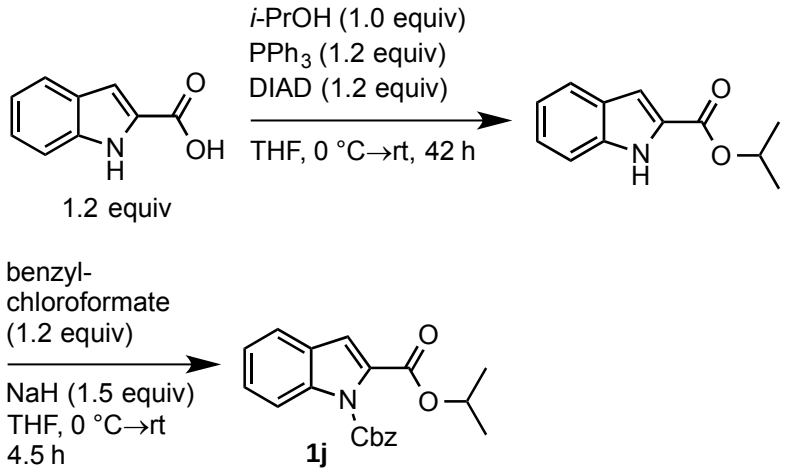
Preparation of 1-benzyl 2-ethyl 1*H*-indole-1,2-dicarboxylate (1i).



1i

1i was prepared from the corresponding ethyl indole-2-carboxylate by the same Cbz-protection procedure described above. ^{1}H NMR (392 MHz, $CDCl_3$,): 1.26 (t, *J* = 7.2 Hz, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 5.41 (s, 2H), 7.12 (s, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.32 7.49 (m, 6H), 7.59 (d, *J* = 7.9 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 13.6 (CH_3), 61.0 (CH_2), 69.1 (CH_2), 114.5 (*C*H), 114.9 (*C*H), 121.8 (*C*H), 123.2 (*C*H), 126.5 (*C*H), 127.2 (*C*), 128.17 (*C*H), 128.19 (*C*H), 128.24 (*C*H), 130.3 (*C*), 134.1 (*C*), 137.4 (*C*), 150.2 (*C*), 161.2 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{17}O_4NNa$, 346.10498; found, 346.10494.

Preparation of 1-benzyl 2-isopropyl 1*H*-indole-1,2-dicarboxylate (1j).

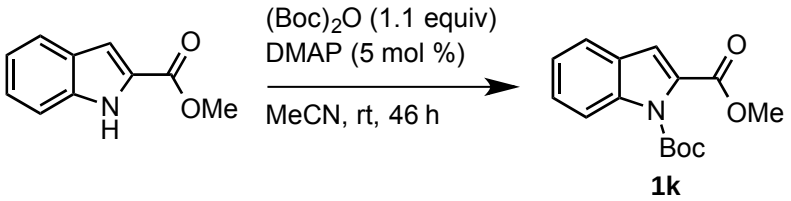


The Mitsunobu reaction was performed according to the literature procedure.[23] In a vacuum dried 100 mL round bottomed flask, indole-2-carboxylate (1.94 g, 12.0 mmol) and triphenylphosphine (3.14 g, 12.0 mmol), 2-PrOH (764.6 L, 10.0 mmol) were dissolved in dry THF (20.0 mL), and the mixture was cooled to 0 °C under nitrogen atmosphere. Diisopropyl azodicarboxylate (2.36 mL, 12.0 mmol) was then added dropwise. After stirred for 42 h at room temperature, the reaction mixture was passed through a short silica gel column eluting with Et_2O/CH_2Cl_2. The crude mixture was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 1:99–7:93) to obtain the corresponding isopropyl ester (1.70 g, 8.4 mmol, 84%) as a

white solid.

In a 100 mL round bottomed flask, NaH (302.4 mg, 7.5 mmol) was dissolved in dry THF (10.0 mL) and the mixture was cooled to 0 °C. The isopropyl ester (1.02 g, 5.0 mmol) was added in three separate times. Benzyl chloroformate (856.5 L, 6.0 mmol) was then added dropwise. After stirred for 4.5 h at room temperature, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2 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 (SiO_2, ethyl acetate/hexane, 3:97–7:93) to obtain **1j** (1.61 g, 4.8 mmol, 96%) as a white solid. ^{1}H NMR (392 MHz, $CDCl_3$,): 1.28 (d, *J* = 6.4 Hz, 6H), 5.15 (sep, *J* = 6.2 Hz, 1H), 5.42 (s, 2H), 7.11 (s, 1H), 7.21 7.49 (m, 7H), 7.59 (d, *J* = 7.9 Hz, 1H), 8.06 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 21.6 (CH_3), 69.1 (*C*H), 69.4 (CH_2), 114.9 (*C*H), 115.2 (*C*H), 122.1 (*C*H), 123.5 (*C*H), 126.8 (*C*H), 127.6 (*C*), 128.48 (*C*H), 128.53 (*C*H), 128.57 (*C*H), 131.1 (*C*), 134.5 (*C*), 137.5 (*C*), 150.6 (*C*), 161.1 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{19}O_4NNa$, 360.12063; found, 360.12064.

Preparation of 1-(*tert*-butyl) 2-methyl 1*H*-indole-1,2-dicarboxylate (1k).



The Boc-protection was performed according to the literature procedure.[24] In a 100 mL round bottomed flask, methyl indole-2-carboxylate (1.76 g, 10.0 mmol) and 4-dimethylaminopyridine (61.1 mg, 0.50 mmol) were dissolved in dry MeCN (10.0 mL) under nitrogen atmosphere. Di-*tert*-butyl dicarbonate (2.53 mL, 11.0 mmol) was then added dropwise. After stirred for 46 h at room temperature, the reaction mixture was quenched by addition of water and extracted with CH_2Cl_2 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 (SiO_2, ethyl acetate/hexane, 0:100–6:94) to obtain **1k** (2.66 g, 9.7 mmol, 97%) as a white solid. ^{1}H NMR (392 MHz, $CDCl_3$,): 1.63 (s, 9H), 3.92 (s, 3H), 7.10 (s, 1H), 7.26 (ddd, *J* = 1.0, 7.2, 8.0 Hz, 1H), 7.41 (ddd, *J* = 1.3, 7.1, 9.3 Hz, 1H), 7.60 (d, *J*

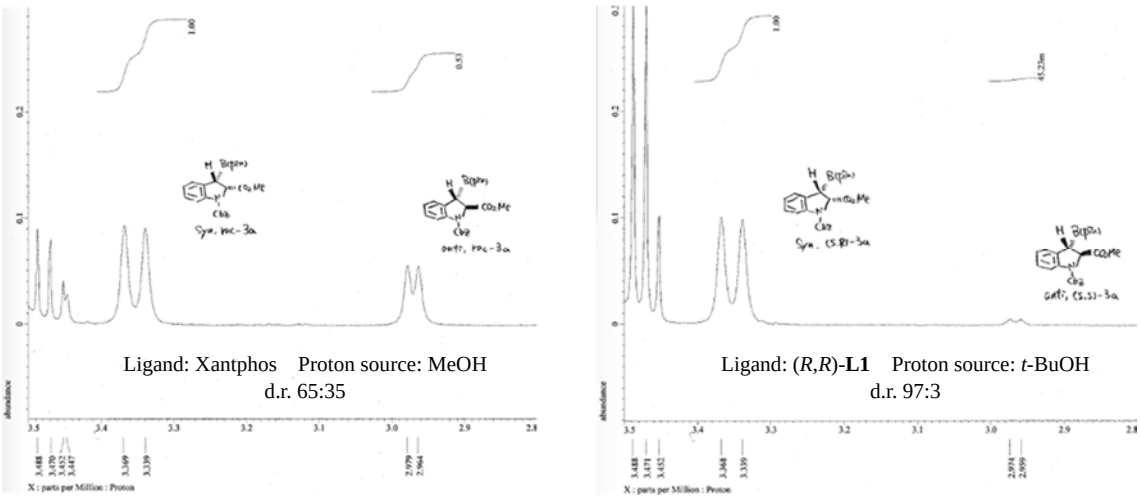
= 7.9 Hz, 1H), 8.09 (dd, J = 0.7, 8.2 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 27.8 (CH_3), 52.3 (CH_3), 84.6 (*C*), 114.8 (*C*H), 122.1 (*C*H), 123.3 (*C*H), 126.8 (*C*H), 127.5 (*C*), 130.4 (*C*), 137.8 (*C*), 149.2 (*C*), 162.3 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{17}O_4NNa$, 298.10498; found, 298.10517.

Determination of Diastereomeric Ratio Values

Diastereomeric ratio values of the borylation products were determined by ^{1}H NMR analysis of the crude reaction mixture (Figure S1). In the case of **1a**, the use of achiral Xantphos ligand and MeOH as a proton source provided a poor diastereoselectivity (65:35, Figure S1a). In contrast, the reaction using (*R*,*R*)-**L1** and *t*-BuOH resulted in a high diastereoselectivity (97:3, Figure S1b). Diastereomeric ratio values of other borylation products were determined in the similar way. The minor diastereomer could be completely separated by silica gel column chromatography because their R_f values are different enough for separation.

Figure S1. Determination of diastereomeric ratio values by crude ^{1}H NMR.

a) b)



Borylation Product Characterization

^{1}H and ^{13}C NMR spectra for all borylation products contain conformational isomers, which is caused by the restricted C–N bond rotation around the carbamate group.

Borylation Product Characterization

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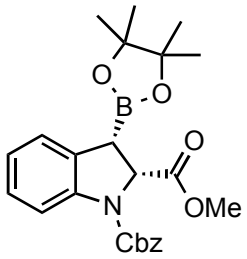
(*S,R*)-1-Benzyl 2-methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1,2-dicarboxylate [(*S,R*)-3a].

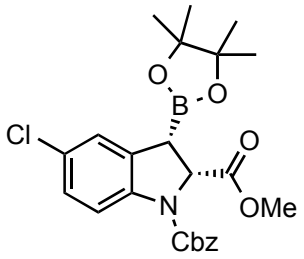


(*S,R*)-**3a**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.27 (s, 12H), 3.35 (d, *J* = 11.5 Hz, 1H), 3.53 and 3.71 (a pair of s, 3H), 5.08–5.41 (m, 3H), 6.97 (t, *J* = 7.4 Hz, 1H), 7.11–7.23 (m, 2H), 7.25–7.51 (m, 5H), 7.90 (d, *J* = 7.9 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.6 (CH_3), 24.9 (CH_3), 29.0 (br, B CH), 52.0 and 52.1 (a pair of s, CH_3), 62.7 and 62.9 (a pair of s, *C*H), 67.1 and 67.9 (a pair of s, CH_2), 84.2 (*C*), 114.6 and 114.8 (a pair of s, *C*H), 122.9 and 123.0 (a pair of s, *C*H), 124.1 and 124.5 (a pair of s, *C*H), 127.3 (*C*H), 127.9 (*C*H), 128.1 (*C*H), 128.4 (*C*H), 130.6 (*C*), 135.9 (*C*), 142.0 (*C*), 152.0 (*C*), 171.3 and 171.5 (a pair of s, *C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{24}H_{28}O_6N^{10}BNa$, 459.19382; found, 459.19421. $[\alpha]_D^{22.1}$ +19.94 (*c* 1.6 in $CHCl_3$, 93% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 2/98, 0.5 mL/min, 40 °C, (*S,R*)-isomer: t_R = 33.65 min., (*R,S*)-isomer: t_R = 29.23 min.

(*S,R*)-1-Benzyl 2-methyl 5-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1,2-dicarbo

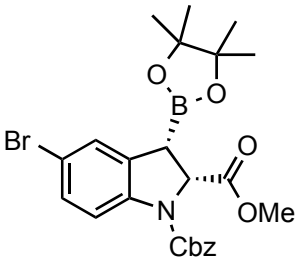
xylate [(*S,R*)-3b].



(*S*,*R*)-**3b**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.26 and 1.28 (a pair of s, 12H), 3.30 (d, *J* = 11.5 Hz, 1H), 3.53 and 3.71 (a pair of s, 3H), 5.05–5.40 (m, 3H), 7.01–7.20 (m, 2H), 7.24–7.47 (m, 5H), 7.81 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.6 (CH_3), 24.9 (CH_3), 29.0 (br, B *C*H), 52.0 (CH_3), 62.9 and 63.2 (a pair of s, *C*H), 67.3 (CH_2), 83.4 and 84.4 (a pair of s, *C*), 115.4 and 115.5 (a pair of s, *C*H), 124.5 (*C*H), 127.2 (*C*H), 127.9 (*C*), 128.0 (*C*H), 128.2 (*C*H), 128.5 (*C*H), 132.7 (*C*), 135.7 (*C*), 140.7 (*C*), 152.0 and 153.0 (a pair of s, *C*), 171.2 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{24}H_{27}O_6N^{10}BClNa$, 493.15485; found, 493.15576. $[\alpha]_D^{23.9}$ +15.77 (*c* 1.1 in $CHCl_3$, 95% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 2/98, 0.5 mL/min, 40 °C, (*S,R*)-isomer: t_R = 29.04 min., (*R,S*)-isomer: t_R = 27.73 min.

(*S,R*)-1-Benzyl 2-methyl 5-bromo-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1,2-dicarbo xylate [(*S,R*)-3c].

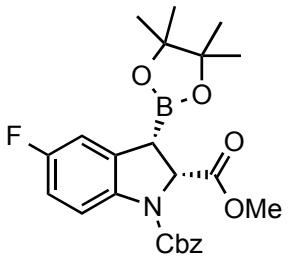


(*S*,*R*)-**3c**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.26 and 1.28 (a pair of s, 12H), 3.31 (d, *J* = 11.5 Hz, 1H), 3.53 and 3.71 (a pair of s, 3H), 5.00–5.42 (m, 3H), 7.24–7.46 (m, 7H), 7.77 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.6 (CH_3), 24.8 (CH_3), 29.0 (br, B *C*H), 52.0 and 52.2 (a pair of s, CH_3), 62.9 and 63.1 (a pair of s, *C*H), 67.3 and 68.2 (a pair of s, CH_2), 84.4 (*C*), 115.4 (*C*), 115.9 and 116.0 (a pair of s, *C*H), 127.3 (*C*H), 128.0 (*C*H), 128.2 (*C*H), 128.4 (*C*H), 130.1 (*C*H),

133.0 (*C*), 135.7 (*C*), 141.2 (*C*), 151.9 (*C*), 171.2 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{24}H_{27}O_6N^{10}BBrNa$, 537.10433; found, 537.10518. $[\alpha]_D^{24.5}$ +7.88 (*c* 0.9 in $CHCl_3$, 92% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, (*S*,*R*)-isomer: t_R = 44.15 min., (*R*,*S*)-isomer: t_R = 27.31 min.

(*S*,*R*)-1-Benzyl 2-methyl 5-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) indoline-1,2-dicarboxylate [(*S*,*R*)-3d].

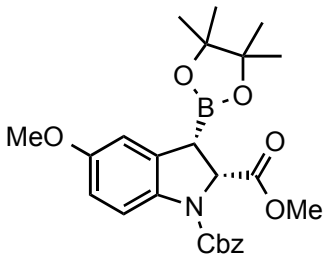


(*S*,*R*)-**3d**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.26 and 1.28 (a pair of s, 12H), 3.31 (d, *J* = 11.5 Hz, 1H), 3.54 and 3.72 (a pair of s, 3H), 5.10–5.45 (m, 3H), 6.72–6.96 (m, 2H), 7.24–7.48 (m, 5H), 7.82 (q, *J* = 4.5 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.6 (CH_3), 24.8 (CH_3), 29.0 (br, B CH), 52.0 and 52.1 (a pair of s, CH_3), 63.0 and 63.2 (a pair of s, CH), 67.1 and 68.0 (a pair of s, CH_2), 83.4 and 84.3 (a pair of s, *C*), 111.8 (*C* F, d, *J* = 25.4 Hz, CH), 113.3 (*C* F, d, *J* = 23.5 Hz, CH), 115.0 (*C* F, d, *J* = 7.5 Hz, CH), 127.9 (CH), 128.1 (CH), 128.4 (CH), 132.5 and 132.6 (a pair of s, *C*), 135.6 and 135.8 (a pair of s, *C*), 138.0 (*C*), 152.0 (*C*), 158.9 (*C* F, d, *J* = 216.6 Hz, *C*), 171.3 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{24}H_{27}O_6N^{10}BFNa$, 477.18440; found, 477.18502. $[\alpha]_D^{23.0}$ +36.18 (*c* 0.9 in $CHCl_3$, 95% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 2/98, 0.5 mL/min, 40 °C, (*S*,*R*)-isomer: t_R = 28.21 min., (*R*,*S*)-isomer: t_R = 26.16 min.

(*S*,*R*)-1-Benzyl 2-methyl 5-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-

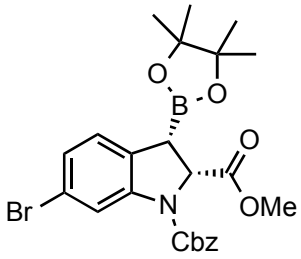
1,2-dicarboxylate [(*S,R*)-3e].



(*S*,*R*)-**3e**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.24 and 1.28 (a pair of s, 12H), 3.33 (d, *J* = 11.5 Hz, 1H), 3.53 and 3.71 (a pair of s, 3H), 3.74 and 3.76 (a pair of s, 3H), 5.05–5.45 (m, 3H), 6.62 and 6.72 (a pair of d, *J* = 7.9 Hz and 8.6 Hz, 1H), 6.74–6.78 (m, 1H), 7.28–7.47 (m, 1H), 7.79 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.6 (CH_3), 24.8 (CH_3), 29.0 (br, B *C*H), 51.9 and 52.1 (a pair of s, CH_3), 55.4 (CH_3), 62.9 and 63.1 (a pair of s, *C*H), 66.9 and 67.8 (a pair of s, CH_2), 84.2 (*C*), 111.0 and 111.1 (a pair of s, *C*H), 111.4 and 111.5 (a pair of s, *C*H), 114.8 and 115.1 (a pair of s, *C*H), 127.8 (*C*H), 128.0 (*C*H), 128.4 and 128.5 (a pair of s, *C*H), 132.1 and 132.9 (a pair of s, *C*), 134.4 and 135.6 (a pair of s, *C*), 135.9 and 136.0 (a pair of s, *C*), 151.9 and 153.2 (a pair of s, *C*), 155.7 and 155.8 (a pair of s, *C*), 171.4 and 171.5 (a pair of s, *C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{25}H_{30}O_7N^{10}BNa$, 489.20439; found, 489.20475. $[\alpha]_D^{24.8}$ +30.04 (*c* 1.3 in $CHCl_3$, 97% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, (*S,R*)-isomer: t_R = 24.09 min., (*R,S*)-isomer: t_R = 21.41 min.

(*S,R*)-1-Benzyl 2-methyl 6-bromo-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1,2-dicarboxylate [(*S,R*)-3f].

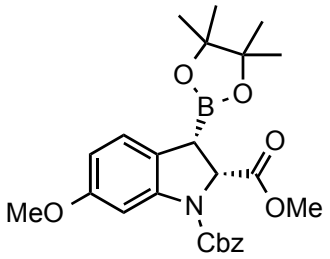


(*S*,*R*)-**3f**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.24 and 1.26 (a pair of s, 12H), 3.26 (d, *J* = 11.5 Hz, 1H), 3.52 and 3.70 (a pair of s, 3H), 5.05–5.42 (m, 3H), 6.97–7.13 (m, 2H), 7.24–7.48 (m, 5H), 8.08 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.6 (CH_3),

24.8 and 24.9 (a pair of s, CH_3), 29.0 (br, B CH), 52.0 (CH_3), 63.1 and 63.2 (a pair of s, CH), 67.4 and 68.2 (a pair of s, CH_2), 83.4 and 84.3 (a pair of s, C), 117.7 (CH), 120.8 (C), 125.3 (CH), 125.8 (CH), 128.0 (CH), 128.2 (CH), 128.5 (CH), 129.8 (C), 135.7 (C), 143.3 (C), 151.9 (C), 171.1 (C). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{24}H_{27}O_6N^{10}BBrNa$, 537.10433; found, 537.10492. $[\alpha]_D^{24.9}$ +37.06 (*c* 1.2 in $CHCl_3$, 86% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 3/97, 0.5 mL/min, 40 °C, (*S,R*)-isomer: t_R = 24.16 min., (*R,S*)-isomer: t_R = 22.73 min.

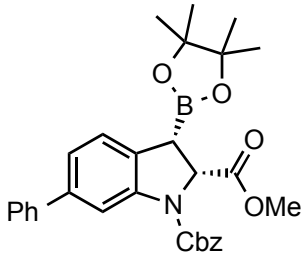
(*S,R*)-1-Benzyl 2-methyl 6-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1,2-dicarboxylate [(*S,R*)-3g].



(*S,R*)-**3g**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.26 (s, 12H), 3.28 (d, *J* = 11.1 Hz, 1H), 3.53 and 3.62 (a pair of s, 3H), 3.71 and 3.80 (a pair of s, 3H), 5.05–5.40 (m, 3H), 6.43–6.58 (m, 1H), 7.01 (dd, *J* = 1.1, 8.3 Hz, 1H), 7.05–7.49 (m, 5H), 7.58 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.6 (CH_3), 24.8 (CH_3), 29.0 (br, B CH), 51.9 (CH_3), 55.1 and 55.4 (a pair of s, CH_3), 63.5 (CH), 67.0 and 68.1 (a pair of s, CH_2), 84.1 (C), 100.8 and 101.6 (a pair of s, CH), 108.4 and 109.2 (a pair of s, CH), 122.4 (C), 124.2 and 124.6 (a pair of s, CH), 127.8 (CH), 128.06 and 128.15 (a pair of s, CH), 128.4 (CH), 135.8 (C), 143.1 (C), 152.0 (C), 159.3 and 159.4 (a pair of s, C), 171.4 and 171.5 (a pair of s, C). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{25}H_{30}O_7N^{10}BNa$, 489.20439; found, 489.20487. $[\alpha]_D^{25.1}$ +52.91 (*c* 1.0 in $CHCl_3$, 93% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, (*S,R*)-isomer: t_R = 24.16 min., (*R,S*)-isomer: t_R = 21.69 min.

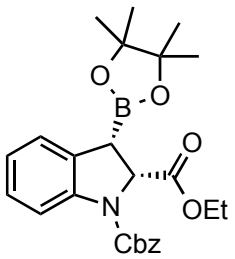
(*S,R*)-1-Benzyl 2-ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1,2-dicarboxylate [(*S,R*)-3h].



(*S,R*)-**3h**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.29 (s, 12H), 3.39 (d, *J* = 11.7 Hz, 1H), 3.54 and 3.73 (a pair of s, 3H), 5.14–5.38 (m, 3H), 7.20 (s, 2H), 7.28–7.50 (m, 9H), 7.61 (d, *J* = 7.7 Hz, 1H), 8.18 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.7 (CH_3), 24.9 (CH_3), 29.0 (br, B *C*H), 52.0 and 52.1 (a pair of s, *C*H), 63.1 (CH_3), 67.1 and 68.3 (a pair of s, *C*H), 84.2 (*C*), 113.5 and 113.9 (a pair of s, *C*H), 121.8 and 122.1 (a pair of s, *C*H), 124.2 and 124.6 (a pair of s, *C*H) 126.9 and 127.0 (a pair of s, *C*H), 127.2 (*C*H), 127.9 (*C*H), 128.1 (*C*H), 128.3 (*C*H), 128.5 (*C*H), 129.9 (*C*), 135.9 (*C*), 140.7 (*C*), 141.2 (*C*), 142.6 (*C*), 152.1 (*C*), 171.5 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{30}H_{32}O_6N^{10}BNa$, 535.22512; found, 535.22522. $[\alpha]_D^{25.1}$ +26.92 (*c* 1.3 in $CHCl_3$, 88% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, (*S,R*)-isomer: t_R = 28.32 min., (*R,S*)-isomer: t_R = 23.75 min.

(*S,R*)-1-Benzyl 2-ethyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1,2-dicarboxylate [(*S,R*)-3i].

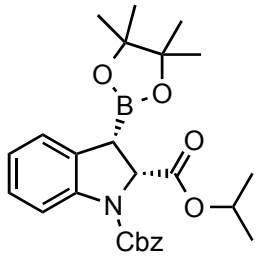


(*S,R*)-**3i**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.07 (t, *J* = 7.3 Hz, 3H), 1.27 (s, 12H), 3.34 (d, *J* = 11.7 Hz, 1H), 3.95–4.30 (m, 2H), 5.09–5.38 (m, 3H), 6.96 (t, *J* = 7.5 Hz, 1H), 7.13–7.22 (m, 2H), 7.26–7.52 (m, 5H), 7.89 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 13.8 (CH_3), 24.6 (CH_3), 24.8 (CH_3), 29.0 (br, B *C*H), 61.1

(CH_2), 62.8 and 63.0 (a pair of s, *C*H), 67.1 and 67.8 (a pair of s, CH_2), 84.1 (*C*), 114.5 and 114.7 (a pair of s, *C*H), 122.9 (*C*H), 124.1 and 124.5 (a pair of s, *C*H), 127.2 (*C*H), 127.9 (*C*H), 128.1 (*C*H), 128.4 (*C*H), 130.7 (*C*), 135.9 (*C*), 142.0 (*C*), 152.1 (*C*), 171.1 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{25}H_{30}O_6N^{10}BNa$, 473.20947; found, 473.20937. $[\alpha]_D^{24.6}$ +25.45 (*c* 1.0 in $CHCl_3$, 95% ee). Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, (*S*,*R*)-isomer: t_R = 32.84 min., (*R*,*S*)-isomer: t_R = 18.16 min.

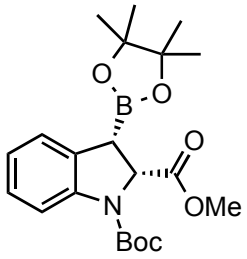
(*S*,*R*)-1-Benzyl 2-isopropyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1,2-dicarboxylate [(*S*,*R*)-3j].



(*S*,*R*)-**3j**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.03 (d, *J* = 6.2 Hz, 3H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.28 (s, 12H), 3.31 (d, *J* = 11.3 Hz, 1H), 4.87 (septet, *J* = 6.3 Hz, 1H), 5.10 (d, *J* = 5.7 Hz, 1H), 5.18 (d, *J* = 12.8 Hz, 1H), 5.26 (d, *J* = 12.5 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 7.08–7.20 (m, 2H), 7.28–7.51 (m, 5H), 7.88 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 21.4 (CH_3), 21.5 (CH_3), 24.6 (CH_3), 24.9 (CH_3), 29.5 (br, B *C*H), 63.1 (*C*H), 67.1 (CH_2), 69.1 (*C*H), 84.1 (*C*), 114.5 (*C*H), 122.9 (*C*H), 124.3 (*C*H), 127.1 (*C*H), 127.9 (*C*H), 128.1 (*C*H), 128.5 (*C*H), 131.0 (*C*), 135.9 (*C*), 142.0 (*C*), 152.2 (*C*), 170.8 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{26}H_{32}O_6N^{10}BNa$, 487.22512; found, 487.22509. $[\alpha]_D^{24.8}$ +31.90 (*c* 1.0 in $CHCl_3$, 90% ee). The ee value was determined by HPLC analysis of the corresponding silyl ether after oxidation, followed by standard silyl protection with TBSCl of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 2/98, 0.5 mL/min, 40 °C, (*S*,*R*)-isomer: t_R = 12.27 min., (*R*,*S*)-isomer: t_R = 25.08 min.

(*S,R*)-1-Benzyl 2-methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indoline-1,2-dicarboxylate [(*S,R*)-3k].



(*S,R*)-**3k**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.27 and 1.28 (a pair of s, 12H), 1.49 and 1.59 (a pair of s, 9H), 3.33 (d, *J* = 11.5 Hz, 1H), 3.70 and 3.74 (a pair of s, 3H), 5.02 and 5.08 (a pair of d, *J* = 11.8 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 7.13 and 7.16 (a pair of d, *J* = 7.2 Hz and 7.5 Hz, 2H), 7.39–7.91 (m, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.6 (CH_3), 24.8 (CH_3), 28.1 (CH_3), 29.0 (br, B CH), 51.8 (CH_3), 62.5 and 63.0 (a pair of s, *C*H), 81.0 and 82.1 (a pair of s, *C*), 84.1 (*C*), 114.4 (*C*H), 122.4 (*C*H), 124.0 and 124.4 (a pair of s, *C*H), 127.1 (*C*H), 130.5 (*C*), 142.3 (*C*), 151.4 (*C*), 171.8 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{30}O_6N^{10}BNa$, 425.20947; found, 425.20959. $[\alpha]_D^{18.6}$ +38.09 (*c* 2.3 in $CHCl_3$, 96% ee). The ee value was determined by HPLC analysis of the corresponding ester after oxidation, followed by standard esterification with *p*-nitrobenzoyl chloride of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 3/97, 0.5 mL/min, 40 °C, (*S,R*)-isomer: t_R = 44.43 min., (*R,S*)-isomer: t_R = 86.51 min.

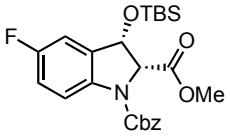
Borylation Product Functionalization Procedure

Procedure for the synthesis of chiral 1,2-aminoalcohol (*S,R*)-4 through the silyl protection following oxidation of (*S,R*)-3d.

The oxidation was performed according to the literature procedure.[24] In a reaction vial, (*S,R*)-**3d** (45.5 mg, 0.10 mmol) was dissolved in THF/H_2O (1:1, 2 mL). $NaBO_3$•$4H_2O$ (61.5 mg, 0.40 mmol) was then added at room temperature. After stirred for 2 h, the reaction mixture was extracted three times with EtOAc, dried over $MgSO_4$, and filtered. The resulting crude material was used in the next reaction without further purification.

The crude material and imidazole (20.4 mg, 0.30 mmol) was dissolved in dry CH_2Cl_2 (1 mL) under a nitrogen atmosphere. TBS chloride (22.6 mg, 0.15 mmol) was then added at room temperature. After stirred for 4 h, the reaction mixture was passed through a short silica gel column eluting with Et_2O/CH_2Cl_2 (50:50). The crude mixture was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 2:98–6:94) to afford the corresponding silyl ether (*S,R*)-**4** (29.5 mg, 0.064 mmol, 64%) as a colorless oil.

(*S,R*)-1-Benzyl 2-methyl 3-((tert-butyldimethylsilyl)oxy)-5-fluoroindoline-1,2-dicarboxylate [(*S,R*)-4].



(*S,R*)-**4**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.17 (s, 3H), 0.24 (s, 3H), 0.92 (s, 9H), 3.52 and 3.73 (a pair of s, 3H), 4.93 (d, *J* = 9.0 Hz, 1H), 5.10 and 5.31 (a pair of d, *J* = 11.8 Hz and 12.2 Hz, 2H), 5.62 (d, *J* = 9.0 Hz, 1H), 6.91 (dd, *J* = 1.8, 7.9 Hz, 1H), 7.00 (t, *J* = 8.6 Hz, 1H), 7.20–7.50 (m, 5H), 7.92 (q, *J* = 4.4 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 4.8 (CH_3), 18.0 (*C*), 25.6 (CH_3), 52.0 (CH_3), 66.6 (CH), 67.4 (CH_2), 71.7 (CH), 111.6 (*C* F, d, *J* = 25.4 Hz, CH), 115.7 (*C* F, d, *J* = 8.5 Hz, CH), 116.2 (*C* F, d, *J* = 24.4 Hz, CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 132.4 and 132.5 (a pair of s, *C*), 135.7 (*C*), 137.5 (*C*), 151.9 (*C*), 159.2 (*C* F, d, *J* = 240.5 Hz, *C*), 168.1 (*C*). HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{24}H_{30}O_5NFNaSi$, 482.17695; found, 482.17679. $[\alpha]_D^{19.2}$ +54.33 (*c* 2.8 in $CHCl_3$, 94% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 2/98, 0.5 mL/min, 40 °C, (*S,R*)-isomer: t_R = 16.44 min., (*R,S*)-isomer: t_R = 22.72 min.

Determination of the Absolute Configurations of Borylation Products

The absolute configuration of the product was determined based on X-ray crystallographic analysis of the compound (*S*,*R*)-**5**, which was derived through the oxidation of borylation product (*S*,*R*)-**3c**. The absolute configurations of other borylation products were deduced by this result. The details were summarized in Figure S2 and Table S1.

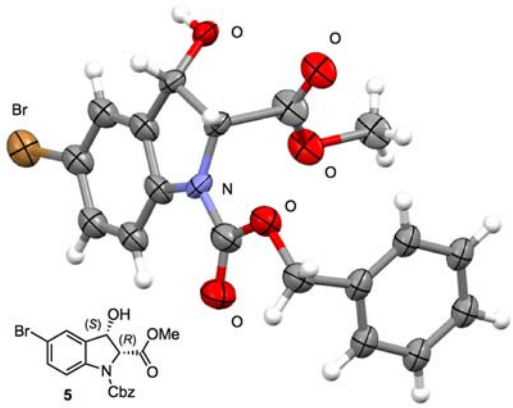
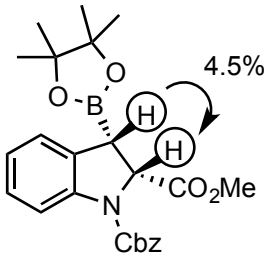


Figure S2. ORTEP structure of (*S*,*R*)-**5**. Thermal ellipsoids are drawn at the 50% probability level.

Table S1. Summary of X-ray crystallographic data for (*S,R*)-**5**.

CCDC Name	1055818
Empirical Formula	$C_{17}H_{16}BrNO_5$
Formula Weight	394.22
Crystal System	triclinic
Crystal Size / mm	0.176 × 0.097 × 0.092
a / Å	11.5617(14)
b / Å	14.7143(19)
c / Å	16.4512(18)
β / º	94.165(3)
V / Å3	2522.0(5)
Space Group	P1 (#1)
Z value	6
*D*calc / g cm^{-3}	1.557
Temperature / K	123
$2\theta_{max}$ / °	45.0
μ (MoK*α*) / cm^{-1}	24.783
No. of Reflections Measured	Total: 15030 Unique: 11291 (R_{int} = 0.0926)
No. of Observations (All reflections)	11291
Residuals: R_1 (I > 2.00σ (I))	0.0995
Residuals: wR_2 (All reflections)	0.3270
Goodness of Fit Indicator (GOF)	1.138
Maximum Peak in Final Diff. Map / $Å^3$	1.24 e-
Minimum Peak in Final Diff. Map / $Å^3$	1.70 e-

We also confirmed the relative configuration of the borylation product (*S*,*R*)-**3a** by ^{1}H NMR NOE experiment. The result was shown as below.



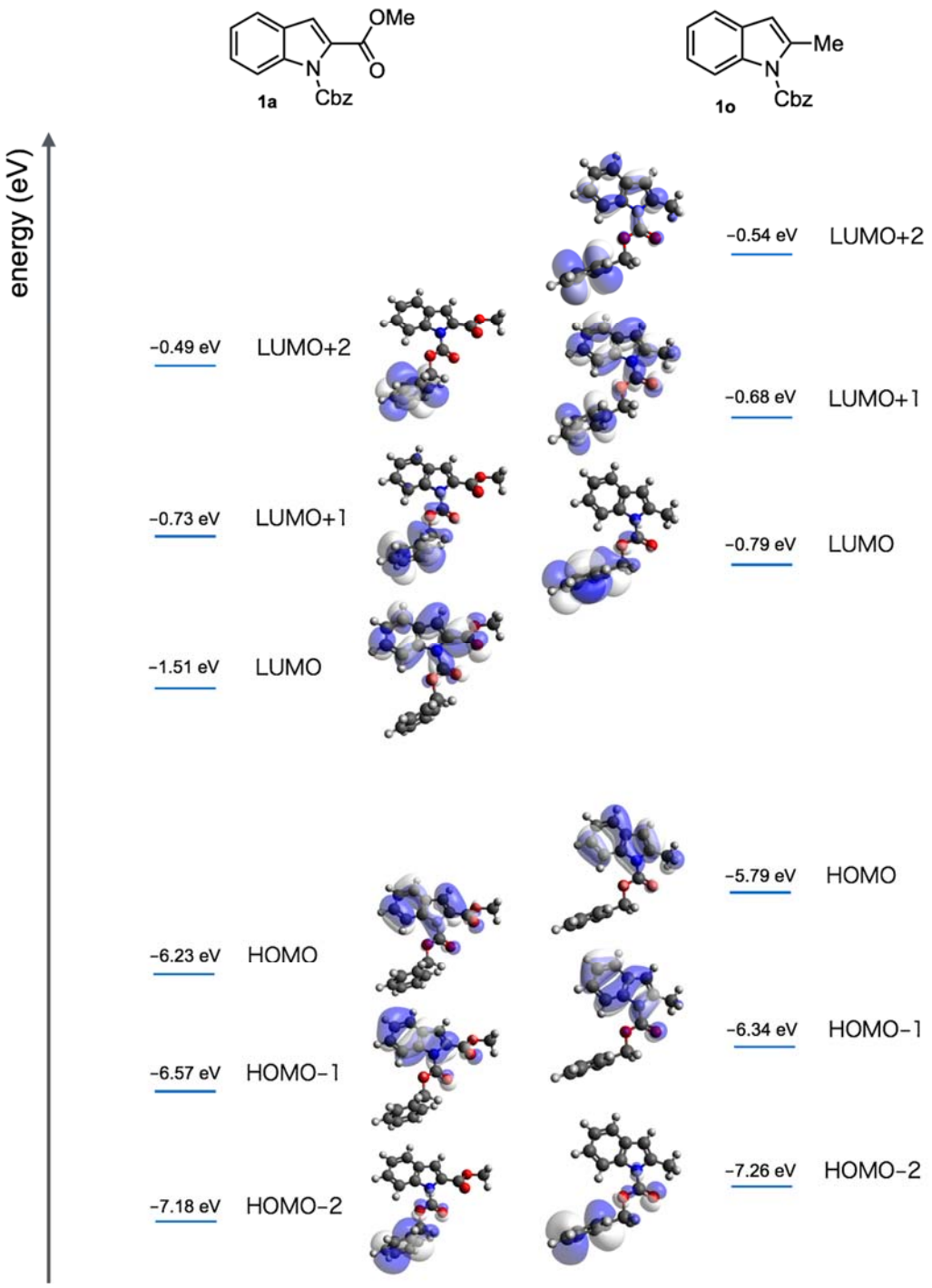
Details of DFT Calculations

All calculations were performed with the Gaussian 09W (revision C.01) program package.[25] Geometry optimizations were performed with B3PW91/cc-pVDZ in the gas-phase. The molecular orbitals were drawn by the GaussView 5.0 program. The frequency calculations were conducted on gas-phase optimized geometries to check the all the stationary points as either minima or transition states.

Theoretical investigation to prove the mechanism of the addition of borylcopper(I) intermediate to indole-2-carboxylate based on HOMO-LUMO orbital analysis (B3PW91/cc-pVDZ) was carried out. According to the mechanistic investigation reported by Marder, Lin and co-workers,[26] copper(I)-catalyzed borylation of , -unsaturated carbonyl compounds would proceed via 3,4-addition pathway because the LUMO of the substrate is mainly located in the C=C double bond, which can interact with the HOMO of borylcopper(I) intermediate. Although the current substrate is aromatic indole-2-carboxylate, we found that C2 C3 double bond makes the higher contribution than that of carbonyl moiety in the LUMO orbitals, indicating the boryl cupration of the indoles would proceed via 3,4-addition pathway in a similar manner to the borylation of α,β-unsaturated carbonyl compounds (Figure S3). Thus, the reactivity for the dearomative borylation can be discussed by comparison between LUMO of **1a** and LUMO+1 of **1o**, which are the most lowest unoccupied orbital around the reactive C2–C3 site of the indole structures. As shown in Figure S3, the LUMO level of **1a** is considerably lower than LUMO+1 of **1o**, indicating that the

electron-withdrawing ester group at the 2-position of indoles facilitate the addition reaction of borylcopper(I) active species to the indoles.

Figure S3. Orbital Analysis of **1a** and **1o**.



As shown in Figure S4, the HOMO orbitals of borylcopper(I) complex can effectively overlap with the LUMO orbitals of indole-2-carboxylate in the 3,4-addition pathway. In contrast, the orbital interaction between HOMO of borylcopper(I) and LUMO of indole-2-carboxylate in the 1,4-addition pathway would be not favorable because the phase of these orbitals are unmatched. Thus, these results also suggest that the borylation of indole-2-carboxylate would proceed via 3,4-addtion pathway.

Figure S4. Orbital Analysis of Borylcopper(I) Complex and **1a**

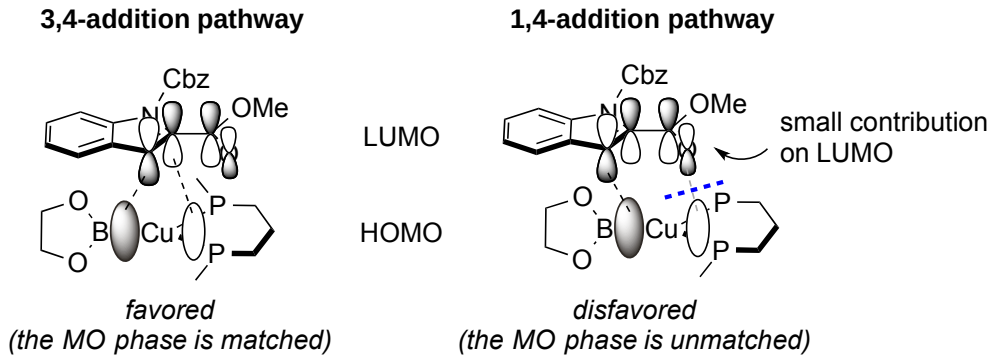
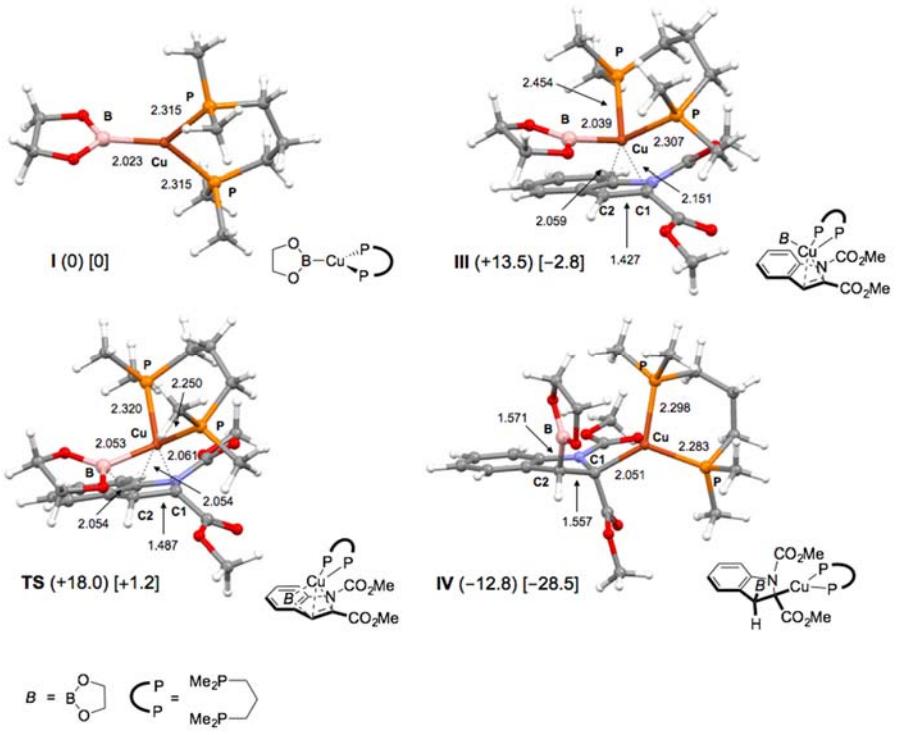


Figure S5. Optimized Structures (I, III, TS, IV) with Structural Parameters and Free (in parentheses) and Electronic (in bracket) Energies in Figure 3b.



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15. Diastereomeric ratio values of the products were determined by ^{1}H NMR analysis of the crude reaction mixture. The minor diastereomer could be completely separated by silica gel column chromatography. The ee values were determined by HPLC analysis of the isolated products. The configuration of the borylation product was determined by NOE analysis of (*S*,*R*)-**3a** and X-ray crystallographic analysis of the compound (*S*,*R*)-**5**,

which has been provided in Figure 2. The details have been provided in the Supporting Information.

16. A method has been developed for the organocatalytic enantioselective oxidation of indoles using a directing group, see: F. Kolundzic, M. N. Noshi, M. Tjandra, M. Movassaghi, S. Miller, *J. Am. Chem. Soc.* **2011**, *133*, 9104–9111.
17. 2-Methyl indole was selected as a substrate to avoid deprotonation at the 2-position by Na(O-*t*-Bu). We also confirmed that the borylation of non-substituted Cbz-protected indole resulted in no reaction.
18. The details of the DFT calculation have been provided in the Supporting Information.
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Chapter 7.

Copper(I)-Catalyzed Regio- and Enantioselective Borylation of 1,2-Dihydropyridines

Abstract

The author reports a novel approach to chiral 3-borylpiperidines via the copper(I)-catalyzed unprecedented regio- , diastereo- and enantioselective protoborylation of 1,2-dihydropyridines derived from partial reduction of pyridine derivatives. This dearomatization/enantioselective borylation sequence of cheap and readily available aromatic compound pyridines provides simple, mild and rapid access to a variety of chiral piperidines in combination with the stereospecific transformation of a stereogenic C–B bond. Theoretical study of the reaction mechanism has also been described.

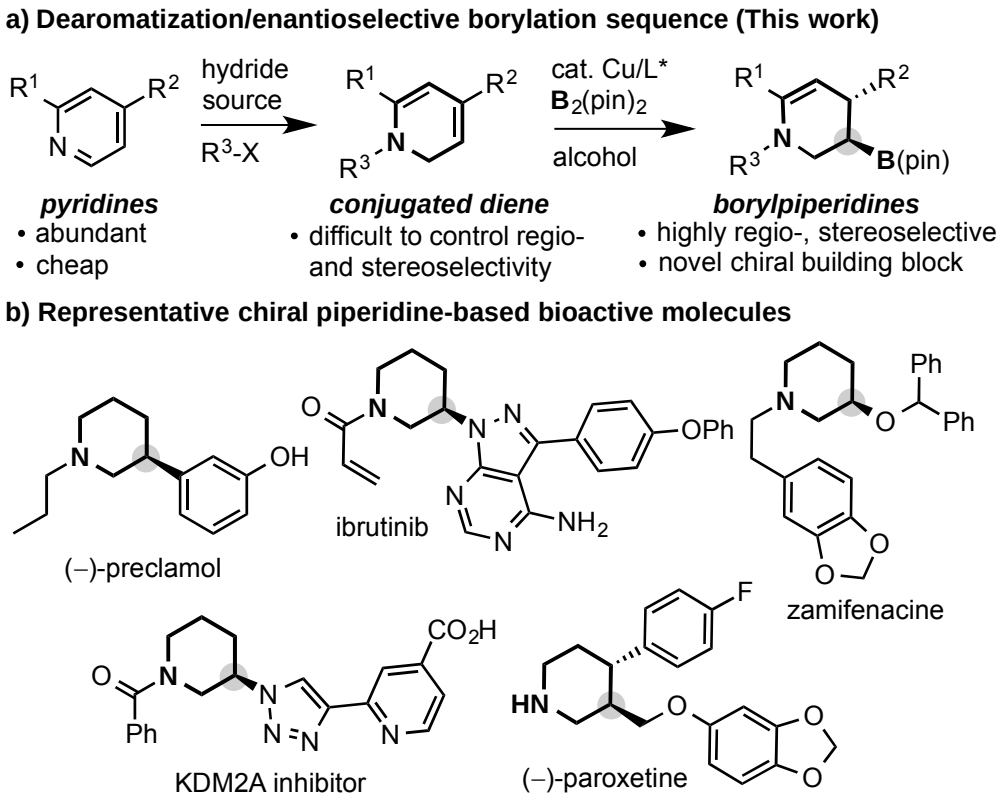
Introduction

Chiral piperidines are very important components in a wide variety of naturally occurring bioactive molecules and pharmaceutical drugs.[1] Despite significant progress in synthetic approaches toward these type of molecules, the development of a simple, mild, and direct method for their preparation is still in great demand. Considering the abundance of readily available aromatic compounds, enantioselective dearomatization reaction of pyridine derivatives is the most efficient and powerful transformation as they can be used to provide a direct route to a variety of saturated chiral nitrogen containing six membered ring systems.[2,3] Over the last decades, several strategies involving nucleophilic addition to a pyridinium salt or stepwise reduction/enantioselective catalysis for the dearomatization of pyridines have been developed.[3,4]

Recently, Ito group reported the first C–B bond forming enantioselective dearomatization of *N*-heteroaromatic compounds, indoles, in the presence of copper(I) catalysis to give the chiral 3-boryl-indolines with excellent regio-, diastereo- and enantioselectivity.[5-7] This type of transformation has great potential in synthetic and medicinal applications because chiral *N*-heterocyclic organoborons are amenable to various stereospecific functionalization of a stereogenic C–B bond.[8,9] Accordingly, his attention was then attracted to the enantioselective preparation of chiral boryl-piperidines through dearomatization of pyridines, which can be employed as a novel nucleophile for the synthesis of piperidine-based

bioactive compounds.[9] Initial effort has been focused on the development of a direct C–B bond forming dearomatization of *N*-acyl pyridinium salts using copper(I) catalysis. Although the 1,2-borylation proceeded, the author failed to isolate the product due to its significant instability toward the purification. Thus, the author turned his attention to the development of an alternative stepwise strategy that combines Fowler's dearomative reduction of pyridines[10] and subsequent copper(I)-catalyzed enantioselective borylation of resulting unstable 1,2-dihydropyridines.[4] However, this novel method has significant difficulty in the control of regioselectivity as well as diastereo- and enantioselectivity for nitrogen containing conjugated diene substrates, which has been no reports on selective borylation reaction of such type of compounds in the literature.[11] Herein the author reports an enantioselective synthesis of chiral 3-boryl-tetrahydropyridines via the chiral diphosphine/copper(I)-catalyzed unprecedented regio-, diastereo- and enantioselective protoborylation of 1,2-dihydropyridines derived from dearomative reduction of readily available pyridine derivatives (Scheme 1a). This stepwise reduction/borylation strategy would have great utility in medicinal chemistry and drug discovery because further derivatization using the boryl group as well as the remaining enamine moiety easily leads to chiral piperidines bearing a C 3 stereocenter that are important components in various pharmaceutical drugs (Scheme 1b).[1]

Scheme 1. (a) Dearomatization/Enantioselective Borylation Stepwise Strategy. (b) Representative Chiral piperidine-based Bioactive Compounds.

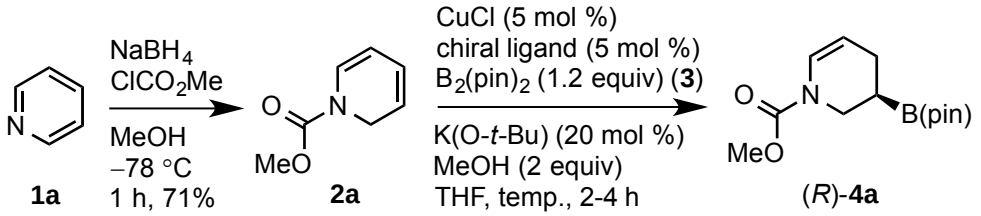


Results and Discussion

The results of an extensive series of optimization experiments revealed that the reaction of methoxycarbonyl-protected 1,2-dihydropyridines **2a**, which was prepared through the Fowler's $NaBH_4$ reduction of pyridine (**1a**), with bis(pinacolato)diboron (**3**) (1.2 equiv) in the presence of CuCl/(*R*,*R*)-QuinoxP* (5 mol %), K(O-*t*-Bu) (20 mol %) and MeOH (2.0 equiv) in THF at 10 °C afforded the desired chiral 3-borylpiperidine (*R*)-**4a** in high yield (93%) with excellent enantioselectivity (99% ee) (Table 1, entry 1). In this reaction conditions, other regioisomers were not detected by ^{1}H NMR analysis of the crude reaction mixture. The use of (*R*,*R*)-BenzP* and (*R*,*R*)-Me-Duphos also provided high enantioselectivities (Table 1, entries 2 and 3, 98% ee and 93% ee, respectively). No product was observed when triarylphosphine type ligand such as (*R*)-BINAP and (*R*)-SEGPHOS ligand were used for the

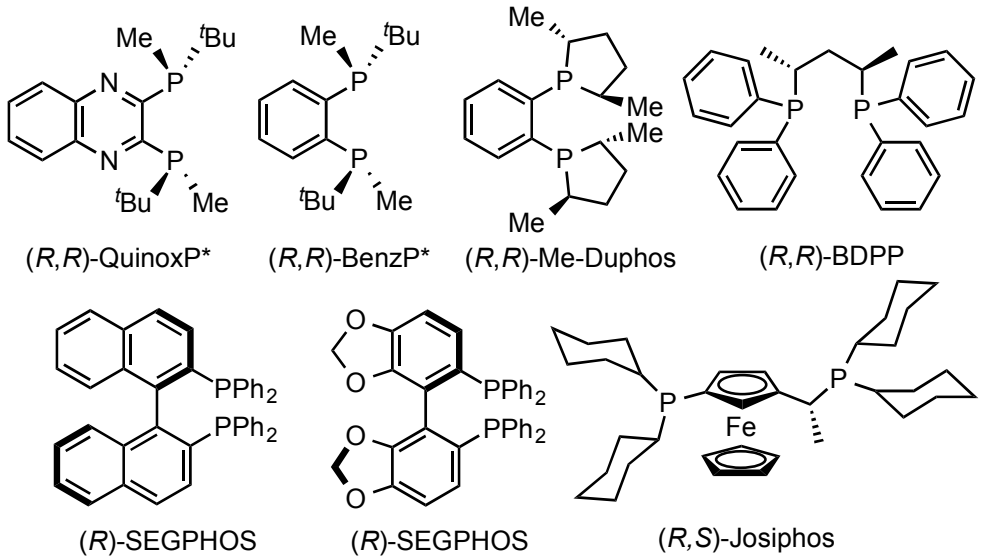
reaction (Table 1, entries 4 and 5). Other chiral ligands including (*R*,*R*)-BDPP and (*R*,*S*)-Josiphos also provided the borylation product, but the enantioselectivities were poor (Table 1, entried 6 and 7, 55% ee and 73% ee, respectively). The nature of the proton source was also important to the reactivity and enantioselectivity observed during the transformation (Table 1, entries 8 and 9). The use of sterically hindered *i*-PrOH instead of MeOH resulted in a low enantioselectivity (Table 1, entry 8, 79% ee). Furthermore, the reaction using PhOH provided a low yield and enantioselectivity (Table 1, entry 9, 40%, 55% ee). Increasing the reaction temperature slightly decreased the enantioselectivity (Table 1, entry 10, 93% ee). Notably, the reaction on 5.0 mmol scale proceeded to give the product at gram scale with excellent enantioselectivity (Table 1, entry 11, 99% ee). This enantioselective borylation also proceeded with 1 mol % copper(I) catalyst and showed high enantioselectivity (99% ee), while longer reaction time was required for the completion of the reaction (Table 1, entry 12).

Table 1. Reaction Optimiazation Study



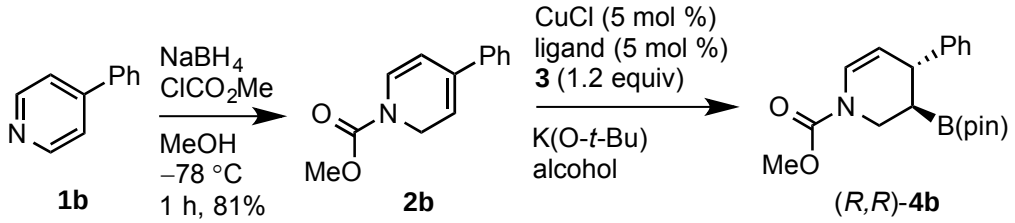
entry	chiral ligand	alcohol	temp. (°C)	NMR yield (%)	ee (%)[b]
1	(*R,R*)-QuinoxP*	MeOH	–10	93	99
2	(*R,R*)-BenzP*	MeOH	–10	92	98
3	(*R,R*)-Me-Duphos	MeOH	–10	82	93
4	(*R*)-BINAP	MeOH	–10	<5	–
5	(*R*)-SEGPHOS	MeOH	–10	<5	–
6	(*R,R*)-BDPP	MeOH	–10	97	55
7	(*R,S*)-Josiphos	MeOH	–10	20	73
8	(*R,R*)-QuinoxP*	*t*-BuOH	–10	92	79
9	(*R,R*)-QuinoxP*	PhOH	–10	40	55
10	(*R,R*)-QuinoxP*	MeOH	30	92	93
11[c]	(*R,R*)-QuinoxP*	MeOH	–10	96	99
12[d,e]	(*R,R*)-QuinoxP*	MeOH	–10	91	99

[a]Conditions: CuCl (0.025 mmol), ligand (0.025 mmol), **2a** (0.5 mmol), bis(pinacolato)diboron (**2**) (0.6 mmol) and K(O-*t*-Bu) (0.1 mmol) in THF (1.0 mL). [b]The ee values for **3a** were determined by HPLC analysis. [c]The reaction was cariied out at 5.0 mmol scale. [d]The reaction was carried out with 1 mol % copper(I) catalyst and the reaction time was 16 h.



Next, the author proceeded to investigate the diastereo- and enantioselective borylation process using 4-phenylpyridine (**2b**) as a substrate (Scheme 2). The 1,2-dihydropyridine **2b** was successfully obtained in good yield (81%) through the dearomative reduction of **1b**. Unfortunately, however, the subsequent enantioselective borylation of **2b** under the optimized reaction conditions proceeded with a significantly low enantioselectivity (39% ee) even though the regio- and diastereoselectivities were excellent (d.r. 99:1). Thus, the reaction optimization using **2b** as a substrate was carried out again (See SI). As a result, it was found that the use of (*R*)-SEGPHOS chiral ligand and *t*-BuOH in toluene/DME/THF co-solvent system gave the desired chiral 3-borylpiperidine bearing consecutive stereogenic centers (*R,R*)-**4b** in good yield (94%) with high diastereo- and enantioselectivities (d.r. 97:3, 93% ee).[12,13] The *anti* configuration of (*R,R*)-**4b** was confirmed by NOE analysis.

Scheme 2. Regio- and Diastereo- and Enantioselective Borylation of 4-Phenyl-1,2-Dihydropyridine (**2b**)

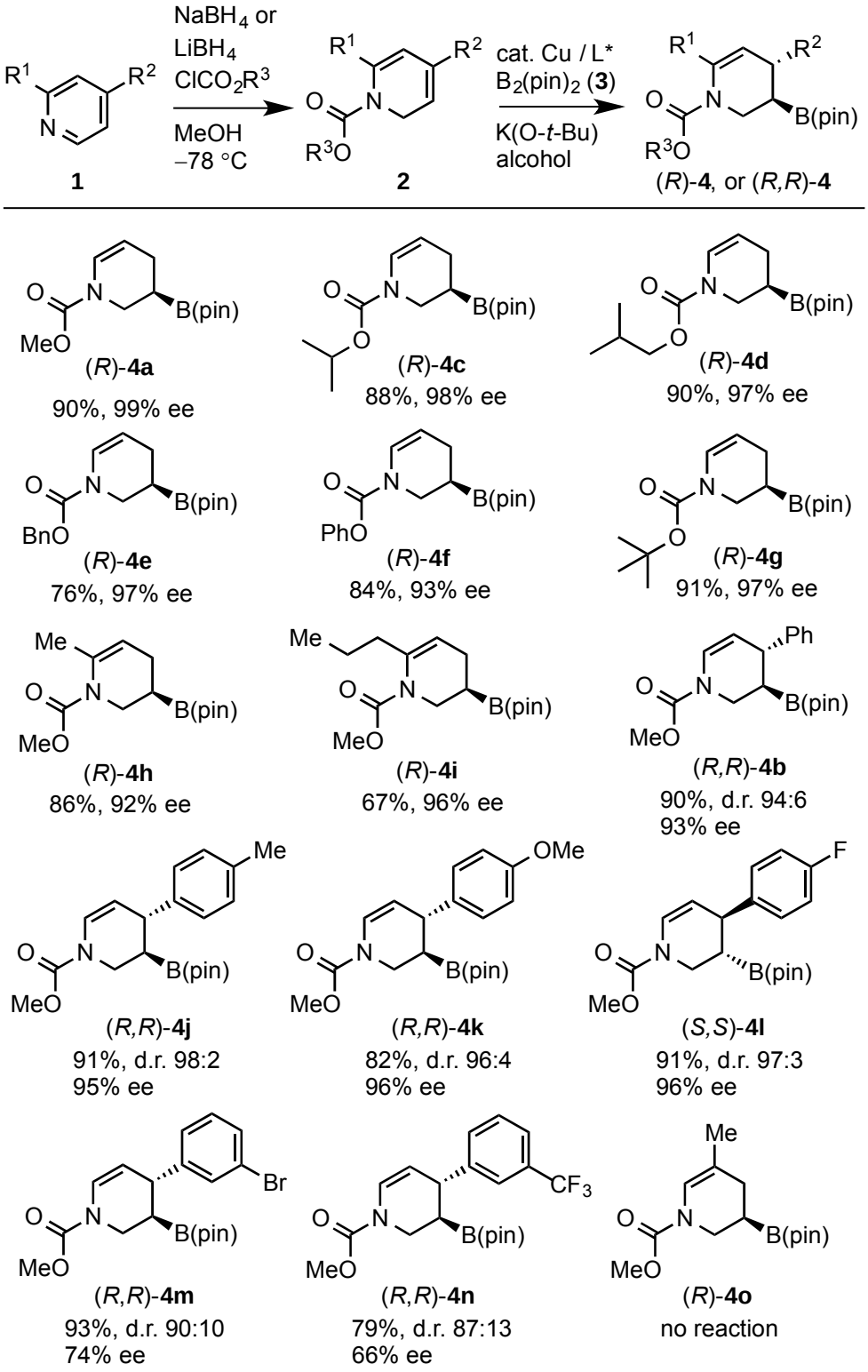


(*R,R*)-QuinoxP*, MeOH, THF, 0 °C: 91%, d.r. 99:1, 39% ee
(*R*)-SEGPHOS, *t*-BuOH, toluene/DME/THF, 0 °C: 94%, d.r. 97:3, 93% ee

With an optimized procedure in hand, the author proceeded to investigate the scope of the reaction using a variety of pyridine substrates (Table 2). The reaction of 1,2-dihydropyridines bearing various carbamate type protecting groups (**2a**, **2c**-**2g**) in the presence of copper(I)/(*R,R*)-QuinoxP* catalyst proceeded well to give the desired products [(*R*)-**4a**, (*R*)-**4c** **g**] in good yields with high enantioselectivities (Table 2, 76 93 ee). The 5-substituted 1,2-dipydropyridines (**2h** and **2i**) were also borylated to afford the chiral 3-borylpiperidines [(*R*)-**4h** and (*R*)-**4i**] with excellent enantioselectivities without other undesirable regioisomers (Table 2, 86%, 92% ee and 67%, 96% ee, respectively). The copper(I)/(*R*)-SEGPHOS complex catalyzed enantioselective borylation of

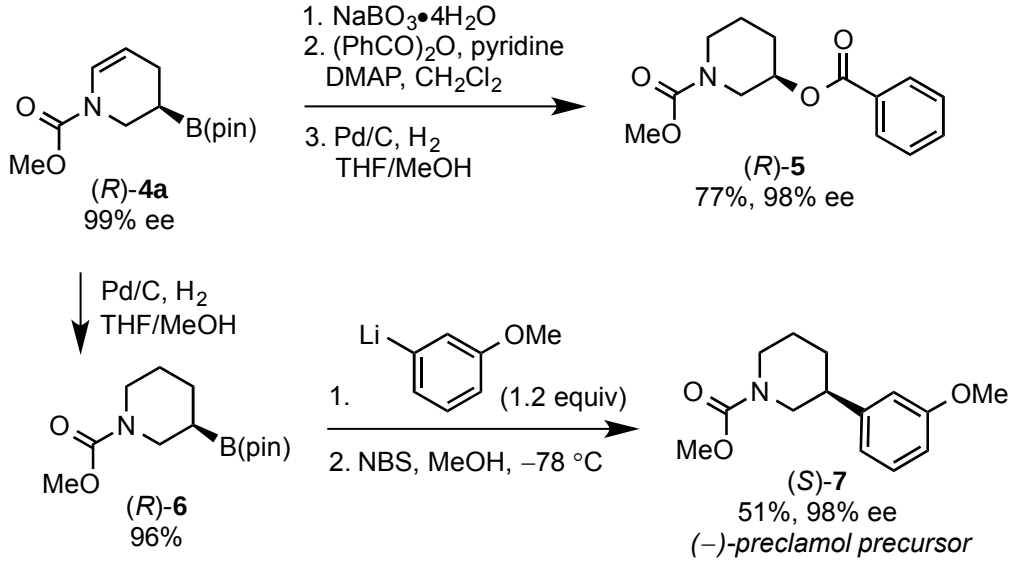
various 4-aryl 1,2-dihydropyridines (**2b**, **2j** **2l**) provided the corresponding products bearing consecutive stereogenic centers with high diastereo- and enantioselectivities (d.r. 94:6 98:2, 93 ee). However, the reactions of 4-(3-bromophenyl) 1,2-dihydropyridine (**2m**) and 4-(3-trifluoromethylphenyl) 1,2-dihydropyridine (**2n**) in the presence of copper(I)/(*R*)-SEGPHOS catalyst resulted in low yields (<10%). Fortunately, the author found that the use of (*R*,*R*)-BDPP allowed to synthesize the corresponding products [(*R*,*R*)-**4m** and (*R*,*R*)-**4n**], but the enantioselectivities were moderate (74% ee and 66% ee, respectively). The present catalytic system could not be applied to the 3-subsstituted 1,2-dihydropyridines **2o**.

Table 2. Substrate Scope



Enantioenriched chiral 3-boryl-tetrahydropyridines could potentially be used as building blocks through the stereospecific functionalization of a stereogenic C–B bond. For examples, the obtained borylation product (*R*)-**4a** was subjected to $NaBO_3$ oxidation, followed by the acylation and reduction of an enamine moiety to afford the chiral piperidinol (*R*)-**5** with high enantiomeric excess (Scheme 3). Furthermore, the Aggarwal's cross-coupling[14] of (*R*)-**6**, which was prepared by reduction of (*R*)-**4a**, with (3-methoxyphenyl)lithium afforded the (–)-preclamol precursor (*S*)-**7** with excellent stereospecificity (Scheme 3).

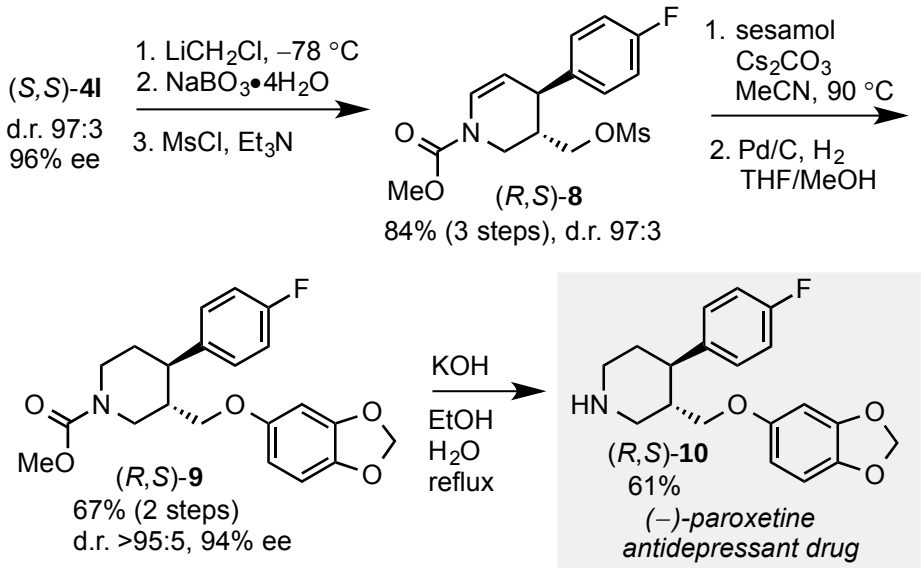
Scheme 3. Stereospecific Functionalization of Borylation Product (*R*)-**4a**



To demonstrate the practical usefulness of this methodology in the selective synthesis of natural products and pharmaceutical drugs, the author applied the obtained product (*S*,*S*)-**4l** to the preparation of antidepressant drug (–)-proxetine (*R*,*S*)-**10** (Scheme 4).[8c,15] The boryl group in the product (*R*,*R*)-**4r** was functionalized through the one carbon homologation[16] and subsequent oxidation, mesyl protection to lead the corresponding mesylate (*R*,*S*)-**8**, which was then subjected to the Williamson esterification, hydrogenation of an alkene moiety with Pd/C to form (*R*,*S*)-**9** with high enantiomeric purity (94% ee). Finally, the deprotection of a methyl carbamate moiety with KOH provided (–)-paroxetine (*R*,*S*)-**10**. Spectroscopic and optical rotation data matched literature values. The author envisions that

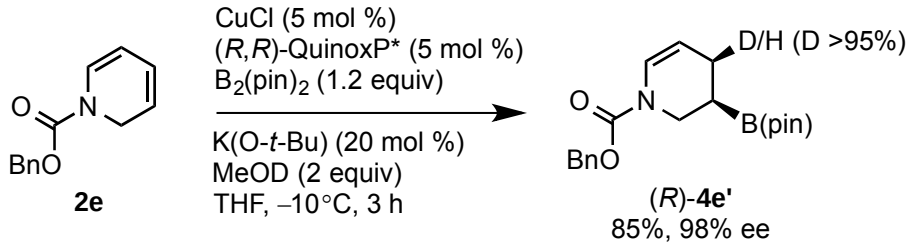
these type of novel chiral boronates will find further application for efficient preparation of piperidine-based bioactive molecules.

Scheme 4. Synthesis of (–)-Paroxetine



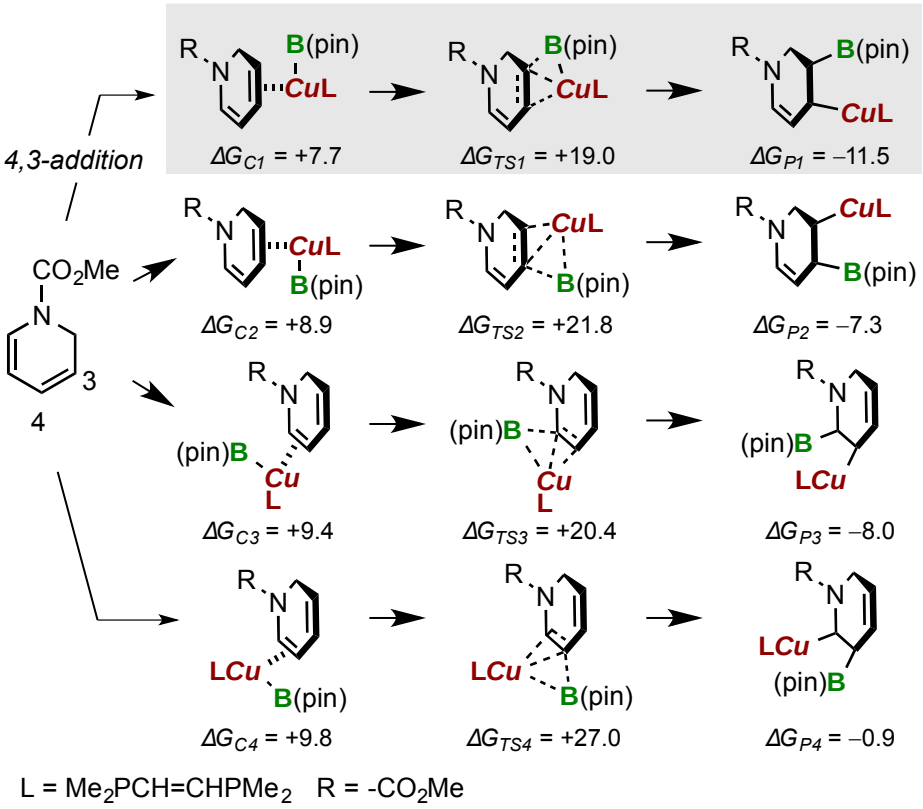
To prove the reaction mechanism, the author conducted a deuterium labeling experiment (Scheme 5). The borylation of **2e** using MeOD instead of MeOH under optimized conditions gave the 4-position labeled product ((*R*)-**4e′**, D >95%) with high enantioselectivity (98% ee). The *syn* configuration between a boryl group and deuterium atom was confirmed by NOE analysis. These results suggest that the current borylation proceeds through the regio- and enantioselective *syn*-4,3-addition of a borylcopper(I) active species to 1,2-dihydropyridines, followed by stereoretentive S_E2 protonation of the allylcopper(I) intermediate by an alcohol additive.[17]

Scheme 5. Deuterium Labeling Experiment



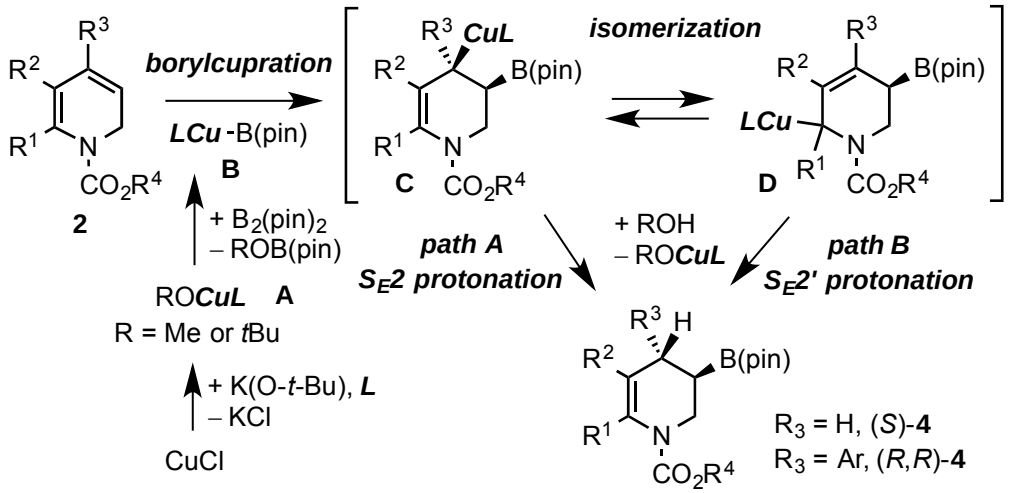
Density functional theory (DFT) calculations (B3PW91/cc-pVDZ) were performed to prove the origin of an unprecedented regioselectivity of current borylation of 1,2-hydropyridines (Figure 2). In this reaction, four different borylcupration pathways can be considered (path A D, Figure 2). Thus, the author calculated all borylation pathways using achiral borylcopper(I)/$Me_2PCH{=}CHPMe_2$ model complex with **2a** as a substrate. The results showed that the activation energies for path A (ΔG_{TS1}) and path C (ΔG_{TS3}) leading to the stable allylcopper(I) intermediates are relatively lower than those of path B and D. As for the path C, the steric congestion between a B(pin) group and a carbamate moiety would cause a destabilization during the borylcupration process.[18] Therefore, the current borylation selectively proceeds through the 4,3-borylcupration to form the intermediate P1.

Figure 2. Density Functional Theory Calculation of Four Regioisomeric Pathways (B3PW91/cc-pVDZ)



A reaction mechanism for the current copper(I)-catalyzed enantioselective borylation of 1,2-dihydropyridines is proposed based on the DFT calculations and deuterium labeling experiment as shown in Figure 3. The reaction of CuCl with the ligand and K(O-*t*-Bu) would result in the formation of copper(I) alkoxide **A**, which would initially react with diboron **3** to afford the boryl copper(I) intermediate B. The subsequent addition of **B** into **2** would give the allylcopper(I) intermediate **C** with concomitant formation of a stereogenic C–B bond at 3-position. The S_E2-type protonation of **C** by alcohol would produce the corresponding borylation product (path A). The *syn*-stereoselectivity observed in the borylation of 4-aryl-1,2-dihydropyridine was in good agreement with this reaction mechanism. However, another possible pathway, which would be involved the isomerization of **C** leading to **D** and subsequent S_E2'-type protonation of **D** (path B), cannot be completely excluded at this stage.

Figure 3. Proposed Reaction Pathway



Conclusion

In summary, the author has developed the novel dearomatization/enantioselective protoborylation sequence of pyridines to afford the chiral 3-borylpiperidine derivatives with excellent regio-, diastereo- and enantioselectivity. This methodology provides a simple and direct way of synthesizing optically active piperidines bearing a

C3-stereocenter, which are privileged components in a wide variety of bioactive molecules, in combination with the stereospecific functionalization of a stereogenic C–B bond. Further investigation of stereospecific transformations including Suzuki-Miyaura coupling reaction of this novel 3-borylpiperidines for the synthesis of natural products and pharmaceutical drugs is now ongoing.

Experimental

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 4Å). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^{1}H: 400 MHz and ^{13}C: 100 MHz). Tetramethylsilane (^{1}H) and $CDCl_3$ (^{13}C) were employed as external standards, respectively. CuCl (ReagentPlus® grade, 224332-25G, ≥99%) was purchased from Sigma-Aldrich Co. and used as received. 2-Phenylethyl chloride was used as an internal standard to determine NMR yields. 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 was recorded at the Center for Instrumental Analysis, Hokkaido University.

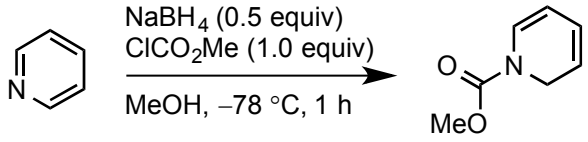
Procedure for the copper(I)-catalyzed enantioselective borylation of 1,2-dihydropyridines 2a (Table 1).

CuCl (2.5 mg, 0.025 mmol) and bis(pinacolato)diboron (151.7 mg, 0.60 mmol), (*R,R*)-QuinoxP* (8.4 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. THF (1.0 mL) and K(O-*t*-Bu)/THF (1.0 M, 0.10 mL, 0.10 mmol) were added in the vial through the rubber septum. After **2a** (69.6 mg, 0.50 mmol) was added to the mixture at 10°C, MeOH (40.5 μL, 1.0 mmol) was added dropwise. After the reaction was complete, the reaction mixture was passed through a short silica gel column eluting with Et_2O. The crude mixture was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, typically 0:100–10:90) to give the corresponding borylation product (*R*)-**4a** as a colorless oil.

Substrate Preparation

The pyridines **1a** **1h, 1i, 1m** and **1o** were purchased from commercial suppliers. The received materials from the suppliers were subjected to purification by distillation before use. The 4-arylpyridines **1j** **1** **1n** were synthesized through the standard Suzuki-Miyaura coupling reaction of 4-bromopyridine and the corresponding arylboronic acids according to the literature procedure.[18]

Preparation of methyl pyridine-1(2*H*)-carboxylate (2a).[19]



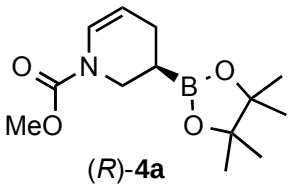
1a **2a**, 71%

Methyl chloroformate (2.3 mL, 30.0 mmol) was added dropwise under nitrogen to a solution of $NaBH_4$ (567.0 mg, 15 mmol), pyridine (**1a**) (2.4 mL, 30.0 mmol) and MeOH (100.0 mL) at –78 °C. The reaction was maintained at 78 °C for 1 h and then poured into ice-water. The product was extracted with CH_2Cl_2 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 (SiO_2, ethyl acetate/hexane, 8:92) to obtain **2a** (2.97 g, 2.1 mmol, 71%) as a clear liquid, which was immediately used in the next borylation reaction in order to prevent decomposition.

The other 1,2-dihydropyridines **2b** **2** **, 2h** **2o** were prepared from the corresponding pyridines according to the procedure described above. As for the synthesis of **2i**, $LiBH_4$ was used instead of $NaBH_4$. The Boc-protected 1,2-dihydropyridine **2g** was prepared from **2f** by the protecting group exchange reaction with K(O-*t*-Bu).

Borylation Product Characterization

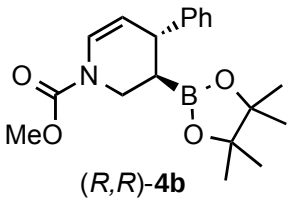
Methyl (*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*)-4a].



(*R*)-**4a**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.23 (s, 12H), 1.37–1.48 (m, 1H), 1.98–2.17 (m, 2H), 3.25 (t, *J* = 11.7 Hz, 0.5H), 3.31 (t, *J* = 11.5 Hz, 0.5H), 3.91 (d, *J* = 12.9 Hz, 0.5H), 4.04 (d, *J* = 12.0 Hz, 0.5H), 4.86–4.93 (m, 0.5H), 4.96–5.03 (m, 0.5H), 6.72 (d, *J* = 8.1 Hz, 0.5H), 6.86 (d, *J* = 8.6 Hz, 0.5H). ^{13}C NMR (99 MHz, $CDCl_3$,): 17.3 (br, B CH), 22.8 and 22.9 (a pair of s, CH_2), 24.5 (CH_3), 43.1 and 43.3 (a pair of s, CH_2), 52.5 and 52.6 (a pair of s, CH_3), 83.1 and 83.2 (a pair of s, *C*), 106.7 and 107.0 (a pair of s, *C*H), 124.6 and 125.1 (a pair of s, *C*H), 153.4 and 153.9 (a pair of s, *C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{13}H_{22}O_4N^{10}B$, 266.16782; found, 266.16720. $[\alpha]_D^{22.9}$ –51.55 (*c* 1.0 in $CHCl_3$, 99% ee). The ee value was determined by HPLC analysis of the corresponding ester after oxidation, followed by standard acylation with 4-nitrobenzoyl chloride of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 7/93, 0.5 mL/min, 40 °C, (*R*)-isomer: t_R = 33.89 min., (*S*)-isomer: t_R = 36.77 min.

Methyl (3*R*,4*R*)-4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*,*R*)-4b].

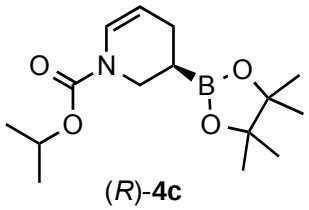


(*R*,*R*)-**4b**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.09–1.19 (m, 12H), 1.43–1.54 (m, 1H), 3.44–3.63 (m, 2H), 3.71 (dd, *J* = 3.2 Hz, 12.6 Hz, 0.5H), 3.77 and 3.78 (a pair of s, 3H), 3.90 (dd, *J* = 3.4 Hz, 12.8 Hz, 0.5H), 4.90 (dd, *J* = 2.9 Hz, 8.3 Hz, 0.5H), 5.00 (dd, *J* = 3.2 Hz, 8.5 Hz, 0.5H), 6.70 (dd, *J* = 1.8 Hz and 8.5 Hz, 0.5H), 7.05 (dd, *J* = 1.4

Hz and 8.1 Hz, 0.5H), 7.15–7.33 (m, 5H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.5 and 24.9 (a pair of s, CH_3), 27.1 (br, B CH), 39.7 and 40.2 (a pair of s, CH), 41.8 and 42.2 (a pair of s, CH_2), 52.8 and 52.9 (a pair of s, CH_3), 83.4 and 83.5 (a pair of s, C), 110.4 (CH), 124.9 and 125.6 (a pair of s, CH), 126.27 and 126.31 (a pair of s, CH), 127.8 and 127.9 (a pair of s, CH), 128.1 (CH), 144.9 and 145.1 (a pair of s, C), 153.5 and 154.0 (a pair of s, C). HRMS–EI (m/z): $[M]^+$ calcd for $C_{19}H_{26}O_4N^{10}B$, 342.19912; found, 342.19813. $[\alpha]_D^{21.9}$ –63.00 (*c* 1.5 in $CHCl_3$, 92% ee). Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, (*R*,*R*)-isomer: t_R = 9.96 min., (*S*,*S*)-isomer: t_R = 11.72 min.

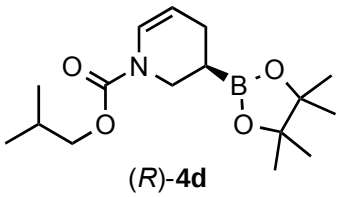
Isopropyl (*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*)-3c].



(*R*)-**4c**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.18–1.29 (m, 18H), 1.35–1.46 (m, 1H), 1.97–2.13 (m, 2H), 3.27 (dd, *J* = 11.2 Hz, 12.6 Hz, 0.6H), 3.37 (dd, *J* = 10.6 Hz, 12.4 Hz, 0.4H), 3.80 (dd, *J* = 2.9 Hz, 12.8 Hz, 0.4H), 4.00 (dd, *J* = 2.7 Hz, 13.0 Hz, 0.6H), 4.87 (quint, *J* = 3.9 Hz, 0.6H), 4.91–5.04 (m, 1.4H), 6.74 (d, *J* = 8.5 Hz, 0.6H), 6.85 (d, *J* = 8.1 Hz, 0.4H). ^{13}C NMR (99 MHz, $CDCl_3$,): 17.5 (br, B CH), 22.1 (CH_3), 23.0 and 23.1 (a pair of s, CH_2), 24.55 and 24.60 (a pair of s, CH_3), 43.0 and 43.2 (a pair of s, CH_2), 68.8 (CH), 83.2 and 83.3 (a pair of s, C), 106.2 and 106.6 (a pair of s, CH), 124.9 and 125.3 (a pair of s, CH), 152.7 and 153.2 (a pair of s, C). HRMS–EI (m/z): $[M]^+$ calcd for $C_{15}H_{26}O_4N^{10}B$, 294.19912; found, 294.19826. $[\alpha]_D^{21.7}$ –32.83 (*c* 1.5 in $CHCl_3$, 98% ee). The ee value was determined by HPLC analysis of the corresponding ester after oxidation, followed by standard acylation with 4-nitrobenzoyl chloride of the borylated product in comparison of the racemic sample.Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*R*)-isomer: t_R = 17.52 min., (*S*)-isomer: t_R = 19.44 min.

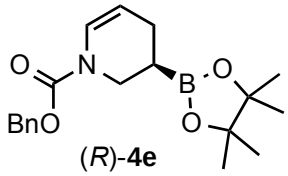
Isobutyl (*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*)-4d].



(*R*)-**4d**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.95 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.2 Hz, 3H), 1.23 (s, 12H), 1.40–1.50 (m, 1H), 1.89–2.18 (m, 3H), 3.27 (dd, *J* = 11.0 Hz, 12.4 Hz, 0.5H), 3.47 (dd, *J* = 9.6 Hz, 12.5 Hz, 0.5H), 3.77–4.08 (m, 3H), 4.89 (quint, *J* = 4.0 Hz, 0.5H), 4.98 (quint, *J* = 3.9 Hz, 0.5H), 6.77 (d, *J* = 8.6 Hz, 0.5H), 6.86 (d, *J* = 8.2 Hz, 0.5H). ^{13}C NMR (99 MHz, $CDCl_3$,): 17.3 (br, B *C*H), 18.9 (*C*H_3), 22.9 and 23.0 (a pair of s, *C*H_2), 24.5 and 24.6 (a pair of s, *C*H_3), 27.8 (*C*H), 43.1 and 43.3 (a pair of s, *C*H_2), 71.5 and 71.6 (a pair of s, *C*H_2), 83.17 and 83.22 (a pair of s, *C*), 106.5 and 106.8 (a pair of s, *C*H), 124.7 and 125.2 (a pair of s, *C*H), 153.1 and 153.6 (a pair of s, *C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{16}H_{28}O_4N^{10}B$, 308.21477; found, 308.21408. $[\alpha]_D^{22.3}$ –38.20 (*c* 1.0 in $CHCl_3$, 97% ee). The ee value was determined by HPLC analysis of the corresponding ester after oxidation, followed by standard acylation with 4-nitrobenzoyl chloride of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 7/93, 0.5 mL/min, 40 °C, (*R*)-isomer: t_R = 20.29 min., (*S*)-isomer: t_R = 22.95 min.

Benzyl (*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*)-4e].

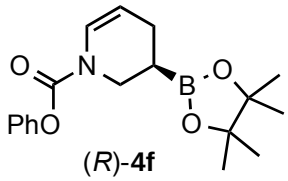


(*R*)-**4e**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.21 (s, 6H), 1.22 (s, 6H), 1.39–1.50 (m, 1H), 1.98–2.18 (m, 2H), 3.29 (dd, *J* = 11.0 Hz, 12.9 Hz, 0.5H), 3.45 (dd, *J* = 10.1 Hz, 12.4 Hz, 0.5H), 3.88 (dd, *J* = 3.1 Hz, 12.7 Hz, 0.5H), 4.05 (dd, *J* = 3.1 Hz, 12.7 Hz, 0.5H), 4.89 (quint, *J* = 3.9 Hz, 0.5H), 5.01 (quint, *J* = 3.9 Hz, 0.5H), 5.12–5.26 (m, 2H), 6.80 (d, *J* = 8.6 Hz, 0.5H), 6.90 (d, *J* = 8.6 Hz, 0.5H), 7.28–7.43 (m,

2H). ^{13}C NMR (99 MHz, $CDCl_3$,): 17.5 (br, B *C*H), 22.9 and 23.0 (a pair of s, *C*H_2), 24.5 (*C*H_3), 24.55 (*C*H_3), 24.6 (*C*H_3), 43.3 and 43.4 (a pair of s, *C*H_2), 67.0 and 67.2 (*C*H_2), 83.2 and 83.3 (a pair of s, *C*), 107.0 and 107.4 (a pair of s, *C*H), 124.7 and 125.2 (a pair of s, *C*H), 127.9 (*C*H), 128.3 (*C*H), 136.3 and 136.4 (a pair of s, *C*), 152.8 and 153.4 (a pair of s, *C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{19}H_{26}O_4N^{10}B$, 342.19912; found, 342.19898. $[\alpha]_D^{25.7}$ –71.25 (*c* 1.0 in $CHCl_3$, 97% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 1/99, 0.5 mL/min, 40 °C, (*R*)-isomer: t_R = 18.39 min., (*S*)-isomer: t_R = 19.80 min.

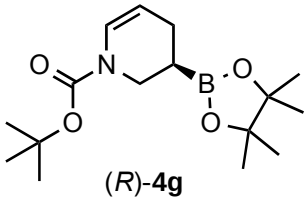
Phenyl
(*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*)-4f].



(*R*)-**4f**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.25 (s, 12H), 1.41–1.60 (m, 1H), 2.05–2.24 (m, 2H), 3.40 (dd, *J* = 10.5 Hz, 12.9 Hz, 0.5H), 3.60 (dd, *J* = 10.5 Hz, 12.9 Hz, 0.5H), 5.00–5.07 (m, 0.5H), 5.08–5.16 (m, 0.5H), 6.89 (d, *J* = 8.6 Hz, 0.5H), 6.96 (d, *J* = 8.6 Hz, 0.5H), 7.09–7.17 (m, 2H), 7.17–7.25 (m, 1H), 7.32–7.41 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$,): 17.4 (br, B *C*H), 24.56 (*C*H_3), 24.61 (*C*H_3), 24.7 (*C*H_3), 43.6 and 44.1 (a pair of s, *C*H_2), 83.3 and 83.4 (a pair of s, *C*), 108.0 and 108.5 (a pair of s, *C*H), 121.5 and 121.6 (a pair of s, *C*H), 124.7 and 125.0 (a pair of s, *C*H), 125.2 and 125.3 (a pair of s, *C*H), 129.1 (*C*H), 151.0 and 151.1 (a pair of s, *C*), 151.3 and 152.0 (a pair of s, *C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{18}H_{24}O_4N^{10}B$, 328.18347; found, 328.18273. $[\alpha]_D^{25.7}$ –71.25 (*c* 1.0 in $CHCl_3$, 93% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 7/93, 0.5 mL/min, 40 °C, (*S*)-isomer: t_R = 13.64 min., (*R*)-isomer: t_R = 15.39 min.

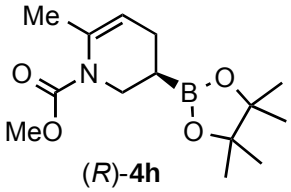
***tert*-Butyl (*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*)-4g].**



(*R*)-**4g**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.22 (s, 12H), 1.48 (s, 9H), 1.65–1.72 (m, 1H), 1.97–2.15 (m, 2H), 3.22 (t, *J* = 11.7 Hz, 0.6H), 3.36 (t, *J* = 11.2 Hz, 0.4H), 3.77 (d, *J* = 11.3 Hz, 0.4H), 4.00 (d, *J* = 11.3 Hz, 0.6H), 4.79–4.88 (m, 0.6H), 4.90–4.98 (m, 0.4H), 6.71 (d, *J* = 8.1 Hz, 0.6H), 6.84 (d, *J* = 8.1 Hz, 0.4H). ^{13}C NMR (99 MHz, $CDCl_3$,): 17.6 (br, B CH), 23.1 (CH_2), 24.6 (CH_3), 28.3 (CH_2), 42.7 and 43.6 (a pair of s, CH_2), 80.2 (*C*), 83.3 (*C*), 105.8 and 106.3 (a pair of s, *C*H), 125.2 and 125.5 (a pair of s, *C*H), 152.2 and 152.7 (a pair of s, *C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{16}H_{28}O_4N^{10}B$, 308.21477; found, 308.21406. $[\alpha]_D^{25.1}$ –52.91 (*c* 1.0 in $CHCl_3$, 97% ee). The ee value was determined by HPLC analysis of the corresponding ester after oxidation, followed by standard acylation with 4-nitrobenzoyl chloride of the borylated product in comparison of the racemic sample.Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 7/93, 0.5 mL/min, 40 °C, (*R*)-isomer: t_R = 17.33 min., (*S*)-isomer: t_R = 20.40 min.

Methyl (*R*)-6-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*)-4h].

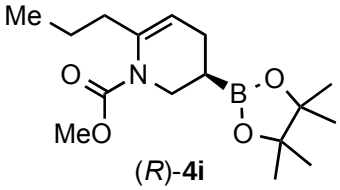


(*R*)-**4h**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.23 (s, 12H), 1.37–1.48 (m, 1H), 2.02–2.20 (m, 2H), 2.06 (s, 3H), 3.28 (dd, *J* = 9.9 Hz and 13.0 Hz, 1H), 3.91 (s, 3H), 3.98 (dd, *J* = 3.2 Hz and 12.5 Hz, 1H), 4.89–4.94 (m, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 18.8 (br, B CH), 22.1 (CH_3), 24.5 (CH_2), 24.6 (CH_3), 45.8 (CH_2), 52.3 (CH_3), 83.2 (*C*), 111.6 (*C*H), 135.1 (*C*), 154.7 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{14}H_{24}O_4N^{10}B$, 280.18347; found, 280.18248. $[\alpha]_D^{23.3}$ –64.18 (*c* 1.1 in $CHCl_3$, 92%

ee). The ee value was determined by HPLC analysis of the corresponding ester after oxidation, followed by standard acylation with 4-nitrobenzoyl chloride of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 7/93, 0.5 mL/min, 40 °C, (*R*)-isomer: t_R = 22.67 min., (*S*)-isomer: t_R = 33.55 min.

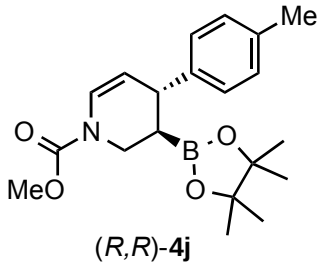
Methyl (*R*)-6-propyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*)-4i].



(*R*)-**4i**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 0.84 (t, *J* = 7.4 Hz, 3H), 1.23 (s, 12H), 1.30–1.48 (m, 3H), 2.04–2.31 (m, 3H), 2.64 (quint, *J* = 6.9 Hz, 1H), 3.19 (dd, *J* = 10.3 Hz, 12.6 Hz), 3.71 (s, 3H), 4.02 (dd, *J* = 3.1 Hz, 12.6 Hz), 5.01 (t, *J* = 3.6 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 13.5 (CH_3), 19.2 (br, B CH), 20.8 (CH_2), 24.5 (CH_2), 24.67 (CH_3), 24.70 (CH_3), 36.9 (CH_2), 46.1 (CH_2), 52.4 (CH_3), 83.3 (*C*), 112.6 (*C*H), 139.3 (*C*H), 154.7 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{16}H_{28}O_4N^{10}B$, 308.21477; found, 308.21368. $[\alpha]_D^{23.5}$ –55.22 (*c* 0.9 in $CHCl_3$, 96% ee). The ee value was determined by HPLC analysis of the corresponding ester after oxidation, followed by standard acylation with 4-nitrobenzoyl chloride of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*S*)-isomer: t_R = 21.15 min., (*R*)-isomer: t_R = 25.25 min.

Methyl (3*R*,4*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(*p*-tolyl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*,*R*)-4j].

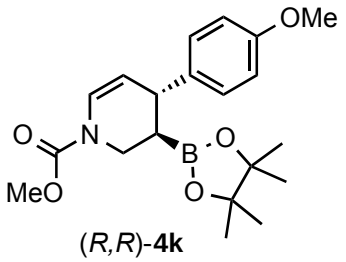


(*R*,*R*)-**4j**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.08–1.22 (m, 12H), 1.41–1.52 (m, 1H), 2.31 (s,

3H), 3.44–3.62 (m, 2H), 3.67 (dd, *J* = 3.4 Hz, 12.9 Hz, 0.5H), 3.77 and 3.78 (a pair of s, 3H), 3.86 (dd, *J* = 3.4 Hz, 12.4 Hz, 0.5H), 4.88 (dd, *J* = 2.9 Hz, 8.2 Hz, 0.5H), 5.00 (dd, *J* = 3.4 Hz, 8.1 Hz, 0.5H), 6.88 (dd, *J* = 1.4 Hz, 8.1 Hz, 0.5H), 7.03 (dd, *J* = 1.4 Hz, 8.1 Hz, 0.5H), 7.05–7.18 (m, 5H). ^{13}C NMR (99 MHz, $CDCl_3$,): 21.1 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 27.3 (br, B *C*H), 39.4 and 39.9 (a pair of s, *C*H), 41.9 and 42.3 (a pair of s, CH_2), 52.9 and 53.0 (a pair of s, CH_3), 83.58 and 83.63 (a pair of s, *C*), 110.8 (*C*H), 125.0 and 125.7 (a pair of s, *C*H), 127.9 and 128.0 (a pair of s, *C*H), 129.0 (*C*H), 135.9 (*C*), 142.1 and 142.3 (a pair of s, *C*), 153.7 and 154.2 (a pair of s, *C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{20}H_{28}O_4N^{10}B$, 356.21477; found, 356.21385. $[\alpha]_D^{25.7}$ –56.00 (*c* 1.0 in $CHCl_3$, 95% ee). Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 3/97, 0.5 mL/min, 40 °C, (*R,R*)-isomer: t_R = 11.63 min., (*S,S*)-isomer: t_R = 12.69 min.

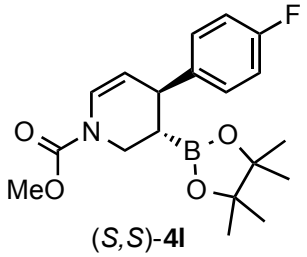
Methyl (3*R*,4*R*)-4-(4-methoxyphenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R,R*)-4k].



(*R,R*)-**4k**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.08–1.22 (m, 12H), 1.40–1.49 (m, 1H), 3.42–3.61 (m, 2H), 3.70 (dd, *J* = 3.4 Hz, 12.9 Hz, 0.5H), 3.78 (s, 6H), 3.89 (dd, *J* = 3.4 Hz, 12.9 Hz, 0.5H), 4.87 (dd, *J* = 2.9 Hz, 8.6 Hz, 0.5H), 4.98 (dd, *J* = 3.4 Hz, 8.6 Hz, 0.5H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 0.5H), 7.02 (d, *J* = 8.6 Hz, 0.5H), 7.15 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.5 (CH_3), 24.6 (CH_3), 27.1 (br, B *C*H), 38.9 and 39.3 (a pair of s, *C*H), 41.9 and 42.2 (a pair of s, CH_2), 52.7 and 52.8 (a pair of s, CH_3), 55.1 (CH_3), 83.37 and 83.43 (a pair of s, *C*), 110.8 (*C*H), 113.5 (*C*H), 124.7 and 125.4 (a pair of s, *C*H), 128.7 and 128.8 (a pair of s, *C*H), 137.0 and 137.2 (a pair of s, *C*), 153.5 and 154.0 (a pair of s, *C*), 158.0 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{20}H_{28}O_5N^{10}B$, 372.20968; found, 372.20878. $[\alpha]_D^{22.7}$ –64.18 (*c* 0.8 in $CHCl_3$, 96% ee). Daicel CHIRALPAK® OZ-3, 2-PrOH/Hexane = 3/97, 0.5 mL/min, 40 °C, (*R,R*)-isomer: t_R = 41.76 min., (*S,S*)-isomer: t_R = 45.68 min.

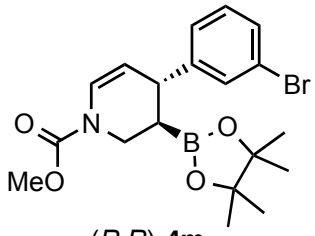
Methyl (3*R*,4*R*)-4-(4-fluorophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*,*R*)-4l].



(*S*,*S*)-**4l**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.09–1.20 (m, 12H), 1.39–1.49 (m, 1H), 3.40–3.61 (m, 2H), 3.73 (dd, *J* = 3.2 Hz, 12.6 Hz, 0.5H), 3.78 and 3.79 (a pair of s, 3H), 3.92 (dd, *J* = 3.1 Hz, 13.0 Hz, 0.5H), 4.84 (dd, *J* = 2.9 Hz, 8.3 Hz, 0.5H), 4.96 (dd, *J* = 3.2 Hz, 8.5 Hz, 0.5H), 6.89 (dd, *J* = 1.6, 8.3 Hz, 0.5H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 7.04 (dd, *J* = 1.4 Hz, 8.5 Hz, 0.5H), 7.15–7.23 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.5 (CH_3), 24.7 (CH_3), 27.8 (br, B CH), 39.1 and 39.6 (a pair of s, *C*H), 42.0 and 42.3 (a pair of s, CH_2), 52.9 and 53.0 (a pair of s, CH_3), 83.5 and 83.6 (a pair of s, *C*), 110.3 (*C*H), 114.8 and 115.0 (a pair of *C*H), 125.1 and 125.7 (a pair of s, *C*H), 129.3 (*C* F, d, *J* = 7.6 Hz, *C*H), 129.4 (*C* F, d, *J* = 7.6 Hz, *C*H), 140.6 and 140.8 (a pair of s, *C*), 153.8 (*C* F, d, *J* = 213.1 Hz, *C*H), 160.2 and 162.7 (a pair of s, *C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{19}H_{25}O_5N^{10}BF$, 360.18970; found, 360.18876. $[\alpha]_D^{18.6}$ +38.09 (*c* 2.3 in $CHCl_3$, 96% ee). Daicel CHIRALPAK® OJ-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, (*R*,*R*)-isomer: t_R = 15.41 min., (*S*,*S*)-isomer: t_R = 17.20 min.

Methyl (3*R*,4*R*)-4-(3-bromophenyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R*,*R*)-4m].

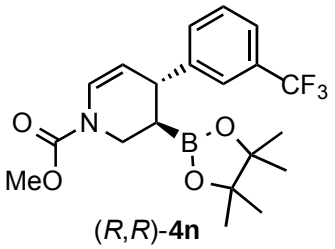


(*R*,*R*)-**4m**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.09–1.23 (m, 12H), 1.38–1.48 (m, 1H), 3.39–3.65 (m, 2H), 3.71 (dd, *J* = 3.1 Hz, 12.7 Hz, 0.5H), 3.79 (s, 3H), 3.91 (dd, *J* = 2.9 Hz, 12.9 Hz, 0.5H), 4.85 (dd, *J* = 2.4 Hz, 8.6 Hz, 0.5H), 4.96 (dd, *J* = 2.9 Hz, 8.6

Hz, 0.5H), 6.92 (d, J = 8.6 Hz, 0.5H), 7.07 (d, J = 8.1 Hz, 0.5H), 7.10–7.22 (m, 2H), 7.32 (dt, J = 2.0 Hz, 7.0 Hz, 1H), 7.39 (br, s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.5 (CH_3), 24.7 (CH_3), 27.3 (br, B CH), 39.4 and 39.9 (a pair of s, *C*H), 41.8 and 42.1 (a pair of s, *C*H), 52.8 and 52.9 (a pair of s, CH_3), 83.6 (*C*), 109.3 and 109.4 (a pair of s, *C*H), 122.1 (*C*), 125.5 and 126.1 (a pair of s, *C*H), 126.3 and 126.4 (a pair of s, *C*H), 129.3 (*C*H), 129.7 (*C*H), 131.1 and 131.2 (a pair of s, *C*H), 147.4 and 147.6 (a pair of s, *C*), 153.4 and 153.9 (a pair of s, *C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{19}H_{25}O_4N^{10}BBr$, 420.10963; found, 420.10843. $[\alpha]_D^{24.2}$ –72.50 (*c* 1.0 in $CHCl_3$, 74% ee). The ee value was determined by HPLC analysis of the corresponding ester after oxidation, followed by standard esterification with *p*-nitrobenzoyl chloride of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 7/93, 0.5 mL/min, 40 °C, (*R,R*)-isomer: t_R = 36.08 min., (*S,S*)-isomer: t_R = 38.99 min.

Methyl (3*R*,4*R*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(3-(trifluoromethyl)phenyl)-3,4-dihydropyridine-1(2*H*)-carboxylate [(*R,R*)-4n].



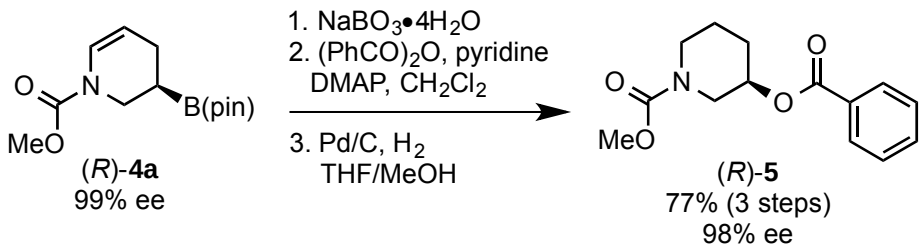
(*R,R*)-**4n**

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.03–1.23 (m, 12H), 1.46 (t, J = 8.4 Hz, 1H), 3.39–3.55 (m, 1H), 3.61–3.69 (m, 1H), 3.73–3.84 (m, 3.5H), 3.96 (dd, J = 3.5, 12.9 Hz, 0.5H), 4.86 (dd, J = 2.4, 8.6 Hz, 0.5H), 4.96 (dd, J = 2.6, 8.3 Hz, 0.5H), 6.95 (d, J = 8.1 Hz, 0.5H), 7.09 (d, J = 8.2 Hz, 0.5H), 7.35–7.55 (m, 4H). ^{13}C NMR (99 MHz, $CDCl_3$,): 24.5 (CH_3), 24.6 (CH_3), 27.3 (br, B CH), 39.7 and 40.1 (a pair of s, *C*H), 42.0 and 42.3 (a pair of s, CH_2), 52.9 and 53.0 (a pair of s, CH_3), 83.7 (*C*), 109.4 and 109.5 (a pair of s, *C*H), 123.3 (*C*H), 125.0 (*C*H), 125.7 (*C*H), 126.3 (*C*H), 128.7 (*C*H), 130.3 (*C* F, q, J = 33.4 Hz, *C*), 131.2 (*C*H), 146.1 and 146.2 (a pair of s, *C*), 153.5 and 154.0 (a pair of s, *C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{20}H_{25}O_4N^{10}BF_3$, 410.18650; found, 410.18546. $[\alpha]_D^{24.4}$ –47.97 (*c* 1.5 in $CHCl_3$, 66% ee). The ee value was determined by HPLC analysis of the corresponding ester after oxidation, followed by standard esterification with

p-nitrobenzoyl chloride of the borylated product in comparison of the racemic sample. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*R,R*)-isomer: t_R = 21.47 min., (*S,S*)-isomer: t_R = 24.24 min.

Borylation Product Functionalization Procedure

Procedure for the synthesis of chiral piperidinol (*R*)-5 through the oxidation following acylation and hydrogenation of (*R*)-4a.



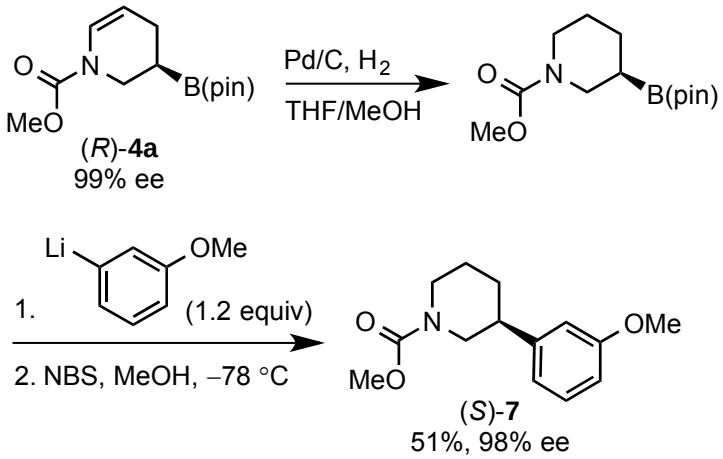
The oxidation was performed according to the literature procedure.[20] In a reaction vial, (*R*)-**4a** (80.2 mg, 0.30 mmol) was dissolved in THF/H_2O (1:1, 2.0 mL). $NaBO_3$•$4H_2O$ (184.6 mg, 1.2 mmol) was then added at room temperature. After stirred for 1 h, the reaction mixture was extracted three times with CH_2Cl_2, dried over $MgSO_4$, and filtered. The resulting crude material was used in the next reaction without further purification.

The crude material, 4-dimethylaminopyridine (7.3 mg, 0.060 mmol) and pyridine (48.3 μL, 0.60 mmol) were dissolved in dry CH_2Cl_2 (1.0 mL) under a nitrogen atmosphere. Benzoic anhydride (67.9 mg, 0.30 mmol) was then added at room temperature. Aqueous NH_4Cl was added to the reaction mixture after 2 h, the mixture was then extracted with CH_2Cl_2 three times and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 1:99–15:85) to afford the corresponding ester (63.5 mg, 0.24 mmol, 81%) as a colorless oil.

The obtained ester (63.5 mg, 0.24 mmol) and Pd/C (10.0 mg, 10%) were dissolved in MeOH/THF (1:1, 2.0 mL) under a nitrogen atmosphere. Hydrogen gas was then introduced to the reaction mixture. After being stirred for 1 hour, the mixture was filtered through short pad of silica gel with Et_2O as an eluent. The solvent was removed by evaporation under reduced pressure to obtain the chiral piperidinol (*R*)-**5** (60.8 mg, 0.23 mmol, 95%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.54–1.72 (m, 1H), 1.76–2.08 (m, 3H), 3.24–3.92 (m, 4H), 3.54 (s, 3H), 5.03–5.16 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.99–8.05 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$,): 21.4 (CH_2), 29.0 (CH_2), 44.2 (CH_2), 47.5 (CH_2), 52.5 (CH_3), 68.2 (*C*H), 128.3 (*C*H), 129.5 (*C*H), 130.1 (*C*), 133.0 (*C*H), 156.2 (*C*), 165.6 (*C*). HRMS–EI (m/z): [M OMe]$^+$ calcd for $C_{13}H_{14}O_3N$, 232.09737; found, 232.09707. $[\alpha]_D^{20.9}$ –15.88 (*c* 1.2 in $CHCl_3$, 98% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*R*)-isomer: t_R = 14.75 min., (*S*)-isomer: t_R = 15.60 min.

Procedure for the synthesis of (*S*)-7 through the hydrogenation following cross-coupling with (3-methoxyphenyl)lithium of (*R*)-4a.



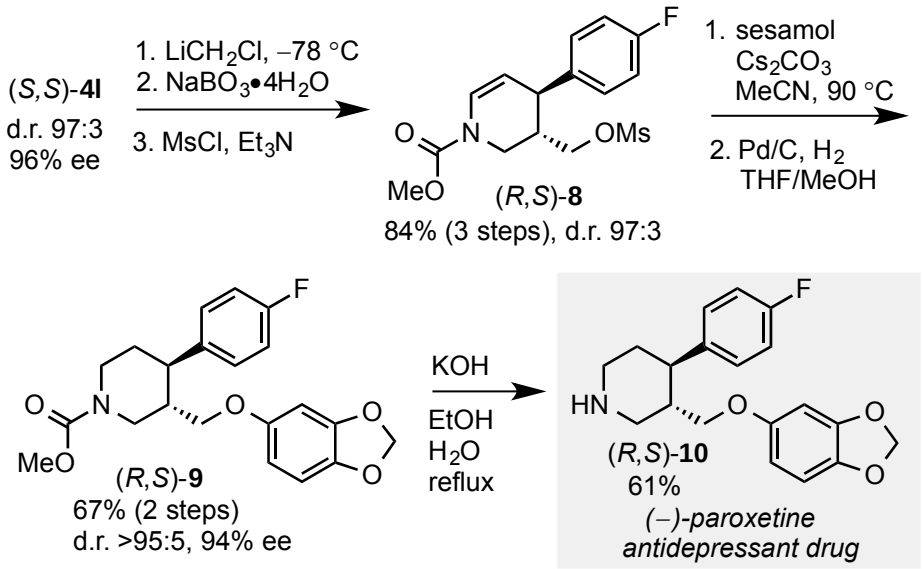
The borylation product (*R*)-**4a** (155.6 mg, 0.58 mmol) and Pd/C (20.0 mg, 10%) were dissolved in MeOH/THF (1:1, 1.0 mL) under a nitrogen atmosphere. Hydrogen gas was then introduced to the reaction mixture. After being stirred for 15 hour, the mixture was filtered through short pad of silica gel with Et_2O as an eluent. The solvent was removed by evaporation under reduced pressure to obtain the chiral piperidine (150.5 mg, 0.56 mmol, 96%) as a colorless oil.

The stereospecific cross-coupling was performed according to the literature procedure.[14] A solution of 1-bromo-3-methoxybenzene (29.0 μL, 0.23 mmol) in THF (1.0 mL) was cooled to –78 °C and treated with *n*-BuLi in hexane (1.63 M, 141.0 μL 0.24 mmol). After being stirred for 1 h at –78 °C, a THF solution (1.0 ml) of (*R*)-**4a** (51.1 mg, 0.19 mmol) was added to the reaction mixture. After being stirred for 1 h at –78 °C, the solvent was removed under reduced pressure and MeOH (2.0 ml) was added to the mixture. A THF solution (3.0 mL) of *N*-bromoscuccinimide (NBS) was then

added at –78 °C and the reaction stirred at the same temperature for 1 h. Aqueous $Na_2S_2O_3$ was added and the reaction mixture was allowed to warm to room temperature. The mixture was extracted three times with CH_2Cl_2, dried over $MgSO_4$, and filtered. The crude material was purified by flash column chromatography (SiO_2, EtOAc/hexane, 2:98–15:85) to give the arylated product (*S*)-**7** (24.2 mg, 0.097 mmol, 51%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.51–1.70 (m, 2H), 1.71–1.82 (m, 1H), 1.98–2.07 (m, 1H), 2.59–2.86 (m, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 4.03–4.45 (m, 2H), 6.74–6.80 (m, 2H), 6.82 (d, *J* = 7.6 Hz, 1H), 7.19–7.25 (m, 1H). ^{13}C NMR (99 MHz, $CDCl_3$,): 25.4 (CH_2), 31.6 (CH_2), 42.7 (CH), 44.2 (CH_2), 50.5 (CH_2), 52.5 (CH_3), 55.1 (CH_3), 111.6 (CH), 113.1 (CH), 119.4 (CH), 129.5 (CH), 144.9 (*C*), 155.9 (*C*), 159.7 (*C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{14}H_{19}O_3N$, 249.13649; found, 249.13599. $[\alpha]_D^{21.2}$ –12.67 (*c* 1.5 in $CHCl_3$, 98% ee). Daicel CHIRALPAK® IC-3, 2-PrOH/Hexane = 5/95, 0.5 mL/min, 40 °C, (*S*)-isomer: t_R = 28.71 min., (*R*)-isomer: t_R = 29.81 min.

Procedure for the synthesis of (*R*,*S*)-7 through derivatization of (*S*,*S*)-4l.



The one-carbon homologation was performed according to the literature procedure.[16] In an oven-dried reaction vial, (*S*,*S*)-**4l** (436.3 mg, 1.2 mmol) and bromochloromethane (160.9 μL, 2.4 mmol) were dissolved in dry THF (9.0 mL) in nitrogen atmosphere. After the mixture was cooled to –78 °C, *n*-BuLi in hexane (1.64 M, 1.1 mL, 1.8 mmol) was added dropwise. The mixture was stirred at –78 °C for 20 min, and then stirred at room temperature for 2 h. The reaction mixture was quenched by the addition of aqueous NH_4Cl, extracted

three times with CH_2Cl_2, dried over $MgSO_4$, and filtered. The crude material was purified by flash column chromatography (SiO_2, EtOAc/hexane, 2.5:97.5–12.5:87.5) to give the homologation product (432.1 mg, 1.2 mmol, 96%) as a colorless oil.

The oxidation was performed according to the procedure described above. In a reaction vial, the homologation product (432.1 mg, 1.2 mmol) was dissolved in THF/H_2O (1:1, 6.0 mL). $NaBO_3 \bullet 4H_2O$ (709.0 mg, 4.6 mmol) was then added at room temperature. After stirred for 30 min, the reaction mixture was extracted three times with CH_2Cl_2, dried over $MgSO_4$, and filtered. The resulting crude material was used in the next reaction without further purification.

The crude material and Et_3N (481.7 μL, 3.5 mmol) were dissolved in dry CH_2Cl_2 (2.0 mL) under a nitrogen atmosphere. Methanesulfonyl chloride (178.3 μl, 2.3 mmol) was then added at 0 °C. After being stirred for 3 h at room temperature, aqueous $NaHCO_3$ was added to the reaction mixture. The mixture was then extracted with CH_2Cl_2 three times and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 7.5:92.5–50:50) to afford the corresponding mesylate (350.0 mg, 1.0 mmol, 88%, 2 steps) as a colorless oil.

In a vacuum dried 100 mL round bottomed flask, the mesylate (350.0 mg, 1.0 mmol), sesamol (281.6 mg, 2.0 mmol) and Cs_2CO_3 (1.3 g, 4.1 mmol) were dissolved in dry MeCN (15.0 mL) and it was warmed to 90 °C under nitrogen atmosphere. After being stirred for 12 h, the reaction mixture was quenched by addition of aqueous NH_4Cl and extracted with CH_2Cl_2 three times. The combined organic layer was then dried over $MgSO_4$. After filtration, the solvents were removed by evaporation. The crude product was then purified by flash column chromatography (SiO_2, ethyl acetate/hexane, 3:97–15:85) to afford the corresponding ether (276.7 mg, 0.72 mmol, 70%) after the treatment with tert-butyldimethylchlorosilane (TBSCl) and imidazole to remove the cesamol as the silylether by silica gel column.

The ester (276.7 mg, 0.72 mmol) and Pd/C (20.0 mg, 10%) were dissolved in MeOH/THF (1:1, 2.0 mL) under a nitrogen atmosphere. Hydrogen gas was then introduced to the reaction mixture. After being stirred for 1 hour, the mixture was filtered through short pad of silica gel with Et_2O as an eluent. The solvent was removed by evaporation under reduced pressure to obtain

the *N*-protected (–)-Paroxeine (*R*,*S*)-**9** (265.5 mg, 0.68 mmol, 95%) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.73 (dt, *J* = 3.4 and 12.5 Hz, 1H), 1.79–1.88 (m, 1H), 1.96–2.07 (m, 1H), 2.64–2.77 (m, 1H), 2.87 (t, *J* = 12.3 Hz, 2H), 3.45 (dd, *J* = 6.3, 9.4 Hz, 1H), 3.60 (dd, *J* = 2.7, 9.4 Hz, 1H), 3.74 (s, 3H), 4.19–4.60 (m, 2H), 5.89 (s, 2H), 6.14 (dd, *J* = 2.7 Hz and 8.5 Hz, 1H), 7.35–7.55 (m, 4H). ^{13}C NMR (99 MHz, $CDCl_3$,): 33.7 (CH_2), 41.8 (*C*H), 43.8 (*C*H), 44.3 (CH_2), 47.2 (CH_2), 52.6 (CH_3), 68.6 (CH_2), 97.9 (CH_2), 101.0 (CH_2), 105.4 (*C*H), 107.7 (*C*H), 115.3 and 115.5 (a pair of s, *C*H), 128.6 and 128.7 (a pair of s, *C*H), 138.8 and 138.9 (a pair of s, *C*), 141.6 (*C*), 148.1 (*C*), 154.1 (*C*), 155.8 (*C*), 160.2 and 162.7 (a pair of s, *C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{21}H_{22}O_5NF$, 387.14820; found, 387.14779. $[\alpha]_D^{22.8}$ +14.35 (*c* 1.0 in $CHCl_3$, 93% ee). Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 10/90, 0.5 mL/min, 40 °C, (*S*,*R*)-isomer: t_R = 23.49 min., (*R*,*S*)-isomer: t_R = 27.17 min.

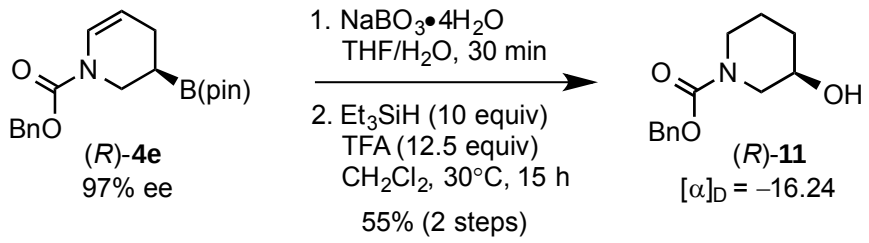
The *N*-protected (–)-Paroxeine (*R*,*S*)-**9** (96.9 mg, 0.25 mmol) was dissolved in EtOH/H_2O (4:1, 1.9 ml). Potassium hydroxide (420.8 mg, 7.5 mmol) was then added to a reaction mixture. After being stirred for 42 hours at 110℃, the mixture was then extracted with CH_2Cl_2 three times and dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford (–)-Paroxeine (265.5 mg, 0.68 mmol, 61%) as a yellow oil. ^{1}H and ^{13}C NMR were in agreement with those in the literature.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.64–1.85 (m, 3H), 2.00–2.11 (m, 1H), 2.58 (dt, *J* = 4.0 and 11.7 Hz, 1H), 2.62–2.79 (m, 2H), 3.18 (d, *J* = 12.2 Hz, 1H), 3.37–3.46 (m, 2H), 3.55 (dd, *J* = 3.1, 9.4 Hz, 1H), 5.86 (s, 2H), 6.11 (dd, *J* = 2.7 Hz and 8.5 Hz, 1H), 6.32 (d, *J* = 2.7 Hz, 1H), 6.61 (d, *J* = 8.5 Hz, 1H), 6.92–7.01 (m, 2H), 7.11–7.19 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$,): 32.8 (CH_2), 41.2 (*C*H), 43.1 (*C*H), 45.7 (CH_2), 48.6 (CH_2), 68.4 (CH_2), 97.8 (CH), 101.0 (CH_2), 105.4 (*C*H), 107.8 (*C*H), 115.5 (*C* F, d, *J* = 86.0 Hz, *C*H), 128.8 (*C* F, d, *J* = 128.8 Hz, *C*H), 138.6 (*C*), 141.7 (*C*), 148.1 (*C*), 154.0 (*C*), 161.6 (*C* F, d, *J* = 246.4 Hz, *C*). HRMS–EI (m/z): $[M]^+$ calcd for $C_{19}H_{20}O_3NF$, 329.14272; found, 329.14205. $[\alpha]_D^{20.5}$ 92.79 (*c* 1.2 in $CHCl_3$).

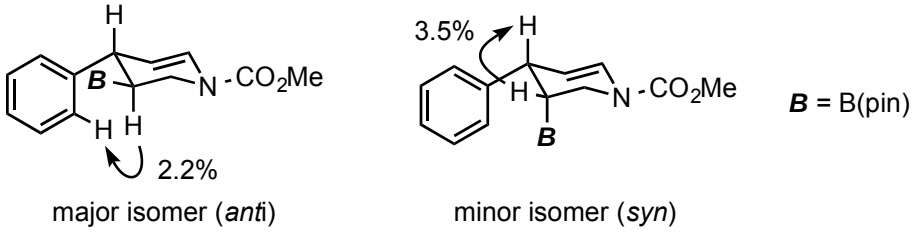
Determination of the Absolute Configurations of Borylation Products

The absolute configuration of borylation product (*R*)-**4e** was determined by comparison of the optical rotation of the alcohol (*R*)-**11** **[**$[\alpha]_D^{20}$ 16.24 (*c*

1.1 in $CHCl_3$)] and the literature value for (*R*)-**11**.[21]



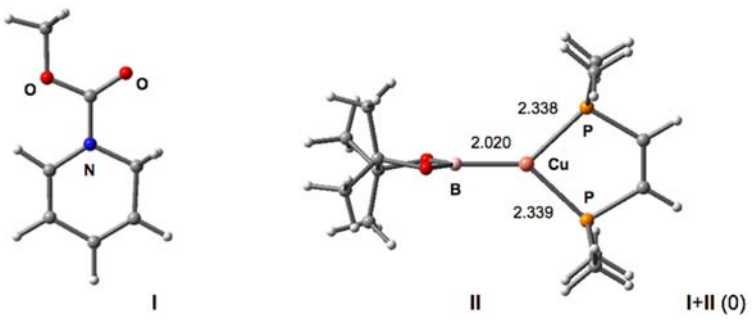
The *anti* configuration of borylation product (*R*,*R*)-4b was confirmed by NOE analysis as shown below.

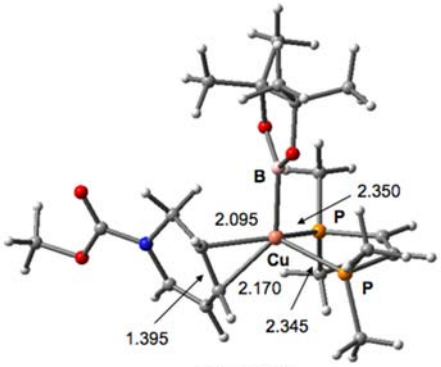


Details of the DFT Calculations

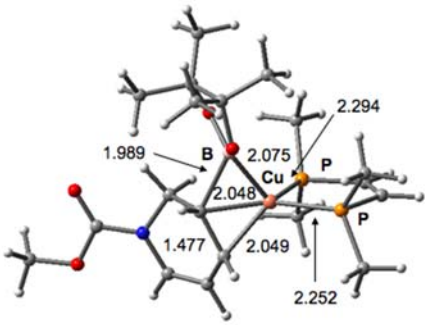
All calculations were performed with the Gaussian 09W (revision C.01) program package.[22] Geometry optimizations were performed with B3PW91/cc-pVDZ in the gas-phase. The frequency calculations were conducted on gas-phase optimized geometries to check the all the stationary points as either minima or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

Figure S1. Optimized Structures (I, II, C, TS, P) for Four Regioisomeric Pathway with Structual Parameters and Free Energies.

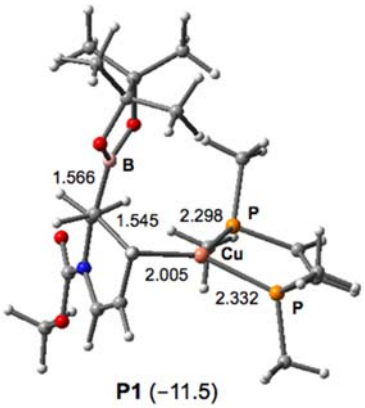




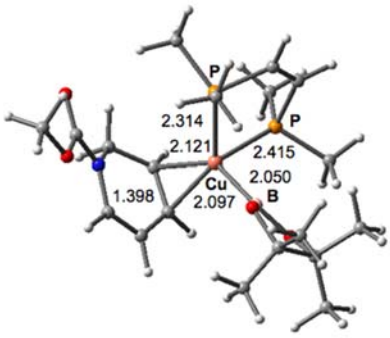
C1 (+7.7)



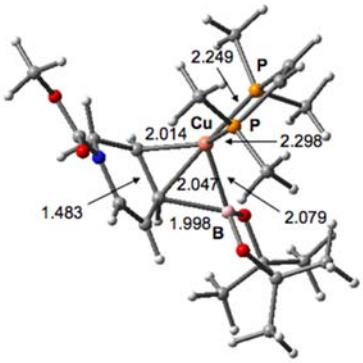
TS1 (+19.0)



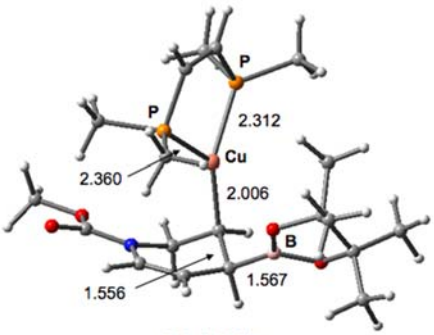
P1 (−11.5)



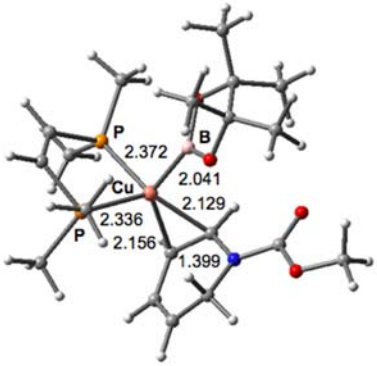
C2 (+8.9)



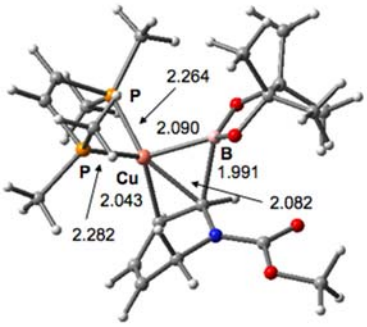
TS2 (+21.8)



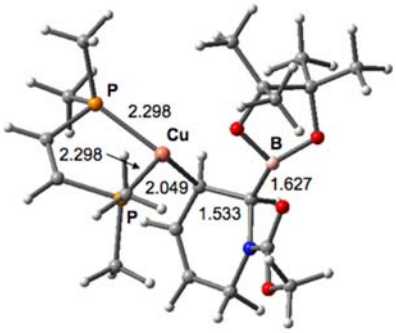
P2 (−7.3)



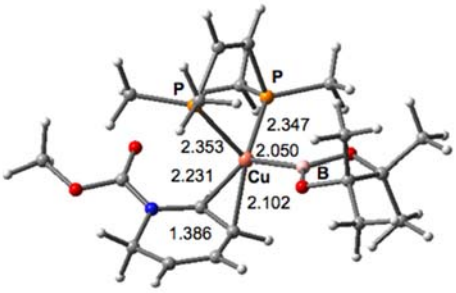
C3 (+9.4)



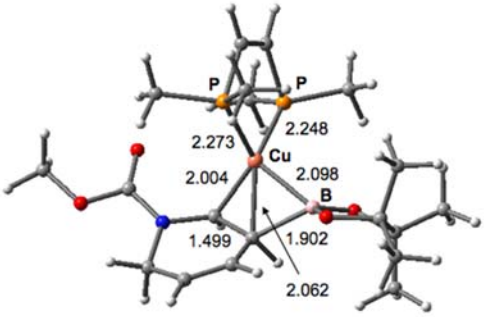
TS3 (+20.4)



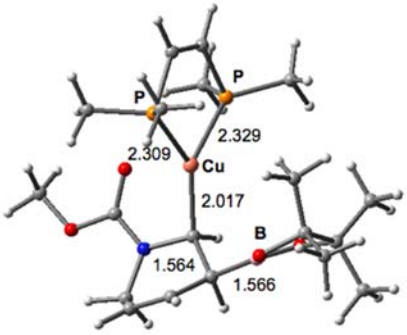
P3 (−8.0)



C4 (+9.8)

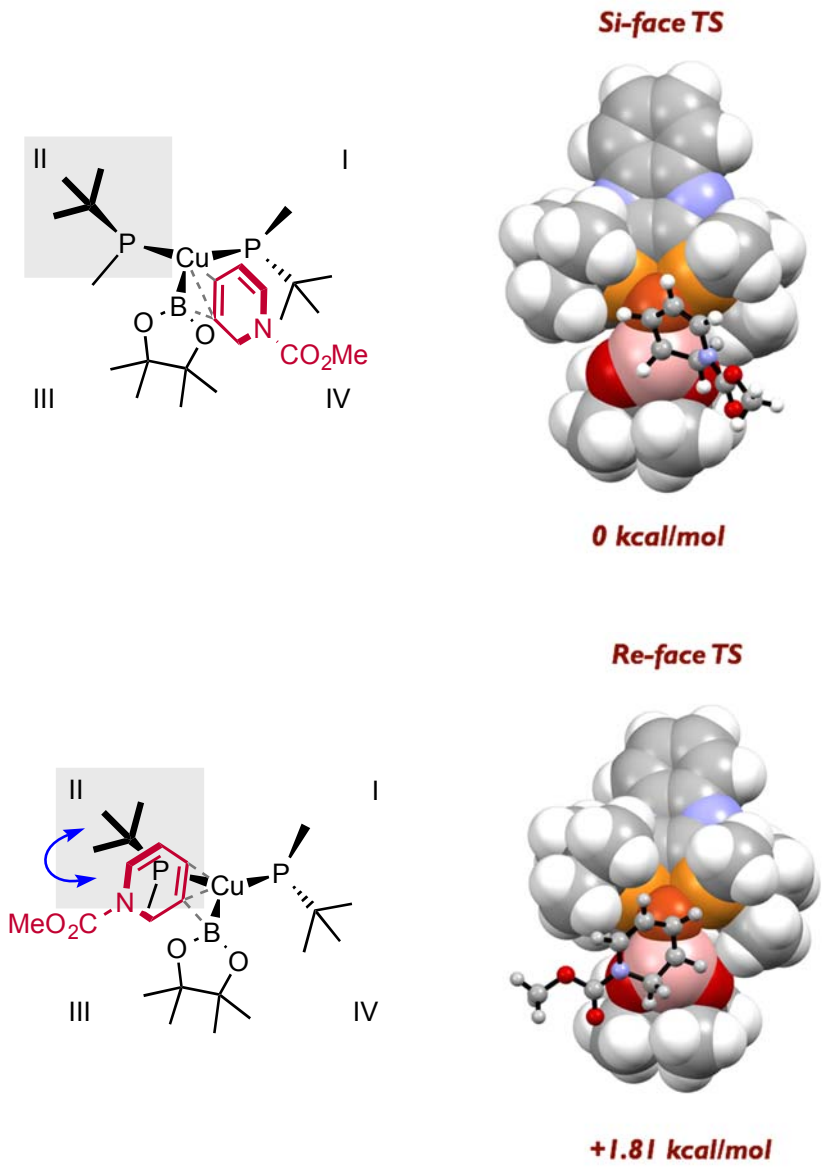


TS4 (+27.0)



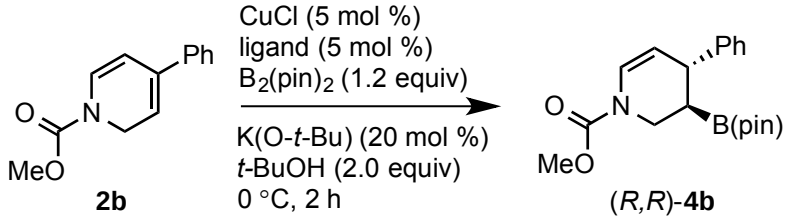
P4 (−0.9)

Figure S2. DFT Calculations (B3PW91/cc-pVDZ) of the Transition States for the (*R*,*R*)-QuinoxP*/Copper(I) Catalyzed Enantioselective Borylation of 1,2-Dihydropyridine. Relative G values (Kcal/mol) at 298 K, 1.0 atom in the Gas Phase.



The DFT study suggested that favored *Si*-face borylcupration of 1,2-dihydropyridine would provide (*R*)-enantiomer product, which corresponds to the experimental results.

Optimization of the Reaction Conditions for the Borylation of 2b



chiral ligand	solvent	conv. (%)[a]	d.r.[a]	ee (%)
(*R*,*R*)-QuinoxP*	THF	>95	99:1	39
(*R*)-SEGPHOS	THF	>95	69:31	91
(*R*)-DM-SEGPHOS	THF	>95	94:6	83
(*R*,*R*)-BDPP	THF	>95	96:4	71
(*R*,*R*)-Me-Duphos	THF	>95	99:1	36
(*R*)-SEGPHOS[b]	toluene/THF (10:1)	75 (61)[c]	94:6	91
(*R*)-SEGPHOS	toluene/DME/THF (6:6:1)	>95 (94)[c]	97:3	92

[a]Determined by GC analysis. [b]10 mol % catalyst was used and the reaction time was 18 h. [c]Determined by ^{1}H NMR analysis. NMR yield is shown in parenthesis.

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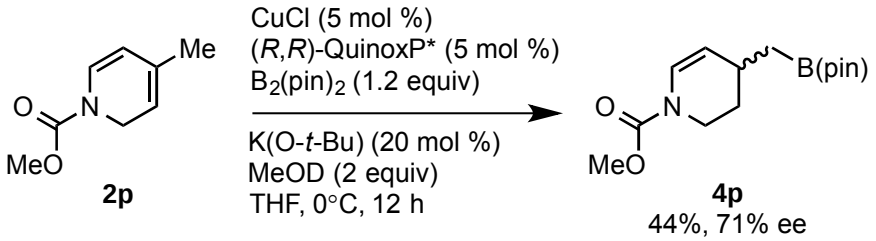
(13) The author also conducted the enantioselective borylation of 4-methyl-1,2-dihydropyridine **2p**, but the reaction provided the primary boronate **4p** as shown in below scheme. The detail is now under investigation.



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Summary of this thesis

Organoboron compounds have found wide application ranging from organic synthesis to anti-cancer medicine and organic materials. Thus, the development of simple, mild and efficient synthetic method for their preparation is in great demand. With this in mind, the author has investigated the copper(I)-catalyzed novel borylation reactions.

In chapters 1 and 2, the auther has developed the new method for the synthesis of various alkylboronate esters from alkyl halides through copper(I) catalysis. The boryl substitution of alkyl halides described in chapter 1 provides a direct umpolung pathway for the conventional carbon nucleophile method, and has high functional group compatibility and interesting stereochemical-controlling properties. The author believes that this procedure will be a powerful synthetic method for a broad range of alkylboronates, including those that could not be synthesized by previous methods. The borylative cyclization reaction described in chapter 2 offers an efficient route to various small carbocyclic boronates from readily available starting materials.

In chapters 3, the auther has developed the enantioselective borylation reaction of alkenylsilanes catalyzed by a copper(I)/chiral diphosphine complex. The product can be converted into various functionalized chiral compounds such as aminoalcohols by stepwise functionalization of a boryl and a silyl groups.

In chapters 4 and 5, the auther has developed the enantioselective borylation reaction of aldehydes catalyzed by a copper(I)/chiral diphosphine complex and conducted the theoretical study for deep understanding of the reaction mechanism. The newly synthesized chiral α-alkoxyorganoboronate esters described in chapter 4 could be transformed to functionalized chiral alcohol derivatives using stereospecific C–C bond forming reactions.

In chapters 6, the auther has developed the enantioselective dearomative borylation reaction of aromatic compound, indoles catalyzed by a copper(I)/chiral diphosphine complex. This is the first example for the C–B bond forming dearomatization of aromatic compounds to give the synthetically useful chiral *N*-heterocyclic boronate directly.

In chapters 7, the auther has developed the enantioselective borylation reaction of 1,2-dihydropyridines catalyzed by a copper(I)/chiral diphosphine

complex. This new method provides simple, mild and rapid access to a variety of chiral piperidines in combination with the stereospecific transformation of a stereogenic C–B bond.

These studies in this thesis will be particularly valuable toward the development and design of novel borylation reactions with transition-metal catalysis.

List of Publications

Chapter 1

Copper(I)-Catalyzed Boryl Substitution of Unactivated Alkyl Halides

Ito, H.; Kubota, K.

Org. Lett. **2012**, *14*, 890.

Chapter 2

Copper(I)-Catalyzed Borylative *exo*-Cyclization of Alkenyl Halides Containing Unactivated Double-Bond

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

J. Am. Chem. Soc. **2013**, *135*, 2635.

Chapter 3

Regio- and Enantioselective Monoborylation of Alkenylsilnes Catalyzed by an Electron-Donating Chiral-Phosphine Copper(I) Complex

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

Adv. Synth. Catal. **2013**, *355*, 3527.

Highlighted in Synfacts 2014.

Chapter 4

Copper(I)-Catalyzed Enantioselective Nucleophilic Borylation of Aldehydes

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

J. Am. Chem. Soc. **2015**, *137*, 420.

Chapter 5

Computational Insight into the Enantioselective Borylation of Aldehydes Catalyzed by Chiral Bisphosphine Copper(I) Complexes

Kubota, K.; Mingoo, J.; Ito, H.

To be submitted.

Chapter 6
Copper(I)-Catalyzed Enantioselective Borylative Dearomatization of Indoles
Kubota, K.; Hayama, K.; Iwamoto, H.; Ito, H.
Angew. Chem., Int. Ed. **2015**, *54*, 8809.

Chapter 7
Copper(I)-Catalyzed Regio- and Enantioselective Borylation of 1,2-Dihydropyridines
Kubota, K.; Watanabe, Y.; Hayama, K.; Ito, H.
To be submitted.

Other 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.
Reaction Optimization, Scalability, and Mechanistic Insight on the Catalytic Enantioselective Desymmetrization of 1,1-Diborylalkanes via Suzuki–Miyaura Cross-Coupling
Sun, H.; Kubota, K.; Hall, D. G. *Chem. Eur. J.* **2015**, Early View.

3.
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. Commum. **2015**, *51*, 9655.

4.
Copper(I)-Catalyzed Diastereoselective Borylative *Exo*-Cyclization of Alkenyl Aryl Ketones
Yamamoto, E.; Kojima, R.; Kubota, K.; Ito, H.
Synlett **2015**, *Just Accepted*.

5. (review)
Selective Synthesis of Organoboron Compounds with Copper(I)-Phosphine Complex Catalysts
Yamamoto, E.; Takenouchi, Y.; Kubota, K.; Ito, H.
J. Synth. Org. Chem. Jpn. **2014**, *72*, 758.

6. (review)
Topochemical Photocyclizations for the Synthesis of Two-Dimensional Polymers
Kubota, K. *J. Synth. Org. Chem. Jpn.* **2014**, *72*, 834.

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