Tetrahedron

Copper-catalyzed borylative transformations of non-polar carbon–carbon unsaturated compounds employing borylcopper as an active catalyst species

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ARTICLE INFO

ABSTRACT

Copper-catalyzed borylative transformations of non-polar carbon–carbon unsaturated compounds using borylcopper as an active catalyst species are described in this review. First, the importance of developing synthetic methods for preparation of organoboronic acids and their derivatives in modern organic synthesis is addressed and the background of this research area is briefly introduced. Subsequently, addition of the borylcopper species across carbon–carbon multiple bonds (borylcupration) is discussed by showing several examples of stoichiometric reactions of the borylcopper with alkenes, alkynes, and 1,2-dienes (allenes), since the borylcupration is the most important elemental step in the copper-catalyzed borylative transformations. Then, copper-catalyzed borylative transformations of non-polar carbon–carbon unsaturated compounds such as formal hydroboration, the S_N2' substitution of allylic or propargylic alcohol derivatives with borylcopper, carboboration, and heteroboration are exemplified and discussed in detail.

1. Introduction

Organoboronic acids and their derivatives are useful reagents in carbon–carbon and carbon–heteroatom bond formations.[1] In addition to having reasonable reactivities, organoboronic acids and their derivatives are often stable in air and moisture. Thus, they are versatile building blocks in organic synthesis. Therefore, methodologies for preparing these compounds have been extensively developed by many researchers. Conventionally, organoboronic acids and their derivatives are prepared by hydroboration of unsaturated compounds[2] and by substitution reactions of boron electrophiles with organolithium or Grignard reagents.[1a] In recent years, transition metal-catalyzed borylation reactions have been powerful synthetic methods for the preparation of them in terms of functional group compatibility and unique reactivity. To date, Pd-catalyzed borylation of organic halides,[3] Pd- and Pt-catalyzed diboration[4] and silaboration[5] of carbon–carbon unsaturated compounds, Pd-catalyzed carboboration,[6] Rh- and Ir-catalyzed C–H borylation[7] have been reported. Recently, base metal catalysts such as Fe,[8] Co,[9] Ni,[10] and Cu,[11] which are more ubiquitous and less toxic than noble metals, have been found to catalyze the aforementioned borylation reactions and new borylation reactions. Among them, Cu-catalyzed borylation reactions, especially borylcopper (Cu–B)-catalyzed borylation, are highly effective for the synthesis of various organoboronic acids and their derivatives that are difficult to be synthesized by other methods. In this review, we describe Cu-catalyzed borylative transformations of non-polar carbon–carbon unsaturated compounds employing borylcopper as an active catalyst species.[12]

2. Isolation of borylcopper and borylcupration of carbon–carbon unsaturated bonds

2.1. Isolation and characterization of borylcopper species

In 2000, borylcopper species was first applied to the conjugate borylation of enones, hydroboration of terminal alkynes, and allylic substitution of allyl chlorides by Ito and Hosomi as well as Miyaura, independently.[13] In 2006, Sadighi and co-workers isolated a 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene (IPr) ligated borylcopper complex **1a** through the reaction of (IPr)CuO*t*Bu with bis(pinacolato)diboron (B$_2$(pin)$_2$) and fully characterized it by NMR spectroscopy and X-ray crystallographic analysis (eq. 1).[14] We also isolated similar borylcopper complexes **1b** and **1c** (eq. 1 and Fig. 1).[15] Although, to date, only NHC ligated borylcopper complexes have been isolated, phosphine ligated borylcopper species have also been considered as active catalyst species in many copper-catalyzed borylation reactions.

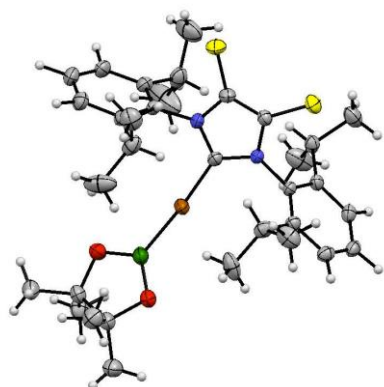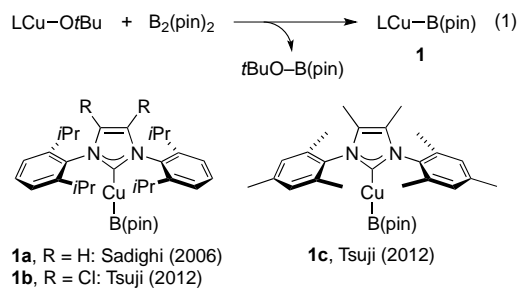* Corresponding author. Tel.: +81-75-383-2514; fax: +81-75-383-2515; e-mail: ytsuji@scl.kyoto-u.ac.jp

$$LCu-OtBu + B_2(pin)_2 \longrightarrow LCu-B(pin) \quad (1)$$

$$tBuO-B(pin) \qquad 1$$

1a, R = H: Sadighi (2006)
1b, R = Cl: Tsuji (2012)

1c, Tsuji (2012)

Fig. 1. Crystal structure of **1b**

2.2. Insertion of borylcopper to carbon–carbon unsaturated bonds

The addition of borylcopper to carbon–carbon multiple bonds (borylcupration) is the most important elemental step in copper-catalyzed borylation reactions of carbon–carbon unsaturated compounds. To date, borylcupration of various carbon–carbon unsaturated bonds such as alkenes, alkynes, 1,2-dienes (allenes), and 1,3-dienes has been proposed. The first example of borylcupration of a carbon–carbon unsaturated bond was demonstrated by Sadighi and co-workers.[16] (IPr)CuB(pin) (**1a**) smoothly reacts with styrene derivatives at room temperature, giving β-borylalkylcoppers in highly regio- and stereoselective manners (eq. 2). The crystal structure of **2a** was determined by X-ray analysis (Fig. 2). DFT calculations by Lin and Marder suggested that the regioselectivity of the borylcupration of styrene could be determined on the basis of the interaction between the σ-orbital of the Cu–B bond and the π*-orbital of the alkene.[17] Such interaction is important in determining the regioselectivity of borylcupration of other carbon–carbon multiple bonds. Hou and co-workers reported the reaction of **1a** with diphenylacetylene (eq. 3).[18] A β-borylalkenylcopper **2c** was obtained in a stereoselective manner (Fig. 3). We found that (ClIPr)CuB(pin) (**1b**) was cleanly inserted into phenylallene to afford a β-boryl σ-allylcopper **2d** (eq. 4 and Fig. 4).[15]
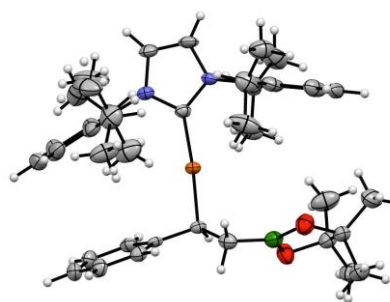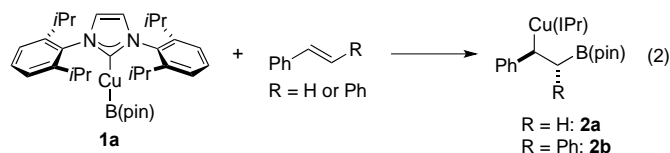

$$R = H: \textbf{2a}$$
$$R = Ph: \textbf{2b}$$

(2)

1a

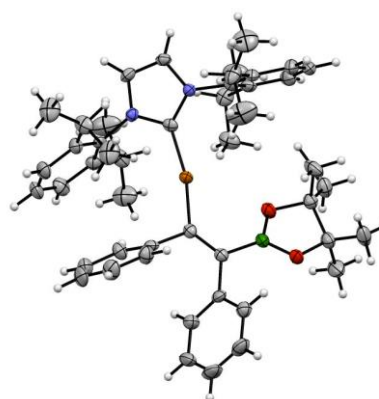**Fig. 2.** Crystal structure of **2a**

(3)

1a + Ph—≡—Ph → Ph—C(=C)(Ph)—B(pin) Cu(IPr)
2c

Fig. 3. Crystal structure of **2c**

(4)

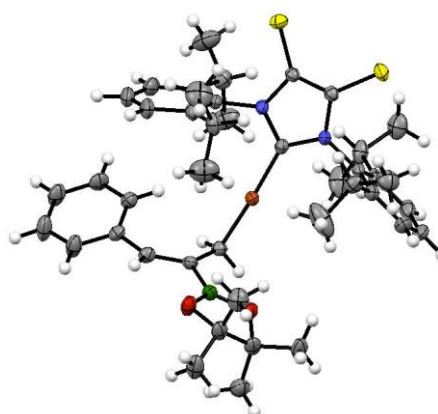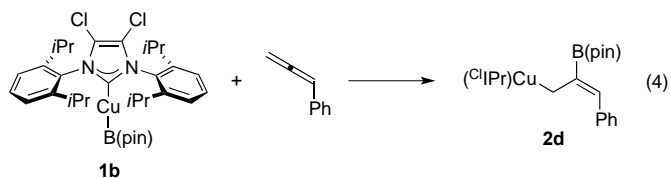**1b** + (allene with Ph) → (ClIPr)Cu—CH2—C(B(pin))=CH—Ph
2d
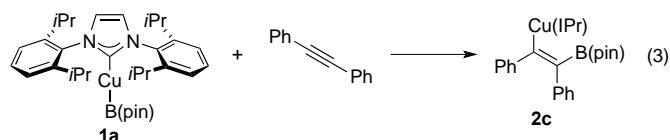
**Fig. 4.** Crystal structure of **2d**

3. Hydroboration using diboron

3.1. Mechanism

Hydroboration of carbon–carbon unsaturated compounds occurs through the protonation (with an alcohol) of
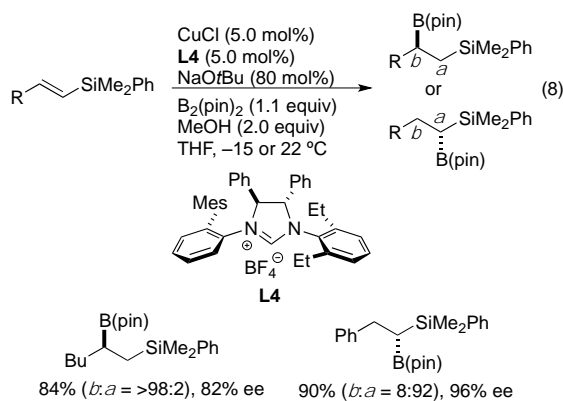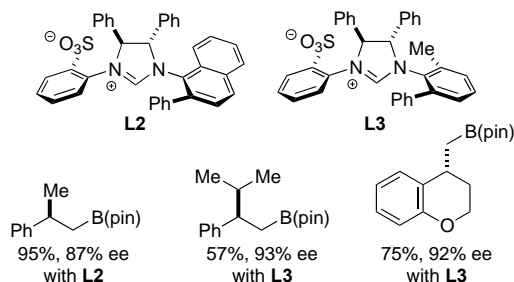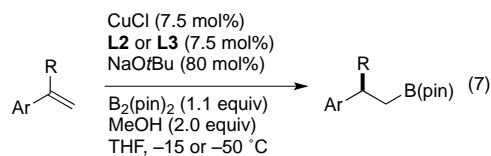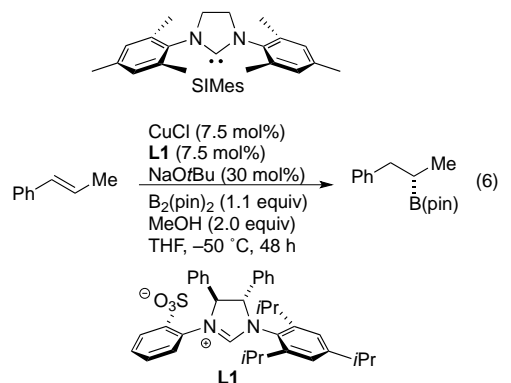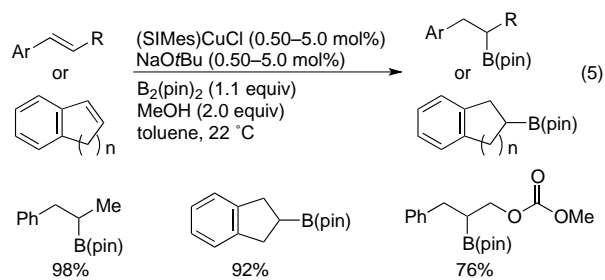
organocopper intermediates, which are generated by the addition of borylcopper to carbon–carbon unsaturated compounds. The plausible reaction mechanism is shown in Scheme 1. *Syn*-addition of borylcopper **1** to the carbon–carbon multiple bond affords organocopper **2** (step a). Subsequently, **2** is protonated by an alcohol, forming the hydroboration product and copper alkoxide **3** (step b). Finally, **3** and diboron react to regenerate **1**, thus completing the catalytic cycle (step c). Yun et al. first discovered that the addition of alcohols significantly accelerated the hydroboration of alkynoates.[19] Since then, studies regarding hydroboration reactions with borylcopper have attracted significant interest.
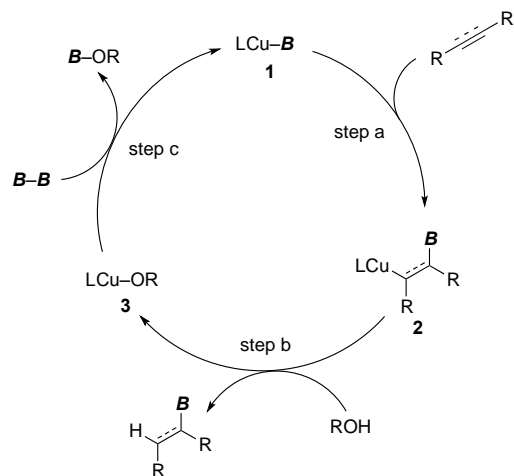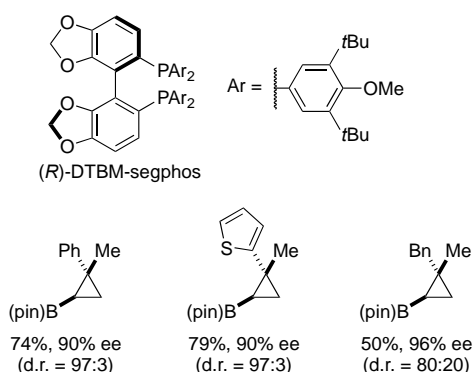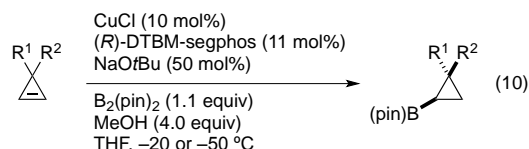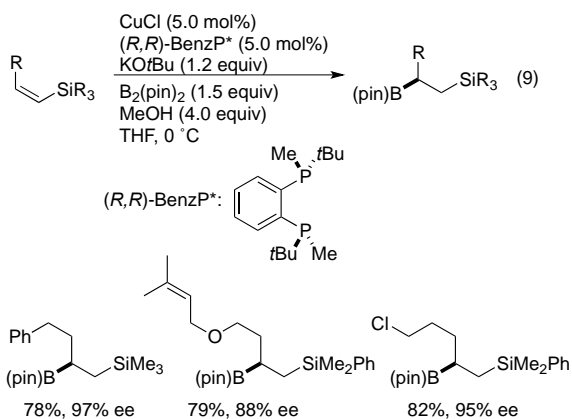
Scheme 1. A plausible reaction mechanism of borylcopper-catalyzed hydroboration

3.2. Hydroboration of alkenes

Hoveyda et al. discovered that the β-selective hydroboration of styrene derivatives proceeded in the presence of a catalytic amount of (SIMes)CuCl (eq. 5).[20] Furthermore, an asymmetric variant was also achieved by using a chiral imidazolinium salt **L1** (eq. 6). They also found the enantioselective hydroboration of 1,1-disubstituted aryl alkenes (eq. 7).[21] The boryl group is introduced at the β-position of the aryl group in a similar fashion as that in the case of styrene derivatives. β-Selective hydroboration is also preferred with alkenylsilanes because of the conjugation of the silicon atom with the alkenes. For example, the asymmetric hydroboration of (*E*)-alkenylsilanes was reported (eq. 8).[22] In the case of an aliphatic alkenylsilane, a β-borylalkylsilane was formed with high regioselectivity, whereas an aromatic alkenylsilane afforded an α-borylalkylsilane selectively. Ito et al. also discovered the β-selective hydroboration of (*Z*)-alkenylsilanes, giving β-borylalkylsilanes in a highly stereoselective manner (eq. 9).[23] Optically active cyclopropylboronates can be synthesized by the enantioselective hydroboration of cyclopropenes (eq. 10).[24]

(9)

(R,R)-BenzP*:

78%, 97% ee   79%, 88% ee   82%, 95% ee

(10)

(R)-DTBM-segphos

74%, 90% ee   79%, 90% ee   50%, 96% ee
(d.r. = 97:3)   (d.r. = 97:3)   (d.r. = 80:20)

The hydroboration of unactivated alkenes such as 1-hexene is facilitated by a CuCl/Xantphos catalytic system, giving a linear product with high regioselectivity (eq. 11).[25] The authors explained the origin of the selectivity by using density functional theory (DFT) calculations (Scheme 2). In the transition state of the addition of borylcopper to the alkene, the carbon atom to which the boryl group adds becomes temporarily pentacoordinated form. Thus, TS_{major} is more favored than TS_{minor} because of less steric repulsion in the former TS.

(11)

91%   7%

Xantphos

Relative G value (kcal/mol) at 298 K, 1.0 atm, gas phase. Electronic energies are shown in parentheses.
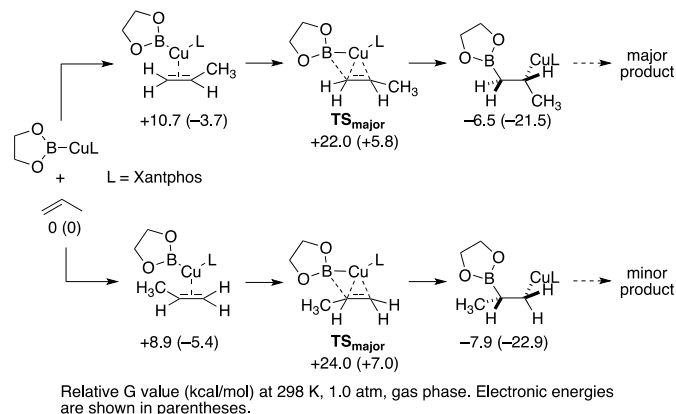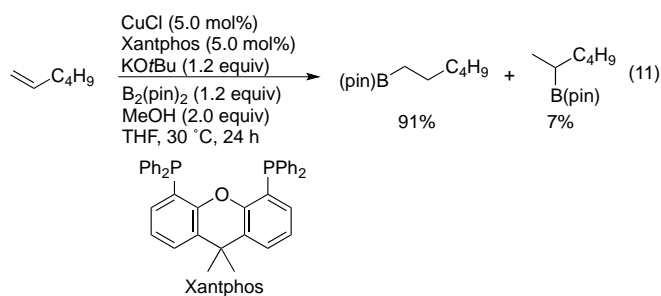
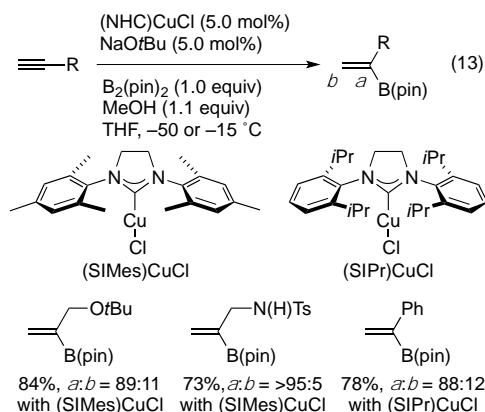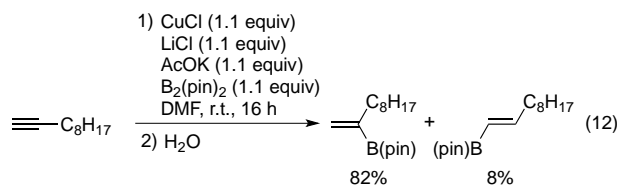**Scheme 2.** DFT calculations relevant to the copper-catalyzed hydroboration of unactivated alkenes

3.3. Hydroboration of alkynes

Miyaura et al. first reported the hydroboration of terminal alkynes using a stoichiometric amount of borylcopper generated from copper(I) chloride with $B_2(pin)_2$ in the presence of AcOK (eq. 12).[13b,c] This reaction proceeds with high branch selectivity, and the products are obtained in good yields. Catalytic hydroboration of terminal alkynes can be achieved by employing NHC copper complexes (eqs. 13 and 14).[26] When employing NHCs having an aryl group on the N atom, such as SIMes and SIPr, α-alkenylboronates are formed preferentially (eq. 13). In contrast, β-products are obtained predominantly with an NHC bearing an adamantyl group on the N atom, SIAd (eq. 14). Yoshida et al. found that α-products could be obtained regioselectively by using an unsymmetrical diboron reagent [(pin)B−B(dan)] in the hydroboration of terminal alkynes (eq. 15).[27]

(12)

82%   8%

(13)

(SIMes)CuCl   (SIPr)CuCl

84%, a:b = 89:11   73%, a:b = >95:5   78%, a:b = 88:12
with (SIMes)CuCl   with (SIMes)CuCl   with (SIPr)CuCl

(SIAd)CuC (5.0 mol%)
NaOtBu (5.0 mol%)
B$_2$(pin)$_2$ (1.0 equiv)
MeOH (1.1 equiv)
THF, 22 °C

(14)

(SIAd)CuCl

80%, a:b = 12:88   70%, a:b = 13:87   81%, a:b = <2:>98

(SIPr)CuCl (5.0 mol%)
NaOtBu (5.0 mol%)
(pin)B–B(dan) (1.2 equiv)
MeOH (3.0 equiv)
THF, 50 °C

(15)

(pin)B–B(dan):

81%, b:a = >99:1   99%, b:a = >99:1   99%, b:a = >99:1
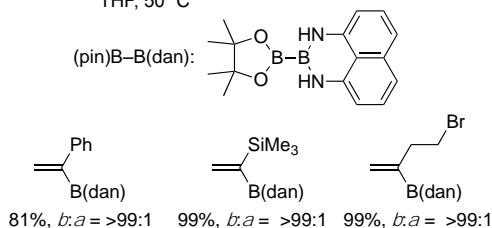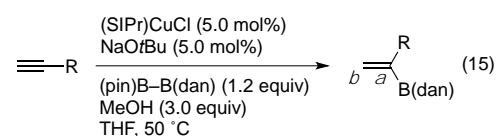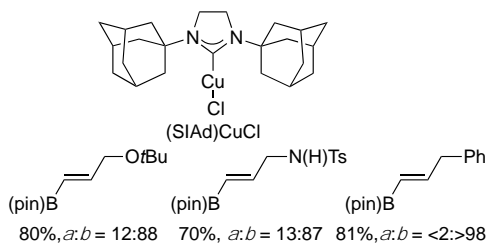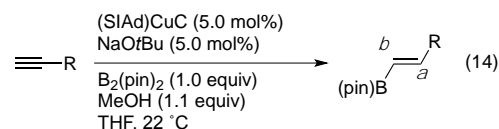
Two consecutive hydroborations of terminal alkynes afford vicinal diboronates (eq. 16).[28] The reaction proceeds enantioselectively, when using an optically active ligand **L1**. Terminal alkenes are intact under the reaction conditions, indicating that *in situ* formed β-borylalkenes are more reactive than simple terminal alkenes.

CuCl (5.0 mol%)
L1 (5.0 mol%)
NaOtBu (20 mol%)
B$_2$(pin)$_2$ (2.1 equiv)
MeOH (3.0 equiv)
THF, −15 °C

(16)

L1

93%, 89% ee   61%, 95% ee   69%, 89% ee
with 7.5 mol% catalyst at 0 °C
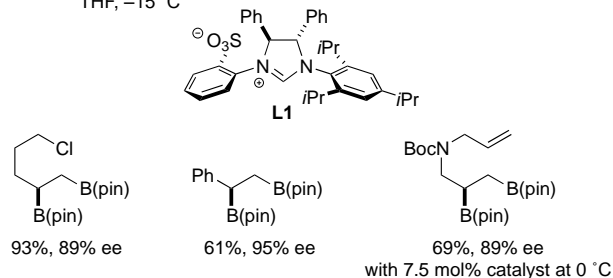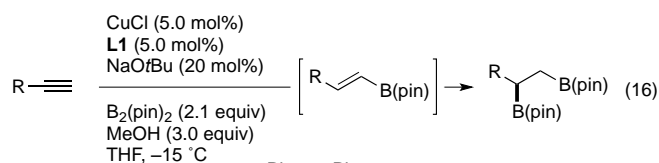
Yun et al. reported that a copper complex with 1,3-dimethylimidazoline-2-thiones (IMS) could be utilized in the regioselective hydroboration of unsymmetrical internal alkynes containing an aryl group (eq. 17).[29] Unfortunatel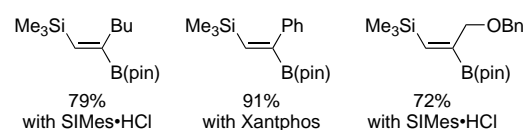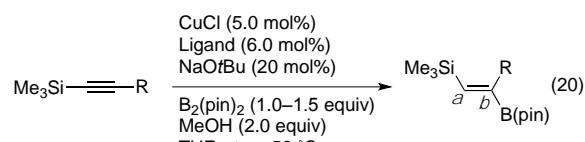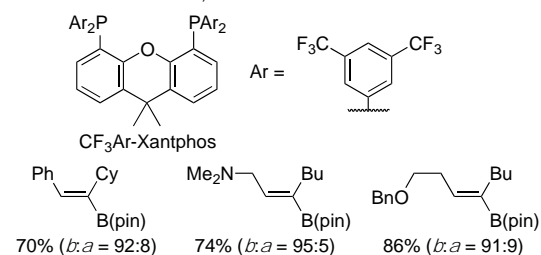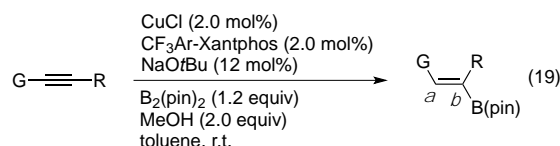y, this system is quite sensitive to steric effects, as switching from a methyl group to an ethyl group results in a significant decrease in the yield. This problem is overcome by employing tri(*para*-tolyl)phosphine [P(*p*-tol)$_3$] as a ligand (eq. 18).[30] A bulky bidentate phosphine ligand is also effective for regioselective hydroboration of aryl-substituted internal alkynes (eq. 19).[31] Furthermore, the catalytic system is found to be effective for the regioselective hydroboration of other internal alkynes bearing a propargyl ether, homopropargyl ether, or propargyl amine moiety. Alkynylsilanes are good substrates for β-selective hydroboration (eq. 20).[32] Alkyl-substituted alkynylsilanes as well as those bearing aryl groups or propargyl ether moieties are effective for the reaction.

(IMS)$_2$CuCl (5.0 mol%)
NaOtBu (20 mol%)
B$_2$(pin)$_2$ (1.1 equiv)
MeOH (2.0 equiv)
THF, r.t.

(17)

(IMS)$_2$CuCl

85%   53%   30%

CuCl (5.0 mol%)
P(*p*-tolyl)$_3$ (6.0 mol%)
NaOtBu (20 mol%)
B$_2$(pin)$_2$ (1.1 equiv)
MeOH (2.0 equiv)
THF, r.t.

(18)

90%   89%   89%

CuCl (2.0 mol%)
CF$_3$Ar-Xantphos (2.0 mol%)
NaOtBu (12 mol%)
B$_2$(pin)$_2$ (1.2 equiv)
MeOH (2.0 equiv)
toluene, r.t.

(19)

Ar =

CF$_3$Ar-Xantphos

70% (b:a = 92:8)   74% (b:a = 95:5)   86% (b:a = 91:9)

CuCl (5.0 mol%)
Ligand (6.0 mol%)
NaOtBu (20 mol%)
B$_2$(pin)$_2$ (1.0–1.5 equiv)
MeOH (2.0 equiv)
THF, r.t. or 50 °C

(20)

79%   91%   72%
with SIMes•HCl   with Xantphos   with SIMes•HCl

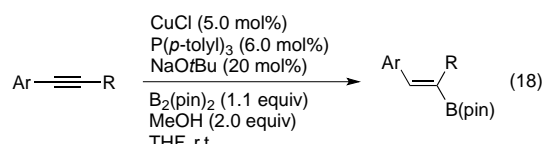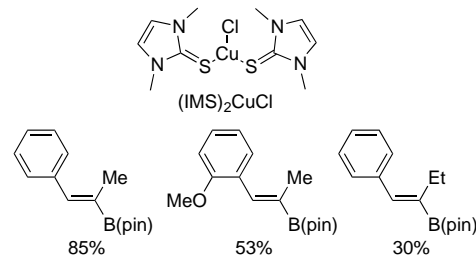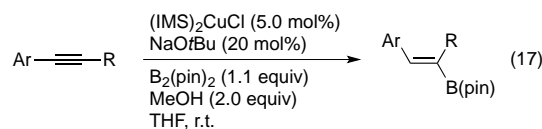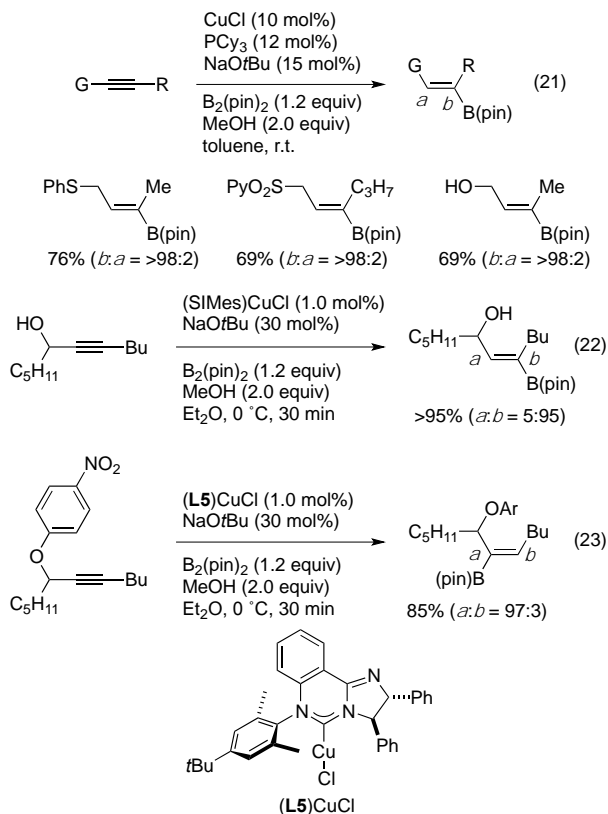The β-selective hydroboration of alkynes bearing a heteroatom at the propargyl position is achieved by using a CuCl/PCy$_3$ catalyst system (eq. 21).[33] The DFT calculations showed that the regioselectivity of this reaction resulted in the stabilization of the transition state of the β–addition reaction with a heteroatom. McQuade et al. reported the regioselective hydroboration of propargyl alcohol derivatives.[34] In the case of alkynes bearing an OH group, β-selective hydroboration occurs when using (SIMes)CuCl as a catalyst (eq. 22). In contrast, alkynes bearing *p*-nitrophenyl moiety afford α-hydroborylated products in a highly regioselective manner by employing (**L5**)CuCl (eq. 23).

CuCl (10 mol%)
PCy₃ (12 mol%)
NaOtBu (15 mol%)

G≡R $\xrightarrow{}$

B₂(pin)₂ (1.2 equiv)
MeOH (2.0 equiv)
toluene, r.t.

(21)

PhS, Me, B(pin)
76% (b:a = >98:2)

PyO₂S, C₃H₇, B(pin)
69% (b:a = >98:2)

HO, Me, B(pin)
69% (b:a = >98:2)

(SIMes)CuCl (1.0 mol%)
NaOtBu (30 mol%)

HO, C₅H₁₁ ≡ Bu $\xrightarrow{}$

B₂(pin)₂ (1.2 equiv)
MeOH (2.0 equiv)
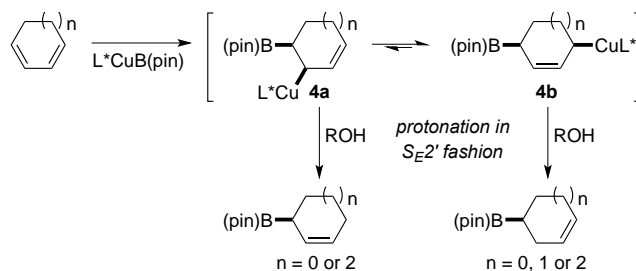Et₂O, 0 °C, 30 min

C₅H₁₁, OH, Bu, B(pin) (22)
>95% (a:b = 5:95)

(L5)CuCl (1.0 mol%)
NaOtBu (30 mol%)

[4-NO₂-phenyl-O-CH(C₅H₁₁)≡Bu] $\xrightarrow{}$

B₂(pin)₂ (1.2 equiv)
MeOH (2.0 equiv)
Et₂O, 0 °C, 30 min

C₅H₁₁, OAr, Bu, (pin)B (23)
85% (a:b = 97:3)

(L5)CuCl
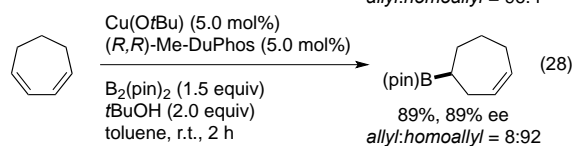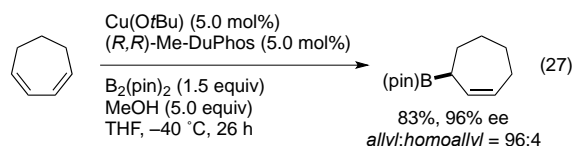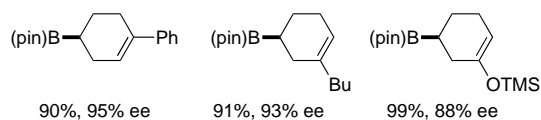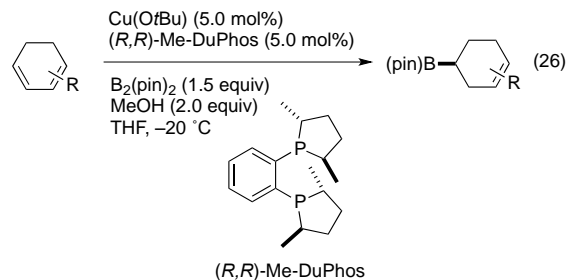
Highly selective hydroboration of 1,3-enynes has been reported by Ito and co-workers.[35] When PPh₃ is utilized as the ligand, hydroboration occurs at the alkyne site (eq. 24). However, when Xantphos is used as the ligand, the reaction takes place selectively at the alkene site (eq. 25). Presently, mechanism of this interesting regioselectivity is not well understood.
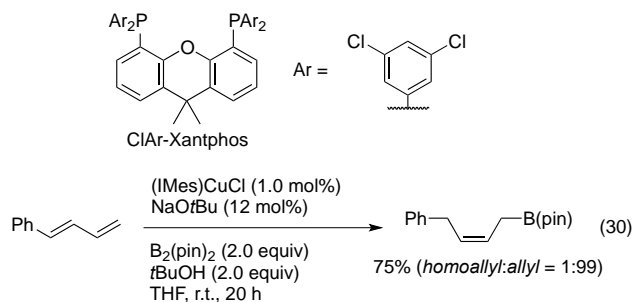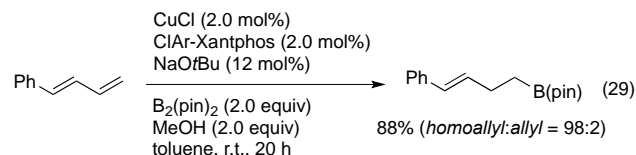
Cu(OtBu) (5.0 mol%)
PPh₃ (5.0 mol%)

Me≡≡Bu $\xrightarrow{}$

B₂(pin)₂ (1.5 equiv)
MeOH (2.0 equiv)
toluene, r.t., 2 h

Me, B(pin), Bu (24)
66%

Cu(OtBu) (5.0 mol%)
Xantphos (5.0 mol%)

Me≡≡Bu $\xrightarrow{}$

B₂(pin)₂ (1.5 equiv)
MeOH (2.0 equiv)
toluene, r.t., 2 h

Me, B(pin), Bu (25)
58%
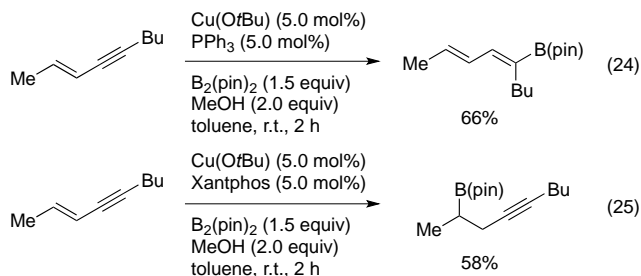
3.4. Hydroboration of 1,3-dienes and allenes

Enantioselective hydroboration of 1,3-dienes is accomplished by using a copper catalyst bearing (*R,R*)-Me-Duphos as the ligand, giving optically active homoallylboronates in high yields (eq. 26).[36] In addition, in the case of cycloheptadiene, it is possible to obtain an allylboronate or a homoallylboronate depending on the choice of the solvent and alcohol (eqs. 27 and 28). The proposed reaction mechanism is depicted in Scheme 3. At low temperature, a kinetically generated allylcopper **4a** through the addition of borylcopper to 1,3-dienes is protonated quickly by MeOH in the S_E2' fashion, giving an allylboronate. On the other hand, at room temperature, thermodynamically stable allylcopper **4b** is formed via the isomerization of **4a**, and is protonated slowly by bulkier *t*BuOH in the same fashion to afford a homoallylboronate. We reported the regioselective hydroboration of 1-phenyl-1,3-butadiene.[15] A homoallylboronate is selectively obtained using a bulky bidentate phosphine ligand (eq. 29). In contrast, an allylboronate is selectively formed in high regio- and stereoselectivities when (IMes)CuCl is used as the catalyst (eq. 30).

Cu(OtBu) (5.0 mol%)
(*R,R*)-Me-DuPhos (5.0 mol%)

$\xrightarrow{}$ (pin)B, R (26)

B₂(pin)₂ (1.5 equiv)
MeOH (2.0 equiv)
THF, −20 °C

(*R,R*)-Me-DuPhos

(pin)B—Ph
90%, 95% ee

(pin)B, Bu
91%, 93% ee

(pin)B, OTMS
99%, 88% ee

Cu(OtBu) (5.0 mol%)
(*R,R*)-Me-DuPhos (5.0 mol%)

$\xrightarrow{}$ (pin)B (27)

B₂(pin)₂ (1.5 equiv)
MeOH (5.0 equiv)
THF, −40 °C, 26 h

83%, 96% ee
allyl:homoallyl = 96:4

Cu(OtBu) (5.0 mol%)
(*R,R*)-Me-DuPhos (5.0 mol%)

$\xrightarrow{}$ (pin)B (28)

B₂(pin)₂ (1.5 equiv)
*t*BuOH (2.0 equiv)
toluene, r.t., 2 h

89%, 89% ee
allyl:homoallyl = 8:92

$\xrightarrow{L^*CuB(pin)}$ [(pin)B, L*Cu **4a** ⇌ (pin)B, CuL* **4b**]

↓ROH   protonation in S_E2' fashion   ↓ROH

(pin)B, n = 0 or 2   (pin)B, n = 0, 1 or 2

Scheme 3. A plausible reaction mechanism of the copper-catalyzed hydroboration of 1,3-dienes

CuCl (2.0 mol%)
ClAr-Xantphos (2.0 mol%)
NaOtBu (12 mol%)

Ph $\xrightarrow{}$

B₂(pin)₂ (2.0 equiv)
MeOH (2.0 equiv)
toluene, r.t., 20 h

Ph, B(pin) (29)
88% (*homoallyl:allyl* = 98:2)

ClAr-Xantphos   Ar = [3,5-Cl₂-phenyl]

(IMes)CuCl (1.0 mol%)
NaOtBu (12 mol%)

Ph $\xrightarrow{}$

B₂(pin)₂ (2.0 equiv)
*t*BuOH (2.0 equiv)
THF, r.t., 20 h

Ph, B(pin) (30)
75% (*homoallyl:allyl* = 1:99)

Hoveyda et al., Ma et al., and we reported the regioselective hydroboration of allenes.[37] Disubstituted alkenylboronates are obtained as the main products using sterically less demanding ligands (eq. 31), whereas monosubstituted alkenylboronates are obtained as the main products with bulky ligands (eq. 32). We observed the selective formation of an allylcopper from borylcopper and an allene (eq. 3, *vide supra*), suggesting the formation of the desired product by the protonation of allylcopper with an alcohol. Hoveyda and co-workers expanded the reaction to the enantioselective variant (eq. 33).[38]

R ⟶ R–B(pin)   (31)

Cu cat.
B$_2$(pin)$_2$, ROH
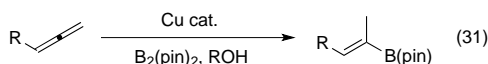
Ma's conditions: CuCl (5.0 mol%), P(C$_6$H$_4$OMe-p)$_3$ (6.0 mol%), NaOtBu (20 mol%)
B$_2$(pin)$_2$ (1.2 equiv), MeOH (2.0 equiv)
THF, r.t.

Tsuji's conditions: (^{Me}IMes)CuCl (2.0 mol%), NaOtBu (12 mol%)
B$_2$(pin)$_2$ (1.1 equiv), MeOH (8.0 equiv)
toluene, −20 °C

Hoveyda's conditons: CuCl (5.0 mol%), **L6** (5.0 mol%), NaOtBu (40 mol%)
B$_2$(pin)$_2$ (1.1 equiv), MeOH (6.0 equiv)
THF, 22 °C

(^{Me}IMes)CuCl

L6

R ⟶ R–B(pin)   (32)

Cu cat.
B$_2$(pin)$_2$, ROH
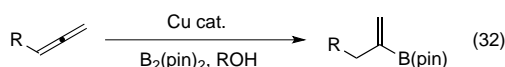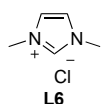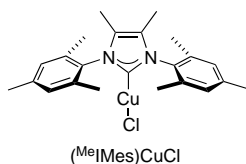
Ma's conditions: CuCl (5.0 mol%), BIPHEP (5.0 mol%), NaOtBu (20 mol%)
B$_2$(pin)$_2$ (1.2 equiv), MeOH (2.0 equiv)
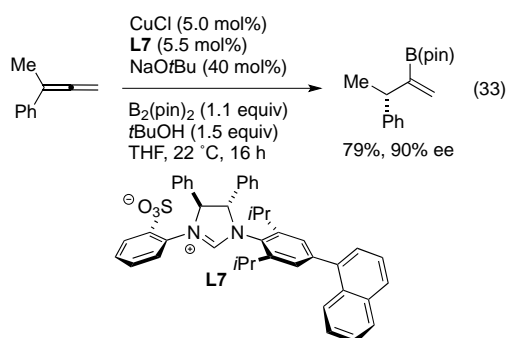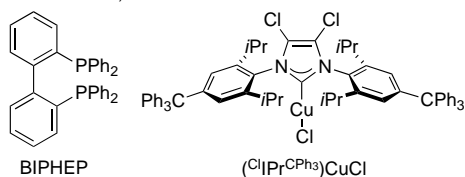THF, r.t.

Tsuji's conditions: (^{Cl}IPr^{CPh3})CuCl (2.0 mol%), NaOtBu (12 mol%)
B$_2$(pin)$_2$ (1.2 equiv), MeOH (2.0 equiv)
THF, r.t.

Hoveyda's conditons: CuCl (5.0 mol%), IPr •HCl (5.0 mol%), NaOtBu (40 mol%)
B$_2$(pin)$_2$ (1.1 equiv), MeOH (6.0 equiv)
THF, 22 °C

BIPHEP   (^{Cl}IPr^{CPh3})CuCl

Me/Ph ⟶ B(pin) product   (33)

CuCl (5.0 mol%)
L7 (5.5 mol%)
NaOtBu (40 mol%)

B$_2$(pin)$_2$ (1.1 equiv)
tBuOH (1.5 equiv)
THF, 22 °C, 16 h

79%, 90% ee

L7
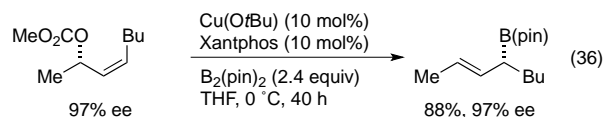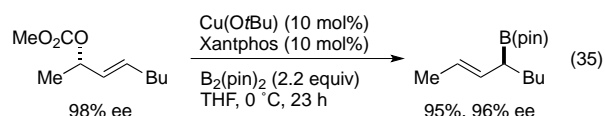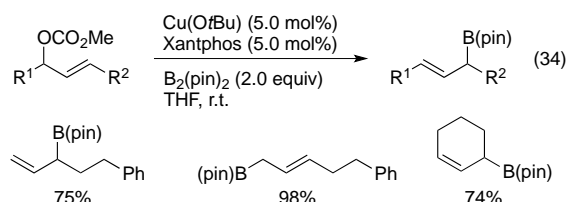
4. Boryl substitution

4.1. Mechanism

The γ-selective boryl substitution occurs with carbon–carbon unsaturated compounds bearing an appropriate leaving group at the α-position of carbon–carbon unsaturated moieties. The general reaction mechanism for this transformation is shown in Scheme 4. The borylcopper **1** adds to the carbon–carbon multiple bond, resulting in the formation of an organocopper intermediate **4** (step a). Subsequently, the β-elimination of the copper and the leaving group from **4** affords the γ–substituted product (step b).
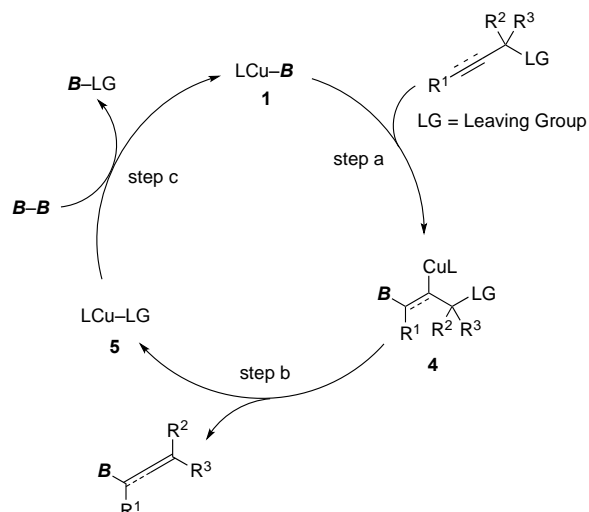
Scheme 4. A plausible mechanism for γ-substitution with a borylcopper complex

4.2. Boryl substitution of allylic alcohol derivatives

A copper-catalyzed γ-selective substitution reaction of allylic carbonates with B$_2$(pin)$_2$ to give various allylboronates was reported (eq. 34).[39] When employing optically enriched allylic carbonates, stereospecific substitution reactions occur (eqs. 35 and 36). A plausible mechanism is depicted in Scheme 5. *Syn*-addition of borylcopper to a carbon–carbon double bond occurs from the opposite side of the carbonate group in a conformation to avoid allylic 1,3-strain, and alkylcopper intermediates **4a** or **4a'** are afforded. Subsequent *anti*-β-elimination of copper and the carbonate group from **4a** or **4a'** produces allylboronates in a stereoselective manner. Tortosa and co-workers applied the copper-catalyzed γ-selective substitution reaction to selective synthesis of *syn* and *anti*-1,4-diols (eqs. 37 and 38).[40] They showed copper-catalyzed borylation of allylic epoxides followed by oxidation of the boryl group afforded *syn* and *anti*-1,4-diols in a diastereoselective manner.

R^1–OCO$_2$Me–R^2 ⟶ R^1–B(pin)–R^2 (34)

Cu(OtBu) (5.0 mol%)
Xantphos (5.0 mol%)
B$_2$(pin)$_2$ (2.0 equiv)
THF, r.t.

75%   98%   74%

MeO$_2$CO–Me–Bu ⟶ Me–B(pin)–Bu   (35)

Cu(OtBu) (10 mol%)
Xantphos (10 mol%)
B$_2$(pin)$_2$ (2.2 equiv)
THF, 0 °C, 23 h

98% ee   95%, 96% ee

MeO$_2$CO–Me–Bu ⟶ Me–B(pin)–Bu   (36)

Cu(OtBu) (10 mol%)
Xantphos (10 mol%)
B$_2$(pin)$_2$ (2.4 equiv)
THF, 0 °C, 40 h

97% ee   88%, 97% ee
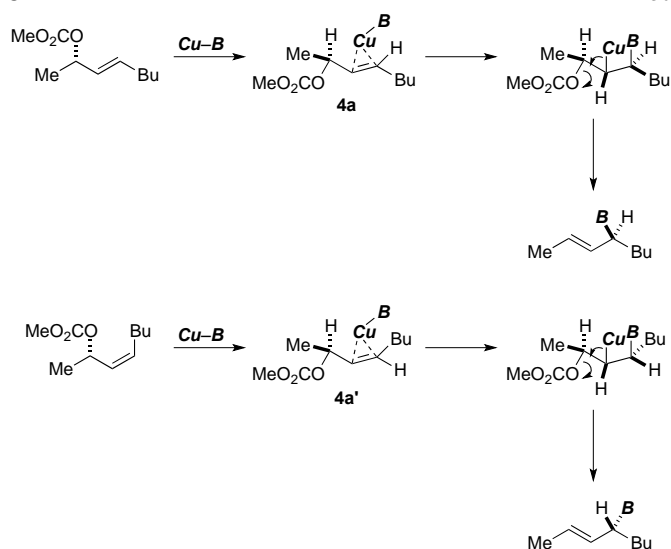
Scheme 5. A plausible mechanism of γ-selective boryl substitution of allylic carbonates
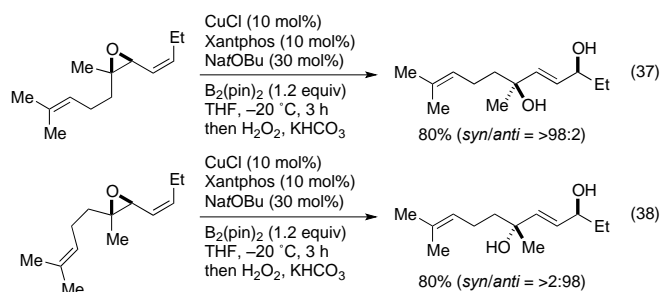
Ito, Sawamura, and co-workers developed the enantioselective γ–substitution reaction of allylic carbonates with diboron to give optically active allylboronates (eq. 39).[41] The reaction occurs with high enantioselectivities when using (Z)-allylic carbonates; however, the enantioselectivity decreases when (E)-allylic carbonates are used. Hoveyda et al. achieved the highly enantioselective γ–substitution reaction of more readily available (E)-allylic carbonates with diboron (eq. 40).[42] The catalytic system is also effective for the reaction of allylic carbonates bearing a trisubstituted alkene moiety. McQuade et al. accomplished the enantioselective γ–substitution reaction of allylic aryl ethers with diboron, giving optically active allylboronates in a stereoconvergent manner (eq. 41),[43] whereas in the studies by Ito et al. and Hoveyda et al., the reaction proceeds in a stereospecific manner. Recently, the enantioselective γ–substitution reaction of allylic acetals has been developed (eq. 42).[44] The reaction was applied to the diastereoselective preparation of 1,2-diol derivatives (eq. 43).
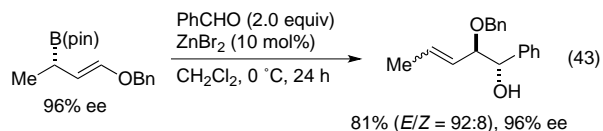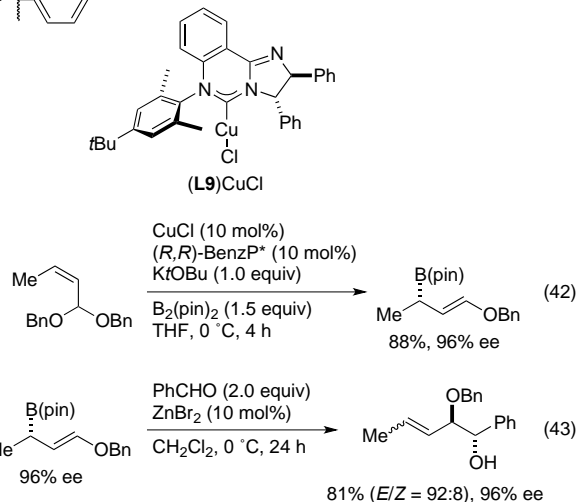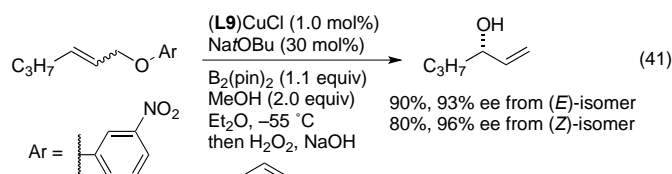
Ito et al. reported the copper-catalyzed direct enantioconvergent borylation of racemic allylic ethers without racemization or symmetrization, forming optically active cyclic allylboronates (eq. 44).[45] The proposed reaction mechanism is shown in Scheme 6. In the case of (S)-isomers, a substitution proceeds through the anti-S_N2' mechanism. In contrast, a substitution reaction occurs via the syn-S_N2' mechanism on the (R)-isomers.

Scheme 6. A plausible reaction mechanism of the copper-catalyzed direct enantioconvergent borylation

4.3. Boryl substitution of propargylic alcohol derivatives

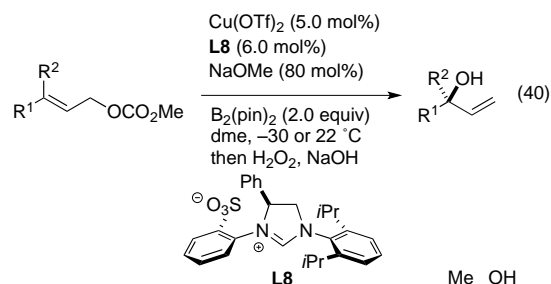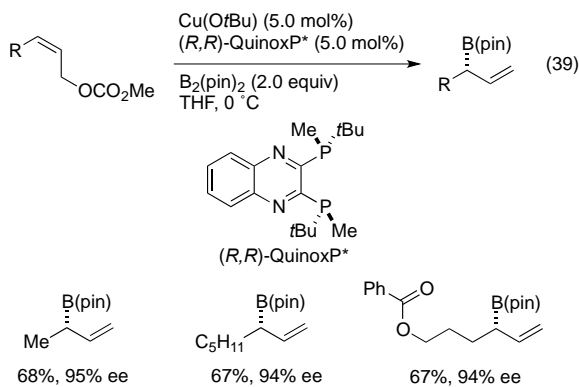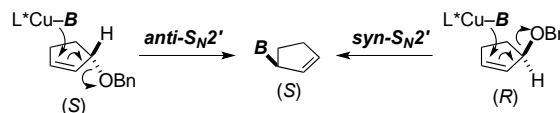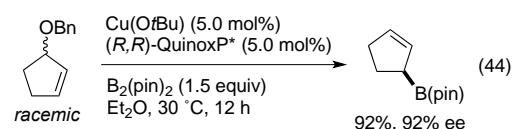Multi-substituted allenylboronates can be accessed by the copper-catalyzed substitution reaction of propargylic carbonates with diboron (eq. 45).[46] The reaction proceeds in a similar mechanism as that of the copper-catalyzed γ-selective substitution reaction of allylic carbonates with $B_2(pin)_2$. A stereospecific boryl substitution of an optically active propargylic carbonate supports the proposed mechanism (eq. 46).

(45)

Me₂C=... structures with B(pin)

87%   75%   55%

(46)

97% ee

60%, >96% ee
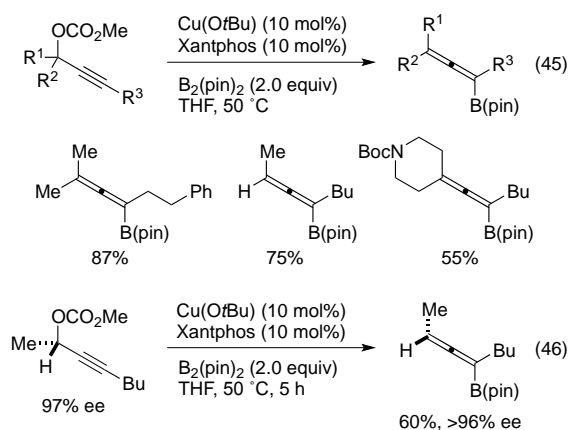
4.4. Boryl substitution of α-alkoxy allenes

We demonstrated the efficient preparation of 2-boryl-1,3-butadiene derivatives via copper-catalyzed borylation of α-alkoxy allenes with $B_2(pin)_2$ (eq. 47).[47] The reaction mechanism is proposed in Scheme 7. The first step involves the addition of borylcopper to an allene, resulting in the formation of an allylcopper species, which may exist as an equilibrium mixture of the two isomers **A** and **B**. The subsequent β–elimination of Cu–OBn from the allylcopper **A** produces the desired product selectively.

(47)

(IPr^CPh3)CuCl

85%   71%   99%   63% (E/Z = 96:4)
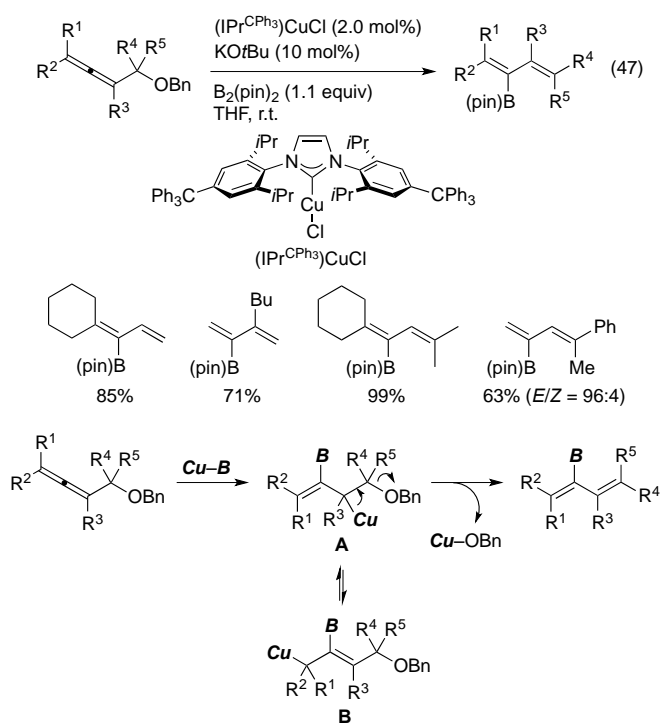
Scheme 7. A possible reaction pathway for the copper-catalyzed borylation of α-alkoxy allenes with $B_2(pin)_2$

5. Carboboration

5.1. Mechanism

Carboboration that involves simultaneous C–B and C–C bond formations can be achieved by using carbon electrophiles. A typical reaction mechanism is shown in Scheme 8. Borylcopper species **1** generated *in situ* adds to carbon–carbon unsaturated compound, giving an organocopper intermediate **2** (step a). **2** reacts with a carbon electrophile in the presence of a suitable base (typically alkoxide) to generate the carboboration product and a

copper alkoxide **3** (step b). Finally, **3** reacts with diboron to regenerate borylcopper **1** and the catalytic cycle is closed (step c).

Scheme 8. A mechanism for the copper-catalyzed carboboration

5.2. Carboboration of alkynes

A borylcyanocuprate reacts with an electron-deficient alkyne to afford the corresponding alkenylcopper intermediate.[48] Then, the carboboration reaction is achieved by trapping the intermediate with a carbon electrophile such as benzoyl chloride or allyl bromide (eq. 48). Tortsa et al.[49] and Yoshida et al.[50]
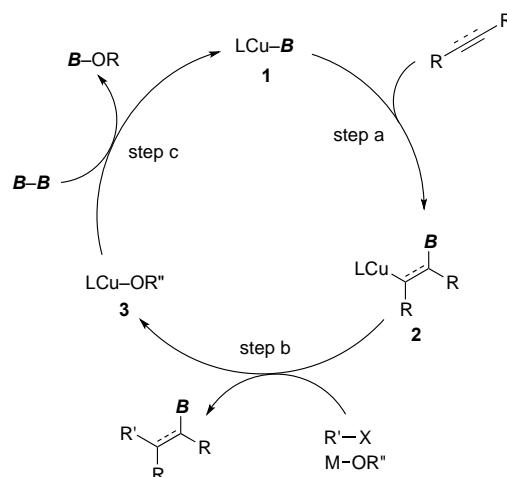
(48)
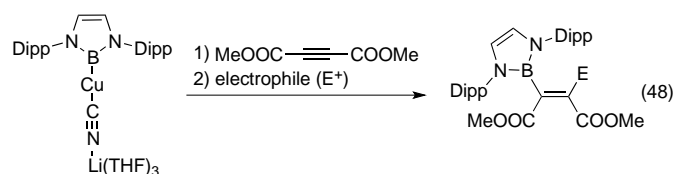
independently reported the copper-catalyzed alkylboration of alkynes with alkyl halides as electrophiles. These reactions involve β-borylalkenylcopper as a key intermediate. In Tortsa's reaction, phenylacetylene reacts with methyl iodide as a carbon electrophile in the presence of B_2pin_2 and CuCl/Xantphos as the catalyst (eq. 49). This reaction proceeds in THF at room temperature, and the corresponding alkylborated products are obtained in good to high yields. In Yoshida's study, carboboration of diphenylacetylene with benzyl bromide as an electrophile occurs in the presence of the $Cu(OAc)_2$/PCy₃ catalyst (eq. 50). Although the yield is moderate when employing 1-phenyl-1-propyne as a substrate, the reaction proceeds regioselectively. Brown et al. found that the arylboration of internal alkynes occurred by using $B_2(pin)_2$ and an aryl iodide (eq. 51).[51] Various alkynes are converted to the corresponding trisubstituted alkenylboronates in good to high yields. The borylative cyclization of cyclohexadiene-containing 1,6-enynes was reported (eq. 52).[52] The reaction proceeds selectively on employing a phosphoramidite as a ligand, giving bicyclic products with an alkenylboronate moiety. Ito et al. reported intramolecular alkylboration of silyl-substituted alkynes (eq 53). The reaction affords silyl-substituted alkenylboronates in regio- and stereoselective manners.[53]

$$
\text{G}\!-\!\!\equiv\!\!-\text{R} \quad \xrightarrow[\substack{\text{B}_2(\text{pin})_2\ (1.1\ \text{equiv})\\ \text{NaO}t\text{Bu}\ (1.1\ \text{equiv})\\ \text{THF, r.t.}}]{\substack{\text{CuCl (10 mol\%)}\\ \text{Xantphos (10 mol\%)}\\ \text{R'-X (4.0 equiv)}}} \quad (49)
$$

74% 60% 50%

$$
\text{G}\!-\!\!\equiv\!\!-\text{R} \quad \xrightarrow[\substack{\text{B}_2(\text{pin})_2\ (1.3\ \text{equiv})\\ \text{NaO}t\text{Bu}\ (1.5\ \text{equiv})\\ \text{DMF, 50 °C}}]{\substack{\text{Cu(OAc)}_2\ (2.0\ \text{mol\%})\\ \text{PCy}_3\ (7.0\ \text{mol\%})\\ \text{R'-X (3.0 equiv)}}} \quad (50)
$$

67% 60% (b:a = >99:1) 46% (b:a = 80:20)

$$
\text{G}\!-\!\!\equiv\!\!-\text{R} \quad \xrightarrow[\substack{\text{B}_2(\text{pin})_2\ (1.5\ \text{equiv})\\ \text{NaO}t\text{Bu}\ (2\ \text{equiv})\\ \text{toluene, 80 °C}}]{\substack{\text{CuCl(PCy}_3)\ (10\ \text{mol\%})\\ \text{Ar-I (1.5 equiv)}}} \quad (51)
$$

91% 55% 62% (b:a = 10:1)

$$
\xrightarrow[\substack{\text{B}_2(\text{pin})_2\ (1.1\ \text{equiv})\\ \text{MeOH (2.0 equiv)}\\ \text{THF, r.t.}}]{\substack{\text{CuCl (10 mol\%)}\\ (S,R,R)\text{-L10 (12 mol\%)}\\ \text{NaO}t\text{Bu (15 mol\%)}}} \quad (52)
$$

(S,R,R)-L10

70%, 94%ee 65%, 92%ee 65%, 90%ee

$$
\xrightarrow[\substack{\text{B}_2(\text{pin})_2\ (1.2\ \text{equiv})\\ \text{THF, 50 °C}}]{\substack{\text{CuCl (5.0 mol\%)}\\ \text{IMes•HCl (5.0 mol\%)}\\ \text{KO}t\text{Bu (1.2 equiv)}}} \quad (53)
$$

86% 80% 42%

The copper-catalyzed boracarboxylation of alkynes was reported by Hou et al.[18] The reaction progresses under an atmospheric pressure of carbon dioxide in the presence of a NHC copper catalyst, B_2pin_2, and a stoichiometric amount of a base (eq. 54). The products are boralactones as shown in eq. 54 and isolated as lithium salts. Furthermore, they synthesized and isolated copper

complexes relevant to the copper catalysis and characterized them by X-ray structural analysis (Scheme 9).

$$
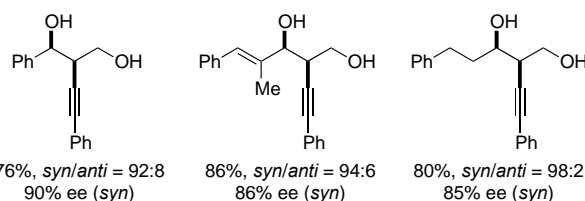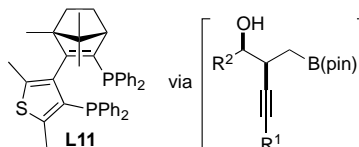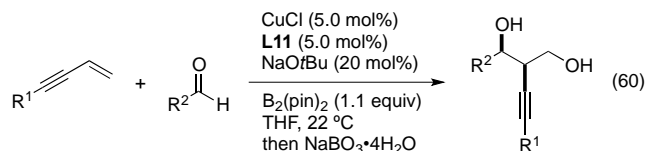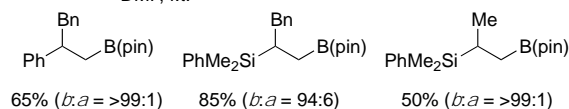\text{G}\!-\!\!\equiv\!\!-\text{R} \quad \xrightarrow[\substack{\text{B}_2(\text{pin})_2\ (1.3\ \text{equiv})\\ \text{LiO}t\text{Bu}\ (1.1\ \text{equiv})\\ \text{THF, 80 °C}}]{\substack{\text{(IMes)CuCl (2.5 mol\%)}\\ \text{CO}_2\ (1\ \text{atm})}} \quad (53)
$$

81% 83% 71%

(IPr)Cu(OtBu)

$$
\text{(IPr)Cu-O}t\text{Bu} \xrightarrow[\substack{\text{hexane}\\ \text{r.t.}}]{\text{B}_2\text{pin}_2} \mathbf{1a} \xrightarrow[\substack{\text{hexane}\\ \text{r.t.}}]{\text{Ph}-\!\!\equiv\!\!-\text{Ph}} \mathbf{2c}
$$

$$
\xrightarrow[\substack{\text{benzene}\\ \text{r.t.}}]{\text{CO}_2} \qquad \xrightarrow[\substack{\text{THF}\\ \text{r.t.}}]{t\text{BuOLi}} \text{(IPr)Cu(O}t\text{Bu)}
$$
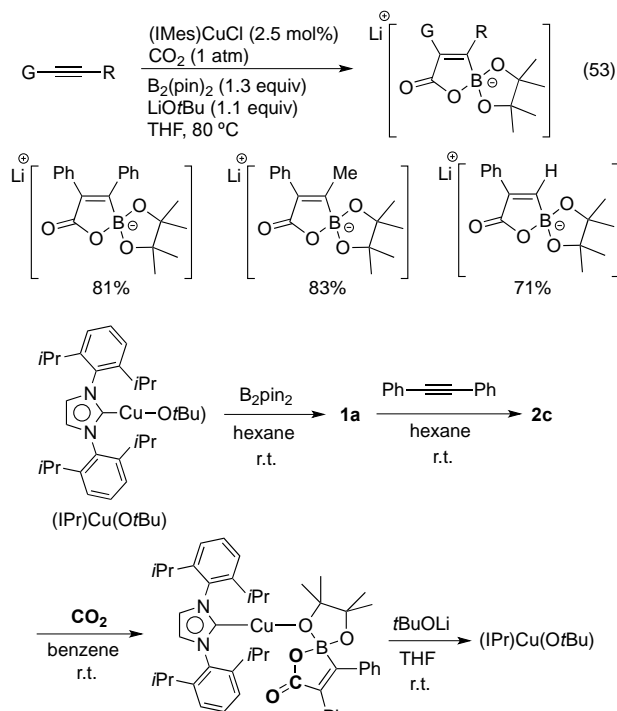
Scheme 9. Stoichiometric reactions relevant to the boracarboxylation of alkynes

5.3. Carboboration of alkenes

The intramolecular enantioselective alkylboration of silyl-substituted allylic carbonates with $B_2(\text{pin})_2$ occurs in the presence of a copper catalyst (eq. 55).[54] The reaction affords optically active cyclopropane derivatives bearing boron and silicon functionalities. When using (R,R)-QuinoxP* as a ligand, a substrate with the trimethylsilyl group affords the corresponding cyclopropane in a good yield with high selectivity. With a dimethylphenylsilyl substituted substrate, (R,R)-segphos is found to be the best ligand. A similar procedure is effective for the stereospecific synthesis of silyl-substituted cyclobutylboronates (eqs. 56 and 57).[55] A (Z)-substrate gives the *trans*-product selectively. In contrast, the *cis*-product is obtained from the (E)-substrate. The reaction also affords cyclopentane derivatives in good yields, whereas cyclohexanes are not obtained. The same group found that *trans*-aryl-substituted cyclopropylboronates were obtained by the reaction of (Z)-allylic phosphates and diboron in the presence of a (R,R)-iPr-Duphos ligated copper catalyst (eq. 58).[56] Recently, the borylative *exo*-cyclization of alkenyl halides has been developed (eq. 59).[25] The reaction involves the regioselective borylcupration of a terminal alkene, followed by the intramolecular cyclization. Various three-, four-, and five-membered rings are constructed in high yields from the corresponding alkenyl halides.

R₃Si—OCO₂Me → Cu(OtBu) (5.0 mol%), Chiral Ligand (5.5 mol%), B₂(pin)₂ (2.0 equiv), THF, 30 °C → R₃Si cyclopropane B(pin) (1S, 2S) (54)

(R,R)-segphos

Me₃Si cyclopropane B(pin) — 99%, 98% ee with (R,R)-quinoxP*

PhMe₂Si cyclopropane B(pin) — 86%, 97% ee with (R,R)-segphos

PhMe₂Si—OMs (Z)-substrate → CuCl (5.0 mol%), dppp (5.0 mol%), B₂(pin)₂ (2.0 equiv), KOtBu (1.0 equiv), THF, 30 °C → PhMe₂Si cyclobutane B(pin) 74% (trans/cis = 99:1) (55)

PhMe₂Si—OMs (E)-substrate → As above → PhMe₂Si cyclobutane B(pin) 76% (trans/cis = 5:95) (56)

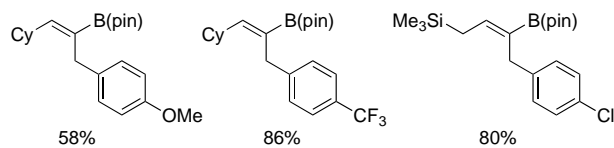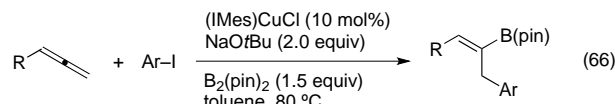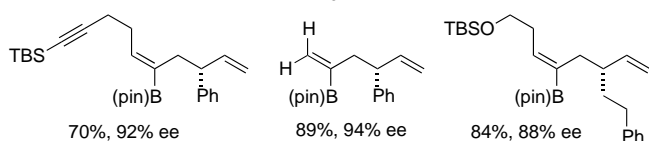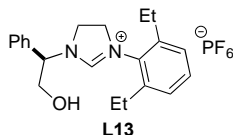Ar—OP(O)(OR)₂ → Cu(OtBu) (5.0 mol%), (R,R)-iPr-DuPhos (6.0 mol%), B₂(pin)₂ (2.0 equiv), KOtBu (1.0 equiv), toluene/THF, 30 °C → Ar cyclopropane B(pin) (1S, 2R) (57)

(R,R)-iPr-DuPhos

89%, 94% ee   70%, 92% ee   54%, 92% ee

allyl-CBr(R²)(R¹) → CuCl (5.0 mol%), Xantphos (5.0 mol%), B₂(pin)₂ (1.2 equiv), KOtBu (1.2 equiv), THF, 30 °C → (pin)B cyclobutane R²R¹ (58)

90%   88%   86%

Yoshida et al. first reported the copper-catalyzed intermolecular carboboration of alkenes, on the basis of their knowledge about alkynes (eq. 60).[50,57] The products are obtained in moderate to high yields employing (SIMes)CuCl as a catalyst. The copper-catalyzed carboboration of 1,3-enynes was also reported employing aldehydes as electrophiles (eq. 61).[58] The reactions progress in highly regio-, diastereo-, and stereoselective manners to afford 1,3-diol derivatives after the oxidation of the boryl group.

R¹—CH=CH₂ → (SIMes)CuCl (2.0 mol%), R²–X (3.0 equiv), B₂(pin)₂ (1.3 equiv), KOtBu (1.5 equiv), DMF, r.t. → R¹(a)(R²)—CH₂(b)—B(pin) (59)

Ph(Bn) B(pin) — 65% (b:a = >99:1)
PhMe₂Si(Bn) B(pin) — 85% (b:a = 94:6)
PhMe₂Si(Me) B(pin) — 50% (b:a = >99:1)

R¹—C≡C—CH=CH₂ + R²CHO → CuCl (5.0 mol%), L11 (5.0 mol%), NaOtBu (20 mol%), B₂(pin)₂ (1.1 equiv), THF, 22 °C, then NaBO₃•4H₂O → R²(OH)—C(CH₂OH)—C≡C—R¹ (60)

L11   via [R²(OH)—C(CH₂B(pin))—C≡C—R¹]

Ph(OH)—C(CH₂OH)—C≡C—Ph — 76%, syn/anti = 92:8, 90% ee (syn)
Ph-CH=C(Me)—C(OH)...(CH₂OH)—C≡C—Ph — 86%, syn/anti = 94:6, 86% ee (syn)
Ph-CH₂CH₂—C(OH)(CH₂OH)—C≡C—Ph — 80%, syn/anti = 98:2, 85% ee (syn)

5.4. Carboboration of allenes

Hoveyda et al. developed asymmetric borylative allylation of aldehydes and ketones by using an allylcopper intermediate generated from the reaction of an allene with diboron in the presence of a suitable copper catalyst (eq. 62).[59] The reaction proceeds in site-selective (>98% γ-selective) and diastereoselective manners; however, the product could be isolated through the conversion of a boron functional group into a hydroxyl group or bromine. We developed the copper-catalyzed borylative allyl–allyl coupling reaction by using allylic phosphates as electrophiles (eq. 63).[60] The reaction involves the formation of a β-borylallylcopper intermediate via borylcupration of an allene followed by a reaction with allylic phosphates. A copper catalyst with the NHC ligand, ICy, is most effective for this reaction, and 1,5-diene derivatives are obtained in high yields and with high selectivities. Furthermore, in the case of allylic phosphates bearing a substituent at α-position, the stereochemistry of products can be controlled by the choice of ligand (eqs. 64 and 65). Hoveyda et al. reported the asymmetric variant (eq. 66).[61] The copper-catalyzed arylboration of allenes is achieved by using aryl iodides as electrophiles (eq. 67).[51] The reaction proceeds in a regioselective manner, giving disubstituted alkenylboronates in high yields.

CuCl (5.0 mol%)
L11 or **L12** (5.0 mol%)
NaO*t*Bu (20 mol%)

NaBO$_3$ 4H$_2$O

ArCOR^2 (1.1 equiv)
B$_2$(pin)$_2$ (1.1 equiv)
THF, 4 or 22 °C

H$_2$O/THF, r.t.

(61)

via

L12

with **L11**
81%, 90% ee
(d.r. = 96:4)

with **L11**
77%, 92% ee
(d.r. = 94:6)

with **L12**
88%, 70% ee
(d.r. = >98:2)

CuCl (10 mol %)
ICy•HBF$_4$ (12 mol %)
KO*t*Bu (1.5 equiv)

B$_2$(pin)$_2$ (1.6 equiv)
THF, 25 °C

(62)

ICy

84%

79%

76%

CuCl (10 mol %)
ICy•HBF$_4$ (12 mol %)
KO*t*Bu (1.5 equiv)

B$_2$(pin)$_2$ (1.6 equiv)
THF, 25 °C, 24 h

(63)

(Z,E)-isomer
65% [(Z,E)/(Z,Z) = 84/16]

(SIMes)CuCl (5.0 mol %)
KO*t*Bu (1.5 equiv)

B$_2$(pin)$_2$ (1.6 equiv)
THF, 25 °C, 24 h

(64)

(Z,Z)-isomer
70% [(Z,E)/(Z,Z) = 4/96]

CuCl (5.0 mol %)
L13 (5.0 mol %)
KO*t*Bu (1.5 equiv)

B$_2$(pin)$_2$ (1.2 equiv)
THF, 4–22 °C

(65)

L13

70%, 92% ee

89%, 94% ee

84%, 88% ee

(IMes)CuCl (10 mol%)
NaO*t*Bu (2.0 equiv)

B$_2$(pin)$_2$ (1.5 equiv)
toluene, 80 °C

(66)

58%

86%

80%

6. Heteroboration

6.1. Mechanism

Replacing carbon electrophiles in the carboboration with heteroatom electrophiles may make it possible to introduce a boron moiety and a heteroatom component simultaneously. A possible reaction mechanism is depicted in Scheme 10. The organocopper **2** is generated by the reaction of borylcopper **1** with the carbon–carbon unsaturated compound (step a). Then, the reaction of **2** with a heteroatom electrophile in the presence of suitable bases affords a heteroboration product and a copper alkoxide **3** (step b). Finally, **3** reacts with diboron to regenerate the borylcopper **1** and the catalytic cycle is closed (step c). Several recent heteroboration reactions are shown below.
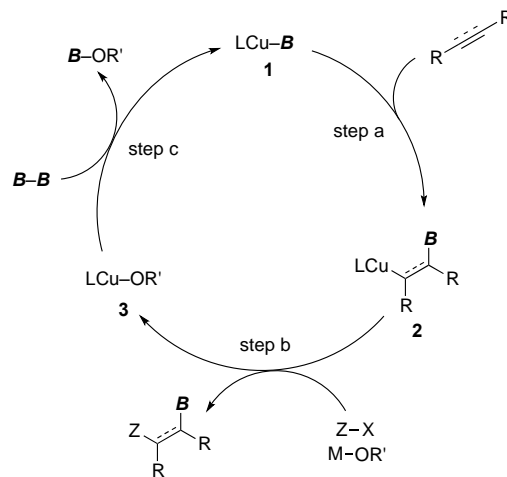
Scheme 10. A mechanism for the copper-catalyzed heteroboration

6.2. Diboration

Diboration of internal alkynes can be accomplished in the presence of the Cu(OAc)$_2$/PCy$_3$ catalyst, giving *cis*-diborylalkenes (eq. 68).[62] A wide variety of products are obtained in good to high yields. 1,2-Diborylbenzene derivatives are also obtained by the diboration of arynes with a similar catalyst system.

Cu(OAc)$_2$ (2.0 mol%)
PCy$_3$ (7.0 mol%)

B$_2$(pin)$_2$ (1.3 equiv)
toluene, 80 °C

(67)

78%

82%

78%

6.3. Stannylboration
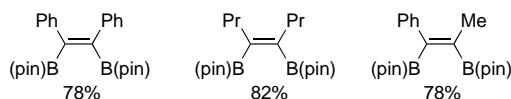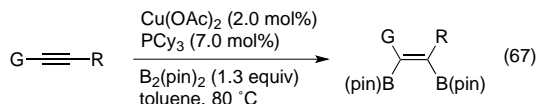
Stannylboration of alkynes occurs stereoselectively in the presence of a copper catalyst, B$_2$(pin)$_2$, and an alkoxy tin compound (eq. 69).[63] The reaction of unsymmetrical internal alkynes such as 1-phenyl-1-propyne proceeds regioselectively and the tin moiety is introduced on the carbon attached to the phenyl

group. These products can be applied to selective cross-coupling reaction by utilizing the difference in reactivity between tin and boron moieties. A synthesis of Tamoxifen was achieved using the present stannylboration as a key step.

$$G\!-\!\!\equiv\!\!-R \quad \xrightarrow[\substack{B_2(pin)_2\ (1.3\ equiv) \\ Bu_3SnOMe\ (1.3\ equiv) \\ toluene,\ r.t.}]{\substack{Cu(OAc)_2\ (2.0\ mol\%) \\ PCy_3\ (7.0\ mol\%)}} \quad (68)$$

87%   71% (b:a = >99:1)   63% (b:a = >93:7)
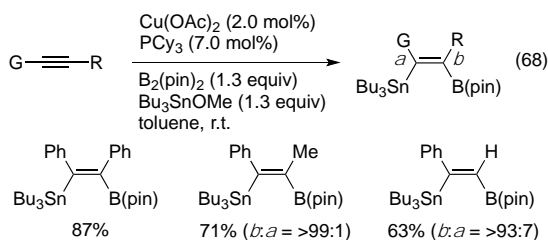
6.4. Aminoboration

Boron and amino functionalities are successfully introduced into styrene derivatives. When *trans-β*-methylstyrene is employed with *O*-benzoyl-*N,N*-diethylhydroxyamine and B$_2$(pin)$_2$ in the presence of a copper catalyst, the reaction proceeds in a *syn*-selective manner and the corresponding product is obtained in high yield (eq. 70).[64] Methylenecyclopropanes are also used as substrates in the aminoboration to afford (borylmethyl)cycloprpylamines in a stereoselective manner (eq. 71).[64] Recently, the copper-catalyzed diastereoselective aminoboration of cyclopropenes to give cyclopropylboronates has been demonstrated by Tortosa and co-workers (eq. 72).[24] The aminoboration of bicyclic alkenes i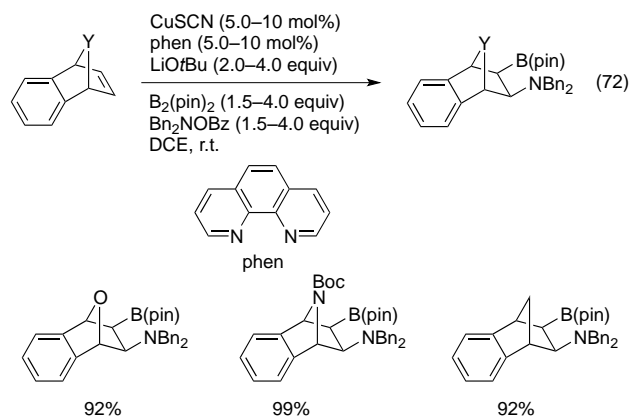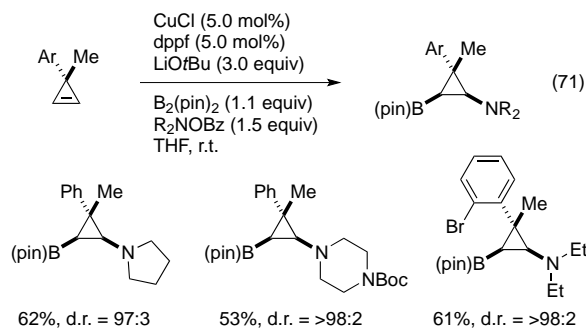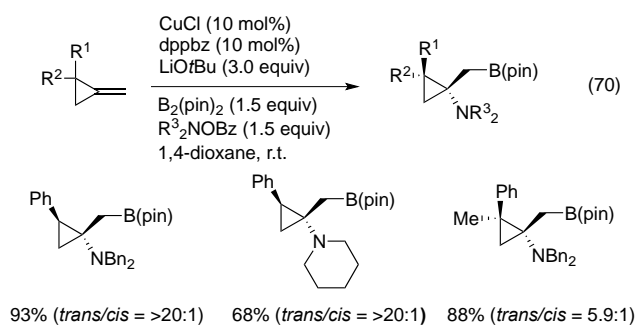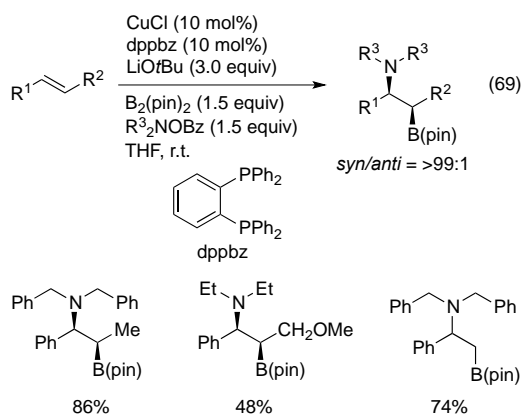s also achieved employing CuSCN and phen (1,10-phenanthroline) as catalysts (eq. 73).[66] Oxa, aza, and methylene-bridged substrates are converted to the aminoborated products in high yields.

(69)

syn/anti = >99:1

dppbz

86%   48%   74%

(70)

93% (*trans/cis* = >20:1)   68% (*trans/cis* = >20:1)   88% (*trans/cis* = 5.9:1)

(71)

62%, d.r. = 97:3   53%, d.r. = >98:2   61%, d.r. = >98:2

(72)

phen

92%   99%   92%

7. Conclusion and outlook

In this review, the borylative transformations of non-polar carbon–carbon multiple bonds using borylcopper (Cu–B) as an active catalyst species have been described. These reactions are versatile methods to prepare organoboronates, because they can afford various organoboronates that could not be accessed by other methods. The transformations proceed via the regioselective borylcupration of carbon–carbon multiple bonds as a key step, giving the corresponding organocopper intermediates. The reactions of an organocopper with various electrophiles or the *β*-elimination of the copper with an appropriate leaving group affords various types of organoboronates, which are useful intermediates in further carbon–carbon and carbon–heteroatom bond formations. Further efforts to expand the scope of unsaturated substrates and electrophiles would make copper-catalyzed borylative transformations more versatile methods for organic synthesis.

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