

Beyond Carbon: Enantioselective and Enantiospecific Reactions with Catalytically Generated Boryl- and Silylcopper Intermediates

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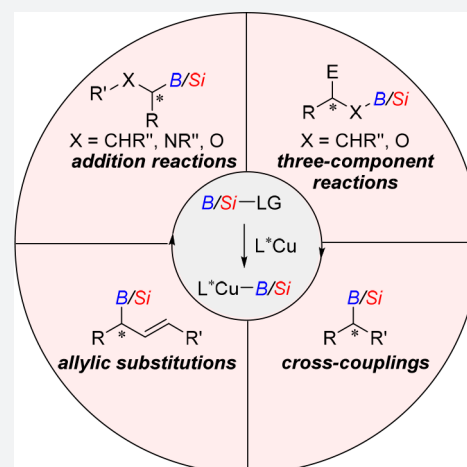
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ABSTRACT: Catalytic asymmetric C–C bond formation with alkylcopper intermediates as carbon nucleophiles is now textbook chemistry. Related chemistry with boron and silicon nucleophiles where the boryl- and accordingly silylcopper intermediates are catalytically regenerated from bench-stable pronucleophiles had been underdeveloped for years or did not even exist until recently. Over the past decade, asymmetric copper catalysis employing those main-group elements as nucleophiles rapidly transformed into a huge field in its own right with an impressive breadth of enantioselective C–B and C–Si bond-forming reactions, respectively. Its current state of the art does not have to shy away from comparison with that of boron's and silicon's common neighbor in the periodic table, carbon. This Outlook is not meant to be a detailed summary of those manifold advances. It rather aims at providing a brief conceptual summary of what forms the basis of the latest exciting progress, especially in the area of three-component reactions and cross-coupling reactions.



1. INTRODUCTION

Copper-catalyzed asymmetric transformations featuring excellent stereocontrol and broad functional-group tolerance are arguably an important part of modern organic synthesis. Accordingly, considerable advances have been made to forge not only C–C but also C–Het bonds by enantiocontrolled copper catalysis,^{1–3} and methods to incorporate main-group elements such as boron^{4–8} and silicon^{6–11} into carbon frameworks have witnessed steady growth over the past two decades (Figure 1). These developments have also been driven by an increasing demand for boron- and silicon-containing molecules with attractive chemical and physical properties in medicinal chemistry and material science (Figure 2).^{12–18} Moreover, both boryl and silyl groups are versatile synthetic linchpins and, for instance, can be used as equivalents of other functional groups, such as a hydroxy group, by stereospecific oxidative degradation of the C(sp³)–B and C(sp³)–Si bonds, respectively.^{19,20}

There are elegant copper-catalyzed asymmetric C–B and C–Si bond-forming reactions employing hydroboranes and hydrosilanes, such as carbene insertion^{21–23} as well as hydroboration^{24,25} and hydrosilylation,²⁶ where the boron and silicon centers are electrophilic.²⁷ Nonetheless, the vast majority of methods rely on the use of boron and silicon nucleophiles, in which nucleophilic L*Cu–B (I) and L*Cu–Si (II) intermediates are formed.^{4–11} In 2000, the seminal applications of the borylcopper intermediate derived from B–

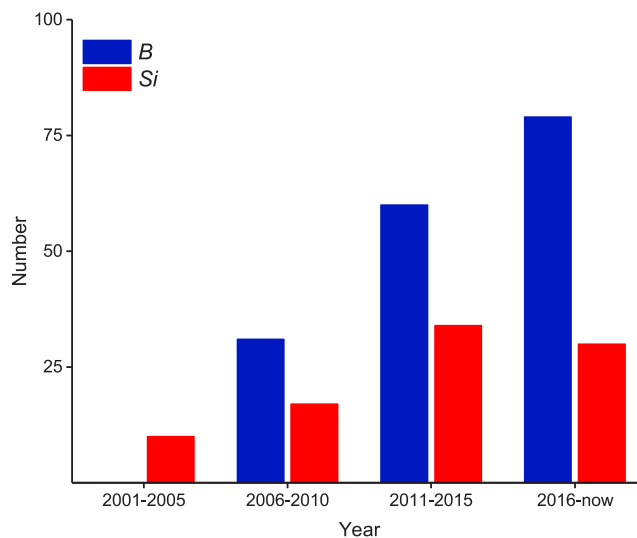


Figure 1. Number of publications containing the keywords “copper”, “enantioselective/enantiospecific”, and “boration/silylation” during the past 20 years from SciFinder (as of May 27, 2020).

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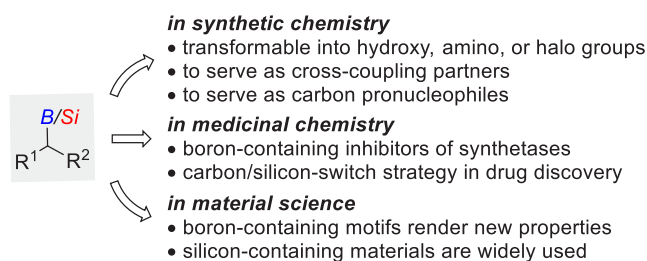


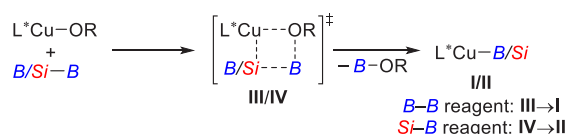
Figure 2. Roles of boron- and silicon-containing molecules in different areas.

Considerable advances have been made to forge not only C–C but also C–Het bonds by enantiocontrolled copper catalysis, and methods to incorporate main-group elements such as boron and silicon into carbon frameworks have witnessed steady growth over the past two decades.

B reagents in conjugate addition were independently disclosed by Hosomi²⁸ and Miyaura.^{29,30} Similar transmetalation approaches to generate silylcopper intermediates were introduced by Hosomi for Si–Si reagents^{31,32} and by Hoveyda, Oestreich, and Riant for Si–B reagents.^{33–35} With respect to silylcopper complexes, there had been a rich chemistry, initially stoichiometric in copper³⁶ but later catalytic with zinc³⁷ and magnesium-based^{38,39} silicon nucleophiles.⁴⁰ Of known boron and silicon (pro)nucleophiles, the widespread use of currently commercially available and storable B–B⁴¹ and Si–B compounds,⁴² e.g., B₂pin₂ (**1**) and Me₂PhSiBpin (**2**), in asymmetric copper catalysis clearly stands out. The activation of B/Si–B interelement bonds and the catalytic generation of L*Cu–B/Si species **I** and **II** are believed to involve σ -bond-metathesis-type transition states such as **III** and **IV** (Scheme 1).^{41,42}

Scheme 1. Formation of Copper–Boryl/Silyl Intermediates from B/Si–B Compounds

transmetalation through σ -bond metathesis



Copper-catalyzed C–B and C–Si bond-forming reactions have been covered in previous reviews.^{4–11} This Outlook is meant not to simply repeat or update those reviews but instead to emphasize the different strategies to apply Cu–B and Cu–Si intermediates to enantioselective and enantiospecific transformations: (i) addition reactions, (ii) allylic substitution reactions, (iii) three-component reactions, and (iv) cross-coupling reactions.

2. ADDITION REACTIONS

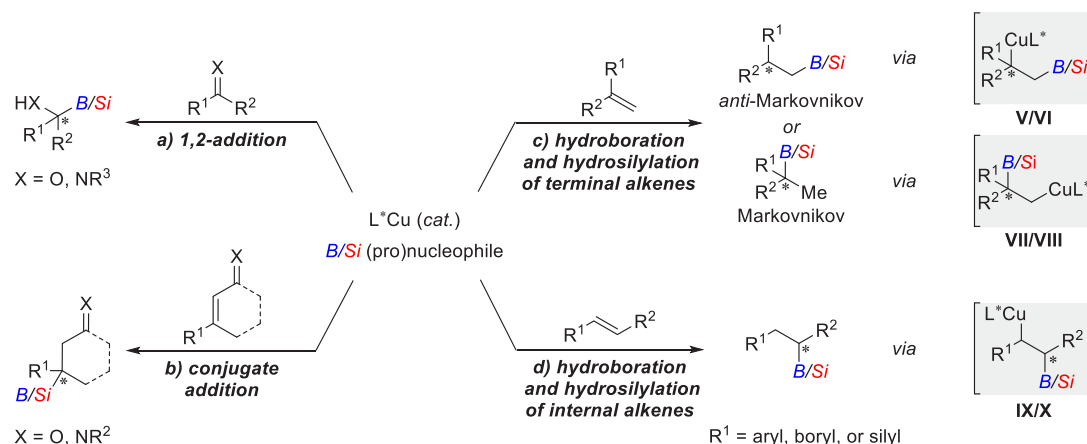
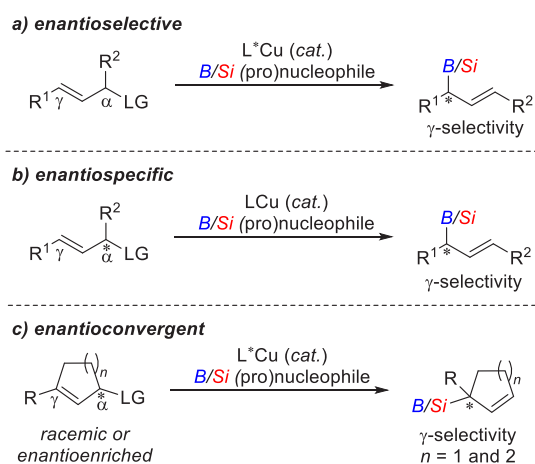
Addition reactions across unsaturated moieties have been established as routine procedures in synthetic applications of nucleophilic Cu–B/Si species. The copper-catalyzed asymmetric addition of boron and silicon pronucleophiles to C=O and C=N bonds as well as Michael acceptors is now at an advanced if not mature stage (Scheme 2a,b).^{43–53} The reaction scope and the corresponding stereocontrol highly rely on the identified chiral ligand, mainly N-heterocyclic carbene (NHC) and bisphosphine ligands.^{54,55}

Alkenes are more delicate substrates. The regioselectivity is an additional complication influenced by the catalytic system and the nature of the substituents on the double bond.⁵⁶ For terminal alkenes, the sterically favored *anti*-Markovnikov-type products are predominantly formed, passing through the branched alkylcopper intermediates V/VI with a stereogenic carbon atom for R¹ ≠ R² (Scheme 2c).^{57–60} The subsequent protonation occurs with retention of the configuration. However, the clever design of bulky chiral ligands enabled hydroboration reactions with Markovnikov regioselectivity through VII/VIII, furnishing the corresponding α -chiral boronates and silanes.^{61,62} The addition of Cu–B/Si species across internal alkenes remains challenging and is restricted to strained cycloalkenes^{63–66} as well as acyclic alkenes^{67–69} bearing a substituent that can stabilize the formed alkylcopper intermediate (Scheme 2d). However, quantum-chemical calculations and experimental investigations have suggested that the migratory insertion of an internal double bond into Cu–B/Si bonds likely proceeds with a *syn* stereochemistry, resulting in the formation of the alkylcopper species IX/X.^{64–70} This also rationalizes the stereochemical outcome of borylative amination and arylation reactions later presented in section 4.^{70,130,131}

3. ALLYLIC SUBSTITUTION REACTIONS

Allylic boranes and silanes are often-used reagents and continue to be used in synthetic chemistry.^{19,20} Hence, copper-catalyzed asymmetric approaches employing boron and silicon (pro)nucleophiles have been well established to access these chiral reagents (Scheme 3). Various protocols are available that differ in catalytic system and allylic precursor but share the features of splendid γ -selectivity and high enantiocontrol.^{54,71–78} It is generally believed that these reactions proceed through an S_N2' substitution mechanism but an alternative pathway involving the intermediacy of a π -allylcopper(III) complex cannot completely be ruled out. For example, in some cases, both (*E*)- and (*Z*)-configured allylic precursors converted into the same enantiomer under identical reaction conditions.^{74,76} Aside from these enantioselective transformations, enantioconvergent variants employing either racemic or enantioenriched cyclic allylic electrophiles have also been achieved (Scheme 3c).^{79–81}

More recent advances in this area lie in the use of allylic trifluorides and difluorides as substrates where one of the fluorides serves as the leaving group. In 2018, copper-catalyzed enantioselective γ -boryl substitutions of trifluoromethyl-substituted alkenes were independently reported by Ito and Shi (Scheme 4a).^{82,83} Both methods make use of Cu(I)/Josiphos complexes, CuCl/(*R,S*)-L1 and CuI/(*R,S*)-L2, but are confined to alkyl-substituted alkenes. Later, Hoveyda and Torker reported another process, employing CuCl as precatalyst and a chiral N-heterocyclic carbene ligand (*S,S*)-

Scheme 2. Representative Asymmetric Addition Reactions Using L^{*}Cu–B/Si IntermediatesScheme 3. Copper-Catalyzed Enantioselective, Enantiospecific, and Enantioconvergent Allylic Boration and Silylation^a^aLG = leaving group.

L3; both aryl- and alkyl-substituted alkenes are compatible with this catalytic system.⁸⁴ By replacing that ligand with (*S,S*)-L4, the method was also applicable to the silicon pronucleophile, i.e., Me₂PhSiBpin (**2**), thereby allowing for the enantioselective formation of the C–Si bond. Just recently, Ito and Hoveyda extended this strategy to allylic difluorides by modification of the reaction setup (Scheme 4b).⁸⁵ Either (*E*)-**6** or (*Z*)-**7** participated in the borylative substitution under slightly different conditions. In addition to high enantioselectivity, good *Z/E* selectivity was also observed in both reactions.

Based on experimental and computational investigations, a general mechanism was eventually proposed (Scheme 4c).^{82–85} The copper–alkoxide complex **XI** reacts with B/Si–B reagents through a σ -bond metathesis, furnishing the Cu–B/Si complexes **I/II**. The subsequent addition occurs at the more electron-positive γ -position with the formation of the alkylcopper intermediates **XII/XIII**. Compared to this addition step, the subsequent β -elimination of CuF is slower and can be facilitated by coordination of an alkali metal ion to the departing fluorine atom. This delivers the enantioenriched products and a Cu–F species **XIV** that can undergo anion exchange with MOR' to regenerate **XI**.

4. THREE-COMPONENT REACTIONS

Copper-catalyzed asymmetric three-component reactions involving Cu–B/Si intermediates have recently turned into a powerful tool for the rapid construction of molecular complexity. By this, molecules containing one or more (contiguous) stereocenters become readily accessible with high stereocontrol, along with the formation a boryl or silyl group for further manipulation.

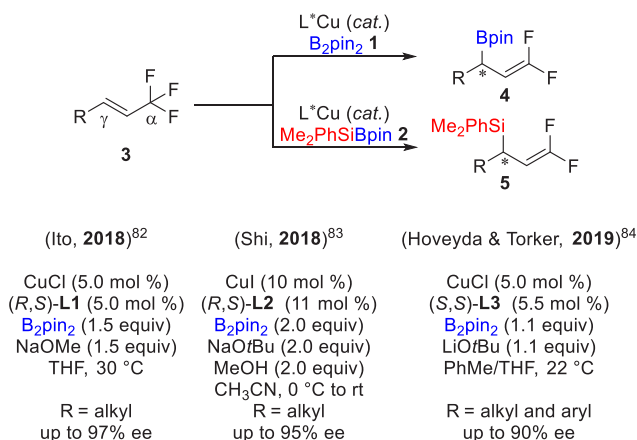
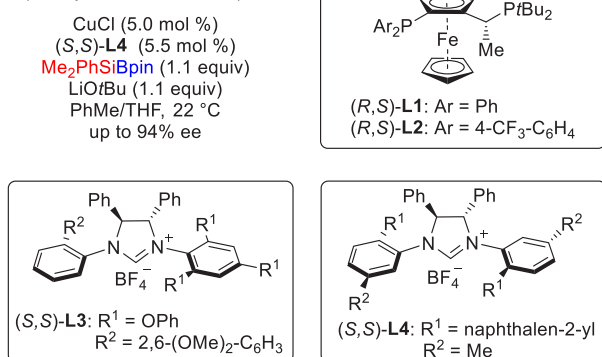
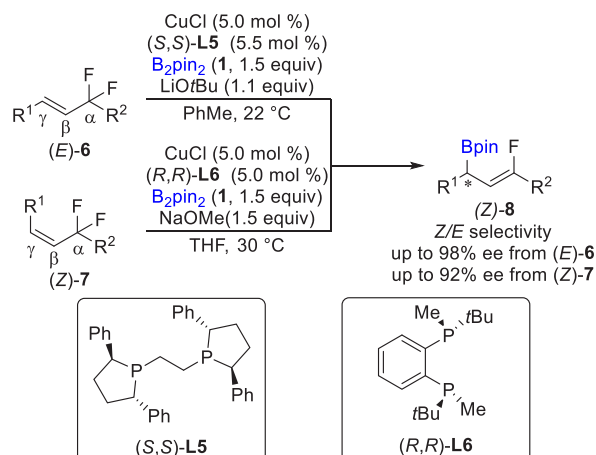
4.1. Cu–B Intermediates in Three-Component Reactions. Copper Catalysis. To a large extent, the rapid growth of enantioselective copper-catalyzed boration chemistry over the past five years can be attributed to the use of Cu–B intermediates in multi-component reactions (see Figure 1). Mechanistically, the Cu–B intermediate **I**, stemming from the metathesis of a copper–alkoxide **XI** and a B–B reagent, engages in a migratory insertion with a double bond to afford the borylorganocopper intermediate **XV** (Scheme 5). This copper complex is a carbon nucleophile that is subsequently quenched by an electrophile E–X already present in the reaction mixture. This electrophilic substitution yields the enantioenriched product and closes the catalytic cycle.

The addition of the Cu–B nucleophile across alkenes has been briefly discussed above (see section 2). Aside from alkenes, allenes and 1,3-dienes as well as 1,3-enynes also serve as substrates in the borylcupration, thus resulting in different types of borylorganocopper intermediates **XV** (Scheme 6).^{86–88} For example, the addition of the Cu–B intermediate across allenes occurs preferentially at the central carbon atom to yield allylcopper complexes **XVIII** and **XIX** after allylic transposition.⁸⁶ Similarly, 1,3-enynes readily undergo 1,2-borylcupration to provide the propargylcopper species **XX**, which can isomerize to the energetically more favorable allenylcopper complex **XXI**.⁸⁷ With regard to 1,3-dienes, both 1,2-addition and 1,4-addition are possible, providing the allylcopper species **XXII** and **XXIII**, respectively.⁸⁸ Alternatively, the 1,4-adduct **XXIII** can also be generated through the isomerization from **XXIII** since the 1,2-addition has been suggested to be an energetically lower pathway.^{89,90}

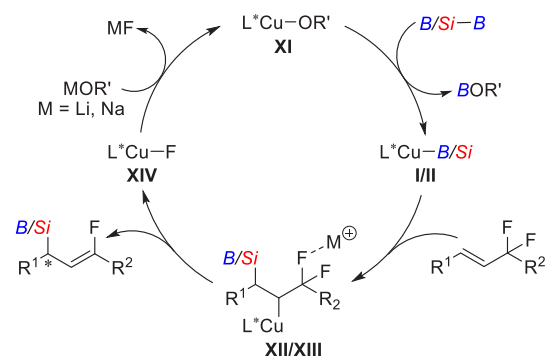
The regioselectivity of the borylcupration together with the stereoselectivity in the subsequent reaction with various electrophiles brings about high complexity and diversity in these three-component reactions. The mechanisms of these borylorganocopper intermediates reacting with prochiral electrophiles depend on reactants as well as reaction conditions and are still speculative in most cases. For this reason, it is

Scheme 4. Recent Advances in Copper-Catalyzed Enantioselective Allylic Boration and Silylation with Fluoride as Leaving Group^a

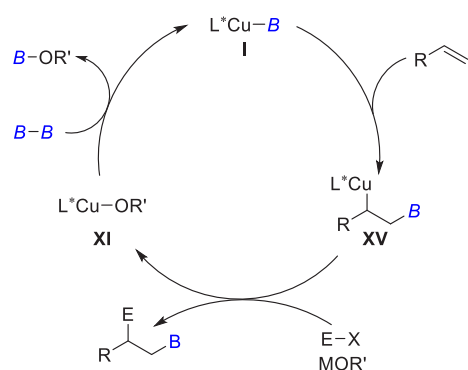
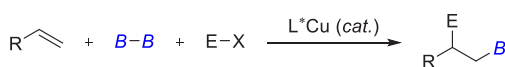
a) boration and silylation of allylic trifluorides

(Hoveyda & Torker, 2019)⁸⁴^apin = pinacolato.b) boration of allylic difluorides (Ito & Hoveyda, 2019)⁸⁵

c) general mechanism



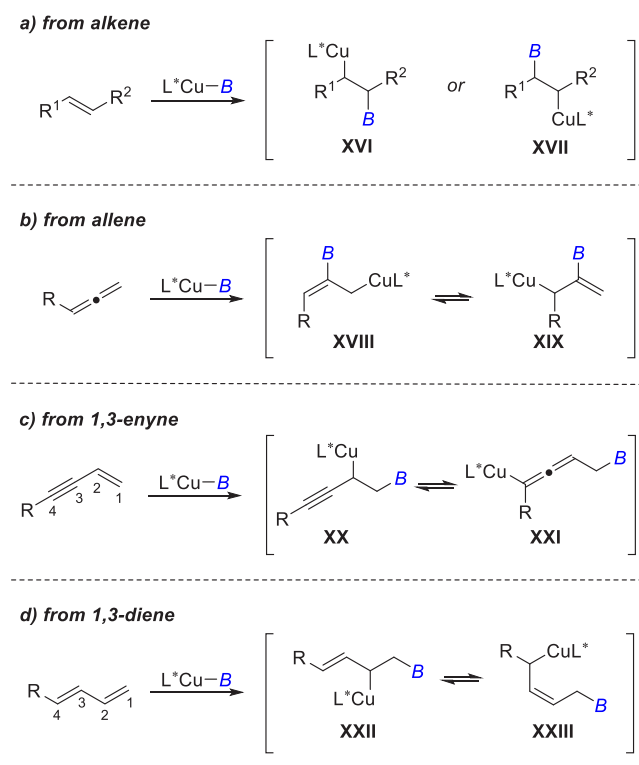
Scheme 5. General Scheme of Copper-Catalyzed Borylative Three-Component Reactions



quite challenging to predict the stereochemical outcome. Nevertheless, the involvement of a 6-membered Zimmerman–Traxler-type transition state is generally proposed, when allylcopper and allenylcopper complexes act as active species to react with electrophiles in the course of reactions (not shown).⁹¹ This has been supported by density functional theory (DFT) calculations in a few examples.^{92,93}

According to the identified electrophiles that can intercept the borylorganocopper complex XV, the resulting approaches can be categorized into two different reaction classes: borylative addition reactions and borylative substitution reactions. In copper-catalyzed borylative addition reactions, a broad range of unsaturated electrophiles containing double bonds such as ketones, imines, isocyanates, and so on have been employed, furnishing the corresponding products with excellent enantio- and diastereocontrol (Scheme 7, top).^{94–109} Notably, the stereodivergent synthesis of different diastereomers is possible by adapting the reaction condition.^{101,105} For substitution, carbon electrophiles bearing a good leaving group also engage in these borylative three-component reactions (Scheme 7, bottom).^{110–117} Next to the boryl group, a new functional group such as cyano and acyl is therefore stereoselectively installed in the same substrate. The application of allylic electrophiles to three-component reactions gained similar success.^{115–117} For example, Hoveyda and co-workers reported a copper-catalyzed asymmetric allyl–allyl coupling reaction where the allylcopper complex XXI derived from allenes could react with γ -substituted allylic phosphates with high enantioselectivity and good γ -selectivity of allylic electrophiles.¹¹⁵ In addition, heteroatom electrophiles such as *O*-benzoyl-hydroxylamine 19 and stannyl ether 20 underwent borylative substitution equally well.^{118–125}

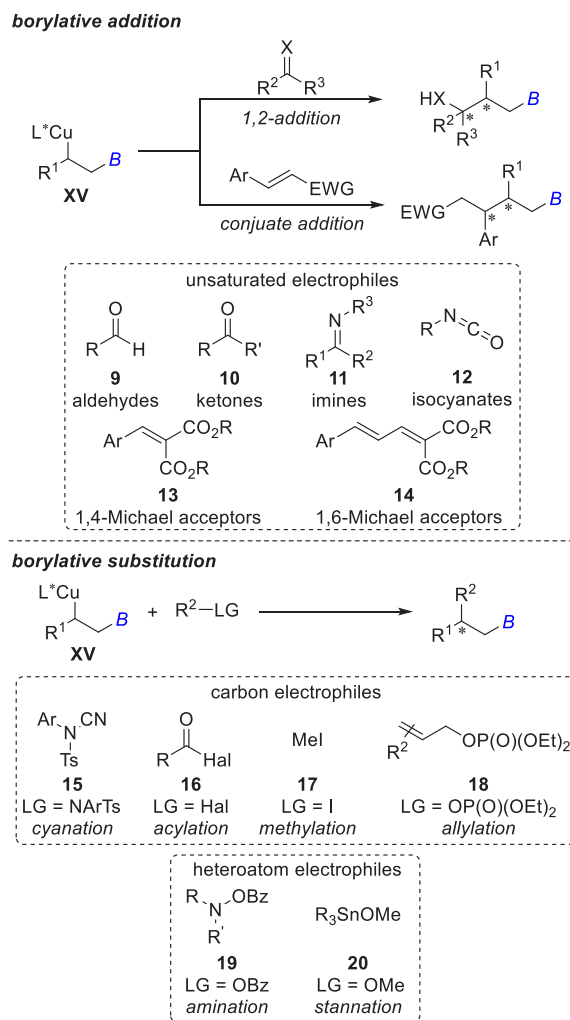
Scheme 6. Key Intermediates in Copper-Catalyzed Borylative Reactions



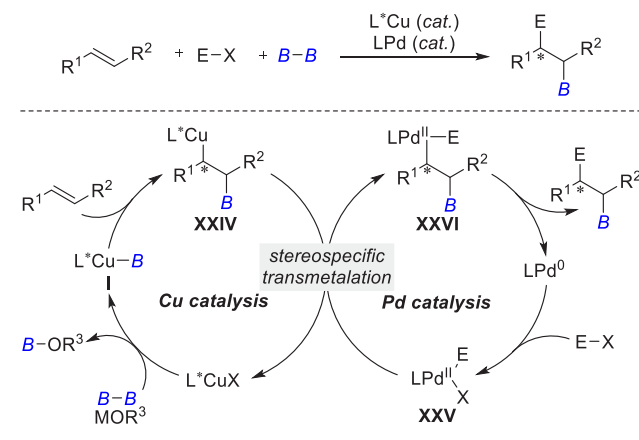
Dual Catalysis. Enantioselective Cu/Pd dual catalysis using B–B reagents emerged as an effective approach where one of the borylorganocopper intermediates depicted in Scheme 6 can be captured by a palladium(II) complex by transmetalation for subsequent cross-coupling. The general mechanism of this protocol involves two *synergistic* catalytic cycles (Scheme 8).^{126,127} The key intermediate XXIV, having a stereocenter at the copper-bearing carbon atom, is formed in the copper-based cycle ($L^*CuX \rightarrow I \rightarrow XXIV$). This is followed by stereospecific transmetalation with the Pd(II) complex XXV, providing the stereodefined Pd(II) complex XXVI, which upon reductive elimination affords the enantioenriched product and regenerates the Pd(0) catalyst. It is worth mentioning that the transmetalation from Cu(I) to Pd(II) generally proceeds with the retention of the configuration, but stereoinversion is also possible by the changing reaction conditions.¹²⁸

A first example of Cu/Pd-catalyzed enantioselective borylative allylation of styrenes was developed by Liao and co-workers in 2015 (Scheme 9, top).¹²⁹ The reaction proceeded with good enantioselectivity, and linear selectivity of allylic precursors was observed. Beyond the borylative allylation, Brown and co-workers disclosed a Cu/Pd-catalyzed enantio- and diastereoselective borylative arylation of (*Z*)-1,2-disubstituted alkenes in 2017 (Scheme 9, bottom).¹³⁰ In addition to the high enantioselectivity, the reaction was also highly *syn*-stereoselective which can be attributed to the *syn*-migratory insertion of the internal double bond into the Cu–B bond (cf. Scheme 2d). As already mentioned, by adapting the Pd complex, base, and solvent, a stereoinvertive transmetalation from Cu to Pd led to the stereodivergent synthesis of the *trans*-diastereomers.

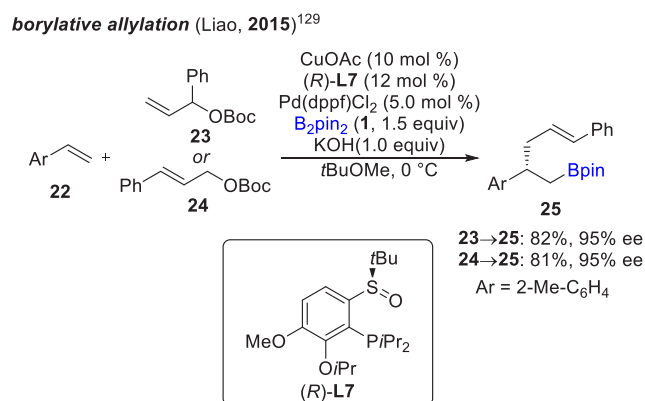
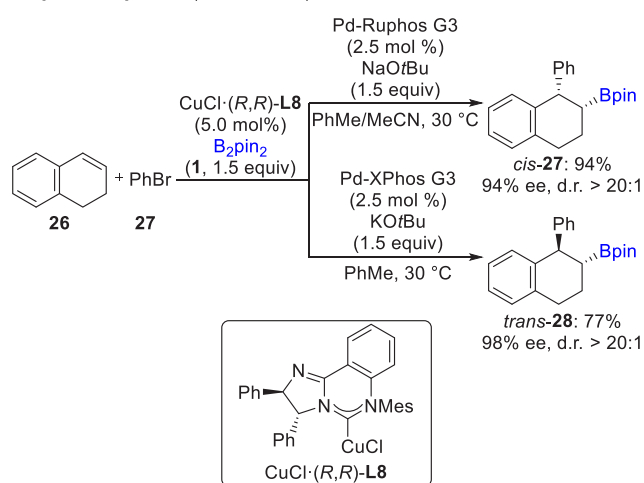
Although allylic electrophiles are capable of engaging in the palladium-based cycle, the method's advantage is to allow the use of aryl and vinyl electrophiles. The resulting overall

Scheme 7. Various Approaches and Electrophiles in Copper-Catalyzed Asymmetric Borylative Three-Component Reactions^a

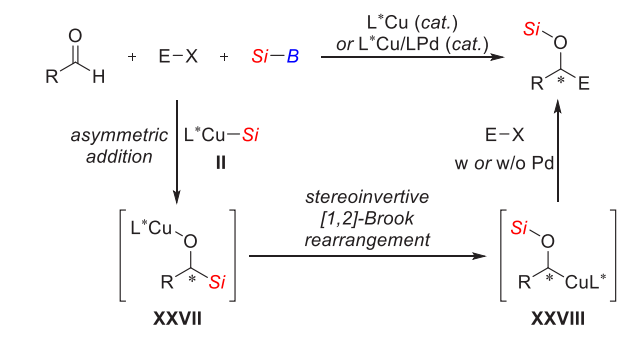
^aBz = benzoyl, EWG = electron-withdrawing group, Ts = toluene-4-sulfonyl.

Scheme 8. General Scheme for Cu/Pd-Catalyzed Borylative Three-Component Reactions Involving Two *Synergistic* Catalytic Cycles

borylative arylation and vinylation are otherwise unprecedented in sole copper catalysis. Since the seminal reports by

Scheme 9. Cu/Pd-Catalyzed Borylative Allylation and Arylation of Alkenes^a**borylative arylation** (Brown, 2017)¹³⁰

Scheme 10. General Scheme of Silylative Reductive Couplings of Aldehydes and Electrophiles



The strategy was then applied to the enantioselective reductive coupling of aromatic aldehydes with ketones or imines employing a combination of CuCl/(S,S)-L9, Me₂PhSiBpin (2) and NaOSiMe₃ in cyclooctane (Scheme 11, top).^{138,139} In both cases, moderate to high enantiomeric excesses of the formed 1,2-diols and β-amino alcohols after desilylation were obtained. However, there was no diastereoselective control. Aside from the reaction of α-alkoxyalkylcopper intermediates with ketones and imines, these can also be further processed in a palladium-catalyzed stereospecific cross-coupling cycle similar to the aforementioned dual catalysis (Scheme 8).^{129–135} The same research group disclosed another enantioselective reductive coupling of aldehydes and aryl or allyl electrophiles using a chiral copper–NHC catalyst and a palladium–bisphosphine catalyst whereby enantioenriched secondary silyl ethers were readily accessed (Scheme 11, bottom).¹⁴⁰ Aryl bromides and allyl carbonates participated in the reaction under different optimized setups with good enantiocontrol. Further experiments indicated that the stereochemical course of the transmetalation between the stereo-defined copper complex XXIX and the achiral arylpalladium complex XXX is stereoretentive.

In addition to intermolecular approaches, intramolecular variants of these three-component reactions or, to be more precise, domino reactions were also realized by several research groups, employing a substrate that contains both an unsaturated and an electrophilic substituent.^{143–149} As a consequence, a library of borylative and silylative cyclization compounds that could serve as versatile building blocks are easily accessible.

5. CROSS-COUPLING REACTIONS

Copper-catalyzed enantioconvergent and enantiospecific cross-coupling of alkyl electrophiles and boron or silicon (pro)-nucleophiles is an effective protocol for the preparation of enantioenriched α-chiral boronates and silanes, which can avoid the regioselectivity issue encountered with unbiased internal alkenes and is complementary to above-mentioned approaches (Scheme 12). Such reactions could proceed through either a radical pathway or an ionic pathway, determined by the leaving group and the catalytic system.^{150–153}

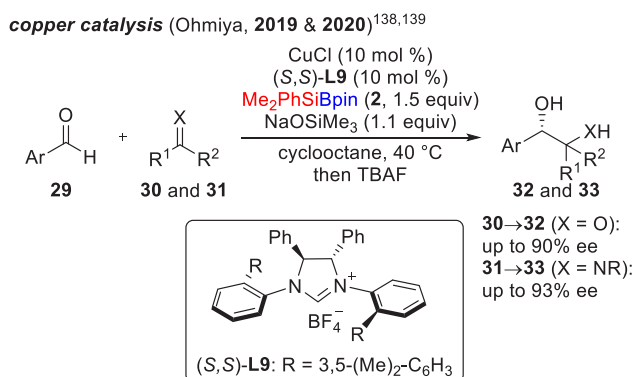
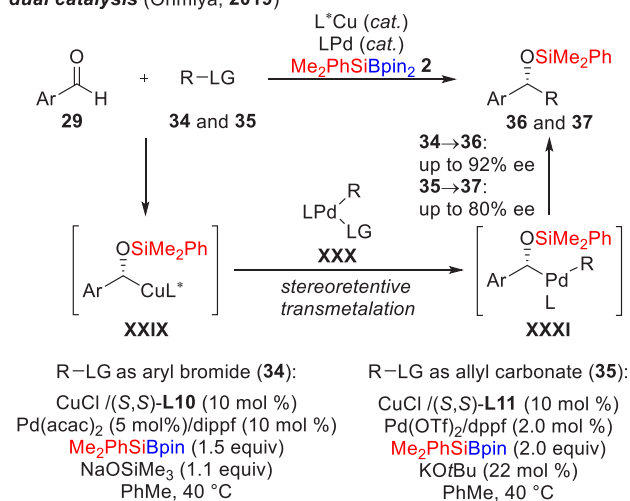
Recently, an enantioconvergent boration of racemic secondary benzyl chlorides was realized by Ito and co-workers, using a chiral copper–bisphosphine complex [Cu(MeCN)₄]-BF₄/(S)-L12 (Scheme 13).^{154,155} The method displays good functional-group compatibility as well as high enantioselectivity. A radical catalytic cycle was proposed based on

^aBoc = *tert*-butyloxycarbonyl.

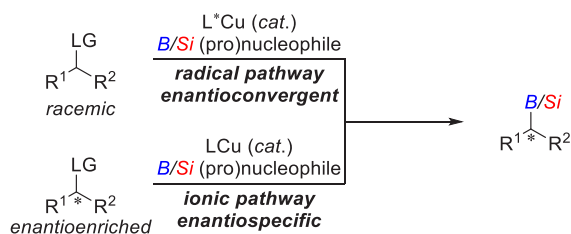
Liao and Brown, continuous efforts in enantioselective borylative arylation reactions have been made to extend the scope of available substrates beyond alkenylarenes,^{131,132} such as alkenylheteroarenes,¹³³ cyclic 1,3-dienes,¹³⁴ and 1,3-enynes.¹³⁵

4.2. Cu–Si Intermediates in Three-Component Reactions. Prior to the application of Cu–B intermediates in three-component reactions, the silylcupration of unsaturated double bonds coupled with capture of the formed silylorganocopper intermediate with electrophiles had been a known strategy, which can be traced back to early efforts in synthetic applications of silylcuprate reagents.^{136,137} The development of catalytic asymmetric versions has been relatively slow though, and just a handful of examples have been reported to date.

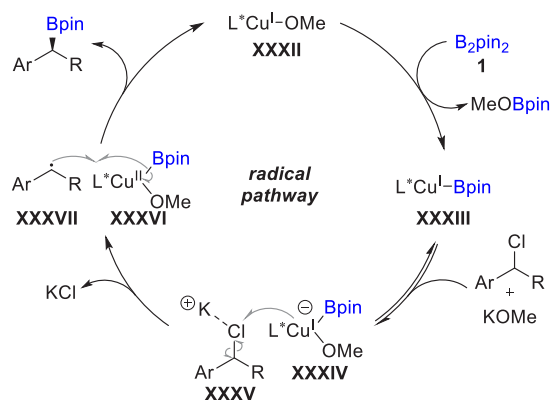
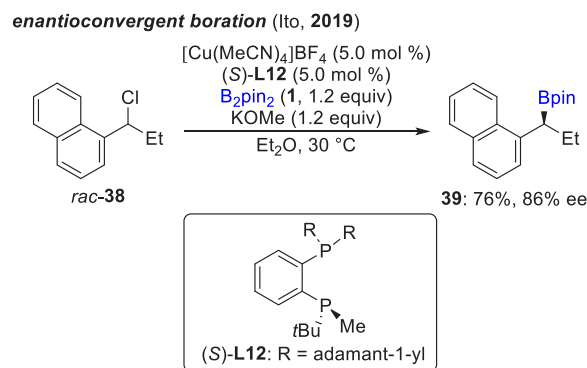
Recently, Ohmiya and co-workers developed an ingenious approach that engages a Cu–Si intermediate in asymmetric three-component transformations (Scheme 10).^{138–140} The success of these reactions hinges on the generation of an α-alkoxyalkylcopper species XXVIII containing a stereogenic carbon center by enantioselective aldehyde insertion into the Cu–Si bond followed by a stereoinvertive [1,2]-Brook rearrangement from the resulting α-silylsubstituted Cu(I)-alkoxide XXVII.^{141,142} This stereodefined complex XXVIII ensues to be intercepted with electrophiles in a stereospecific manner with the formation of enantioenriched silyl ethers.

Scheme 11. Examples of Reductive Couplings of Aldehydes and Electrophiles.^a**dual catalysis** (Ohmiya, 2019)¹⁴⁰

^aTBAF = tetrabutylammonium fluoride, Tf = trifluoromethanesulfonyl.

Scheme 12. Copper-Catalyzed Enantioconvergent and Enantiospecific C(sp³)-B/Si Cross-Coupling

preliminary mechanistic studies. A borylcopper(I) intermediate XXXIII is generated from Cu(I)-alkoxide XXXII and B₂pin₂ (1). Coordination of the alkoxide to the copper center provides the reductive anionic intermediate XXXIV. The single electron transfer from this reductive species to the benzylic chloride occurs to generate the borylcopper(II) complex XXXVI and benzylic radical XXXVII. Subsequent enantioselective C(sp³)-B coupling through radical recombination

Scheme 13. Copper-Catalyzed Enantioconvergent Boration of Racemic Benzyl Chlorides.¹⁵⁴

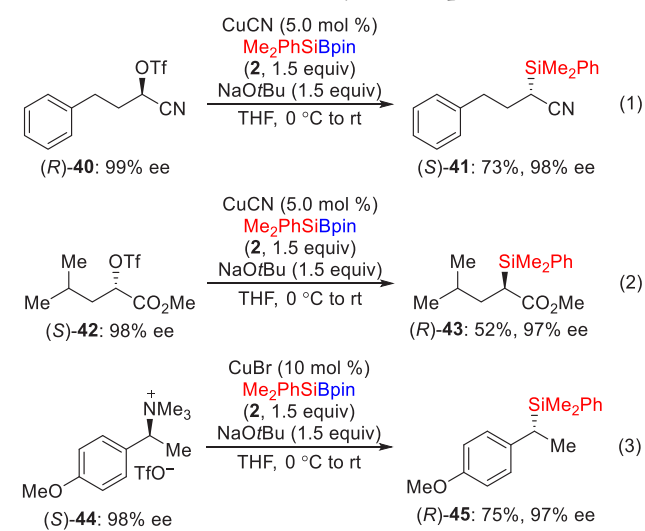
leads to the enantioenriched product associated with the regeneration of XXXII. Computational studies implied that noncovalent interactions, such as hydrogen bonding and C-H/π interactions, and steric repulsion between XXXVI and XXXVII account for the high enantioselectivity.

By contrast, copper-catalyzed enantioconvergent silylation of racemic alkyl electrophiles remains challenging and has not yet been developed. Alternatively, Oestreich and co-workers disclosed copper-catalyzed enantiospecific silylations of enantioenriched alkyl electrophiles to access optically active α-chiral silanes (Scheme 14).^{156,157} The resulting Cu-Si intermediate could react with enantioenriched electrophiles such as α-triflyloxy nitriles and esters as well as benzylic ammonium triflates to afford the corresponding products with high enantiospecificity. These reactions proceed through an S_N2 mechanism with the inversion of configuration.

Although enantioenriched α-chiral boronates and silanes can be accessed by copper-catalyzed C(sp³)-B/Si cross-coupling reactions, such chiral motifs are limited to bearing an electron-withdrawing substituent in the α position. It is important to note here that α-halo alkylboronates and alkylsilanes were capable of engaging in nickel-catalyzed enantioselective alkyl-alkyl Negishi coupling with alkylzinc bromides, therefore providing fully alkyl-substituted α-chiral boronates and silanes that are of value but were previously unavailable.¹⁵⁸⁻¹⁶⁰

6. SUMMARY AND OUTLOOK

The first two decades of the 21st century have witnessed tremendous advances in using catalytically generated Cu-B and Cu-Si intermediates in asymmetric reactions. The progress made in this promising field is evident from the large body of cited literature.⁴⁻¹¹ The area evolved from two-

Scheme 14. Copper-Catalyzed Enantiospecific Silylation of Enantioenriched Activated Alkyl Electrophiles^{156,157}

The area evolved from two-component, such as addition and allylic substitution reactions, to multi-component transformations, which allow for the construction of more than one chiral center in a single synthetic operation while at the same time installing a transformable boryl or silyl group.

component, such as addition and allylic substitution reactions, to multi-component transformations, which allow for the construction of more than one chiral center in a single synthetic operation while at the same time installing a transformable boryl or silyl group.

Future research in this field will, of course, continue to target the discovery of novel reactivity of Cu–B/Si species on the basis of the modular design of chiral ligand platforms. This promises to enable new powerful transformations. Despite a few approaches applied to the synthesis of bioactive molecules to date, more synthetic applications are to be expected. Besides this, owing to the redox nature of the copper catalyst, the incorporation of Cu–B/Si intermediates into radical processes is likely going to lead to new discoveries such as asymmetric C(sp³)–H boration and silylation.¹⁶¹

On the other hand, the creative utilization of the resulting borylcopper or silylcopper intermediate in three-component reactions can be considered as another way to advance this field. Traditionally, such intermediates are used to react with electrophiles; however, it is very exciting that nucleophiles are able to be employed to trap these intermediates, for example, by oxidative cross-coupling or radical chemistry.¹⁶² To close this Outlook, we envision that Cu–B/Si intermediates will find more fascinating applications in asymmetric catalysis, and thus promote the prosperity of synthetic boron and silicon chemistry.

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Notes

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