

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

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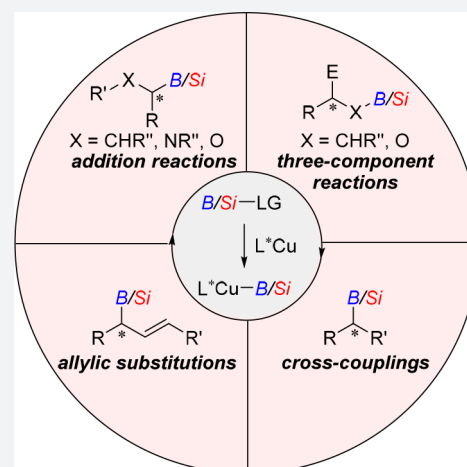
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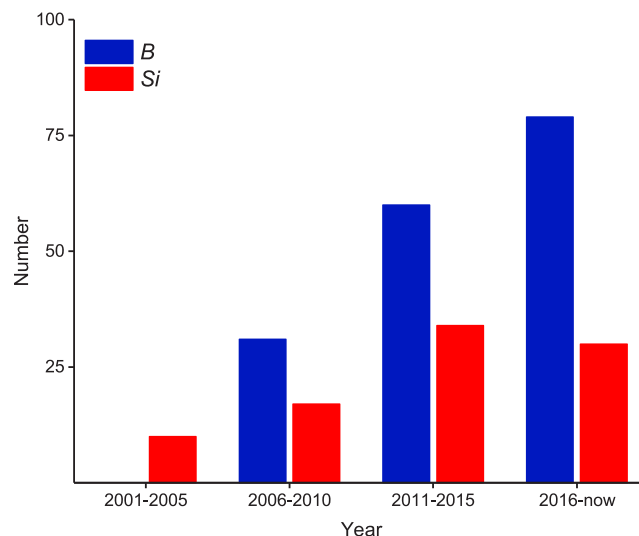
**ABSTRACT:** Catalytic asymmetric C–C bond formation with alkylcopper intermediates as carbon nucleophiles is now textbook chemistry. Related chemistry with boron and silicon nucleophiles where the boryl- and accordingly silylcopper intermediates are catalytically regenerated from bench-stable pronucleophiles 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,<sup>1–3</sup> and methods to incorporate main-group elements such as boron<sup>4–8</sup> and silicon<sup>6–11</sup> 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).<sup>12–18</sup> 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(sp<sup>3</sup>)–B and C(sp<sup>3</sup>)–Si bonds, respectively.<sup>19,20</sup>

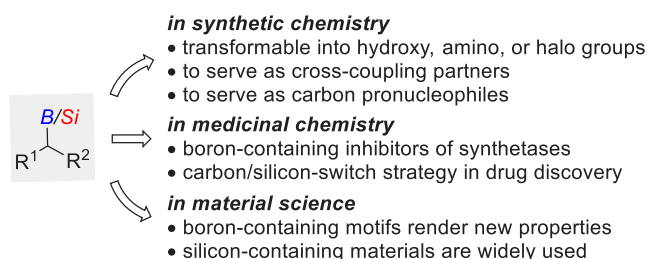
There are elegant copper-catalyzed asymmetric C–B and C–Si bond-forming reactions employing hydroboranes and hydrosilanes, such as carbene insertion<sup>21–23</sup> as well as hydroboration<sup>24,25</sup> and hydrosilylation,<sup>26</sup> where the boron and silicon centers are electrophilic. Nonetheless, 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.<sup>4–11</sup> 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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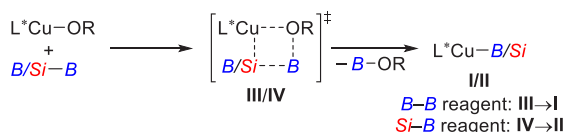
**Figure 2.** Roles of boron- and silicon-containing molecules in different areas.

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 Hosomi<sup>28</sup> and Miyaura.<sup>29,30</sup> Similar transmetalation approaches to generate silylcopper intermediates were introduced by Hosomi for Si–Si reagents<sup>31,32</sup> and by Hoveyda, Oestreich, and Riant for Si–B reagents.<sup>33–35</sup> With respect to silylcopper complexes, there had been a rich chemistry, initially stoichiometric in copper<sup>36</sup> but later catalytic with zinc<sup>37</sup> and magnesium-based<sup>38,39</sup> silicon nucleophiles.<sup>40</sup> Of known boron and silicon (pro)nucleophiles, the widespread use of currently commercially available and storable B–B<sup>41</sup> and Si–B compounds,<sup>42</sup> e.g., B<sub>2</sub>pin<sub>2</sub> (**1**) and Me<sub>2</sub>PhSiBpin (**2**), in asymmetric copper catalysis clearly stands out. The activation of B/Si–B interelement bonds and the catalytic generation of L<sup>\*</sup>Cu–B/Si species **I** and **II** are believed to involve  $\sigma$ -bond-metathesis-type transition states such as **III** and **IV** (Scheme 1).<sup>41,42</sup>

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

transmetalation through  $\sigma$ -bond metathesis



Copper-catalyzed C–B and C–Si bond-forming reactions have been covered in previous reviews.<sup>4–11</sup> 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

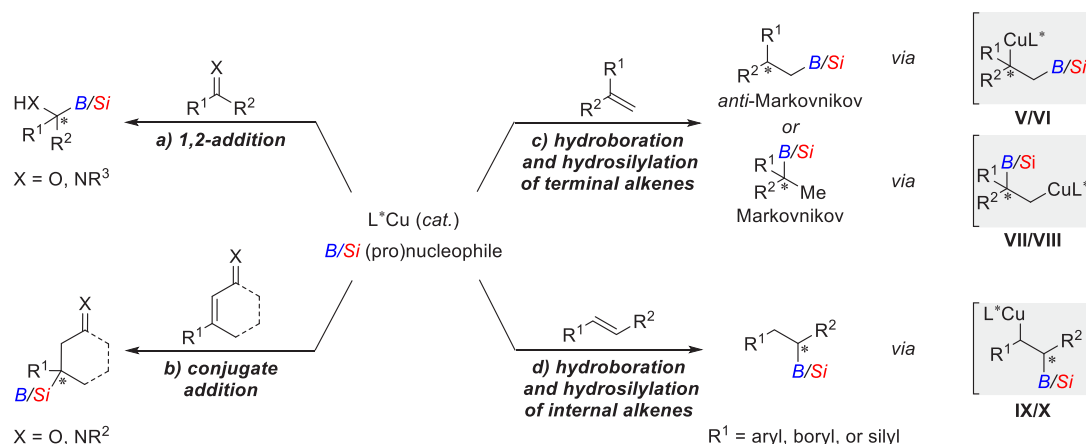
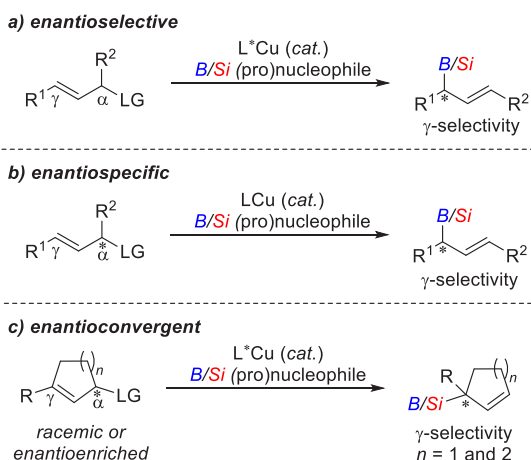
Addition reactions across unsaturated moieties have been established as routine procedures in synthetic applications of nucleophilic Cu–B/Si species. The copper-catalyzed asymmetric addition of boron and silicon pronucleophiles to C=O and C=N bonds as well as Michael acceptors is now at an advanced if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

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.<sup>56</sup> 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 R<sup>1</sup> ≠ R<sup>2</sup> (Scheme 2c).<sup>57–60</sup> 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  $\alpha$ -chiral boronates and silanes.<sup>61,62</sup> The addition of Cu–B/Si species across internal alkenes remains challenging and is restricted to strained cycloalkenes<sup>63–66</sup> as well as acyclic alkenes<sup>67–69</sup> 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.<sup>64–70</sup> This also rationalizes the stereochemical outcome of borylative amination and arylation reactions later presented in section 4.<sup>70,130,131</sup>

## 3. ALLYLIC SUBSTITUTION REACTIONS

Allylic boranes and silanes are often-used reagents and continue to be used in synthetic chemistry.<sup>19,20</sup> 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  $\gamma$ -selectivity and high enantiocontrol.<sup>54,71–78</sup> It is generally believed that these reactions proceed through an S<sub>N</sub>2' substitution mechanism but an alternative pathway involving the intermediacy of a  $\pi$ -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.<sup>74,76</sup> Aside from these enantioselective transformations, enantioconvergent variants employing either racemic or enantioenriched cyclic allylic electrophiles have also been achieved (Scheme 3c).<sup>79–81</sup>

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  $\gamma$ -boryl substitutions of trifluoromethyl-substituted alkenes were independently reported by Ito and Shi (Scheme 4a).<sup>82,83</sup> 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<sup>a</sup><sup>a</sup>LG = leaving group.

**L3**; both aryl- and alkyl-substituted alkenes are compatible with this catalytic system.<sup>84</sup> By replacing that ligand with (*S,S*)-**L4**, the method was also applicable to the silicon pronucleophile, i.e.,  $Me_2PhSiBpin$  (**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).<sup>85</sup> 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).<sup>82–85</sup> The copper–alkoxide complex **XI** reacts with B/Si–B reagents through a  $\sigma$ -bond metathesis, furnishing the Cu–B/Si complexes **I/II**. The subsequent addition occurs at the more electron-positive  $\gamma$ -position with the formation of the alkylcopper intermediates **XII/XIII**. Compared to this addition step, the subsequent  $\beta$ -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.

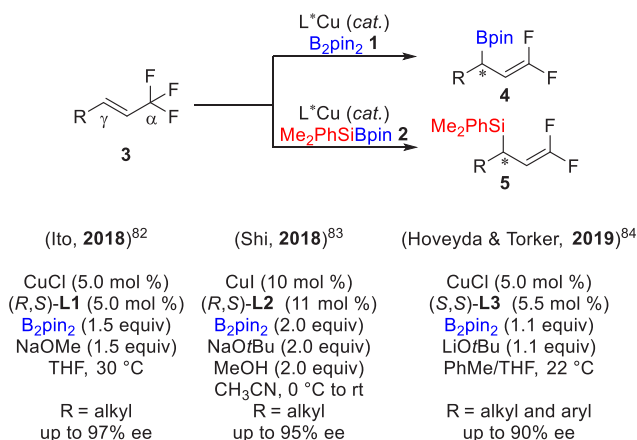
**4.1. Cu–B Intermediates in Three-Component Reactions. Copper Catalysis.** To a large extent, the rapid growth of enantioselective copper-catalyzed boration chemistry over the past five years can be attributed to the use of Cu–B intermediates in multi-component reactions (see Figure 1). Mechanistically, 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 borylcopper 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 borylcopper intermediates **XV** (Scheme 6).<sup>86–88</sup> 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.<sup>86</sup> 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**.<sup>87</sup> With regard to 1,3-dienes, both 1,2-addition and 1,4-addition are possible, providing the allylcopper species **XXII** and **XXIII**, respectively.<sup>88</sup> Alternatively, the 1,4-adduct **XXIII** can also be generated through the isomerization from **XXII** since the 1,2-addition has been suggested to be an energetically lower pathway.<sup>89,90</sup>

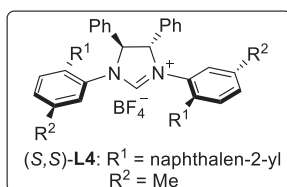
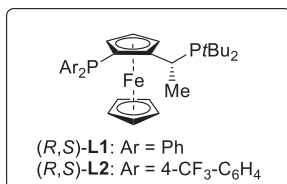
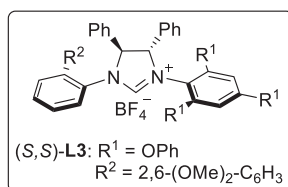
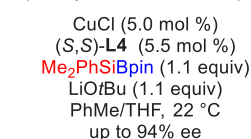
The regioselectivity of the borylcupration together with the stereoselectivity in the subsequent reaction with various electrophiles brings about high complexity and diversity in these three-component reactions. The mechanisms of these borylcopper intermediates reacting with prochiral electrophiles depend 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<sup>a</sup>

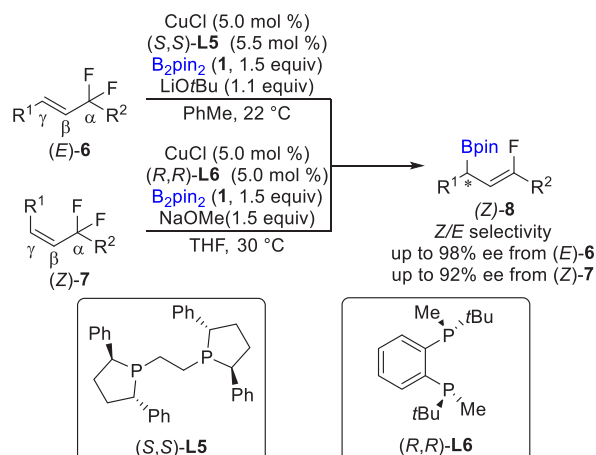
**a) boration and silylation of allylic trifluorides**



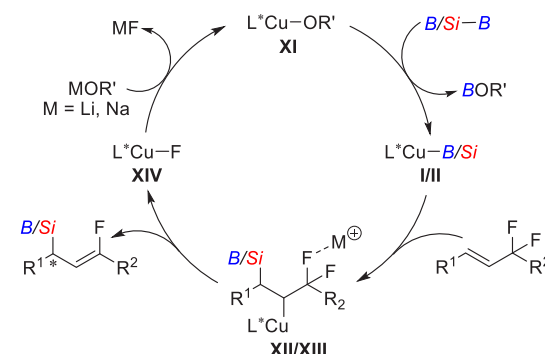
(Hoveyda & Torker, 2019)<sup>84</sup>



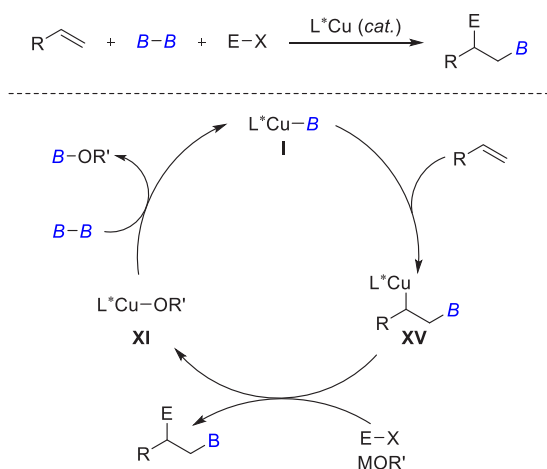
**b) boration of allylic difluorides** (Ito & Hoveyda, 2019)<sup>85</sup>



**c) general mechanism**

<sup>a</sup>pin = pinacolato.

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



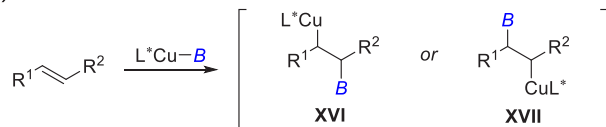
quite challenging to predict the stereochemical outcome. Nevertheless, the involvement of a 6-membered Zimmerman–Traxler-type transition state is generally proposed, when allylcopper and allenylcopper complexes act as active species to react with electrophiles in the course of reactions (not shown).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

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).<sup>94–109</sup> Notably, the stereodivergent synthesis of different diastereomers is possible by adapting the reaction condition.<sup>101,105</sup> For substitution, carbon electrophiles bearing a good leaving group also engage in these borylative three-component reactions (Scheme 7, bottom).<sup>110–117</sup> 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.<sup>115–117</sup> 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  $\gamma$ -substituted allylic phosphates with high enantioselectivity and good  $\gamma$ -selectivity of allylic electrophiles.<sup>115</sup> In addition, heteroatom electrophiles such as *O*-benzoyl-hydroxylamine **19** and stannyl ether **20** underwent borylative substitution equally well.<sup>118–125</sup>

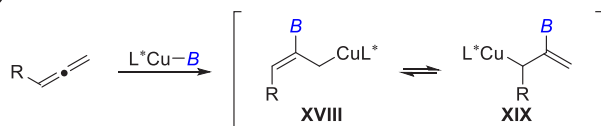


### Scheme 6. Key Intermediates in Copper-Catalyzed Borylative Reactions

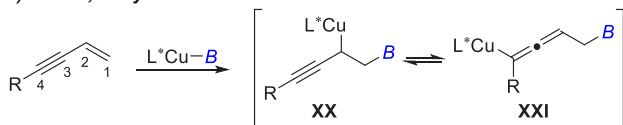
a) from alkene



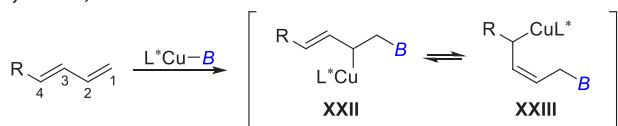
b) from allene



c) from 1,3-enyne



d) from 1,3-diene



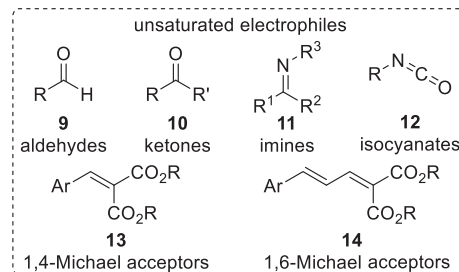
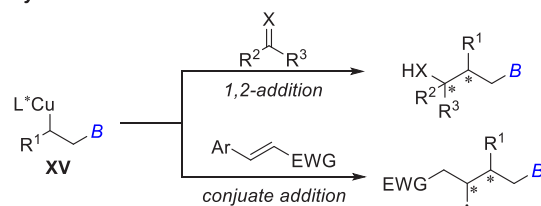
**Dual Catalysis.** Enantioselective Cu/Pd dual catalysis using B–B reagents emerged as an effective approach where one of the borylorganocopper intermediates depicted in Scheme 6 can be captured by a palladium(II) complex by transmetalation for subsequent cross-coupling. The general mechanism of this protocol involves two synergistic catalytic cycles (Scheme 8).<sup>126,127</sup> 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.<sup>128</sup>

A first example of Cu/Pd-catalyzed enantioselective borylative allylation of styrenes was developed by Liao and co-workers in 2015 (Scheme 9, top).<sup>129</sup> 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).<sup>130</sup> 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.

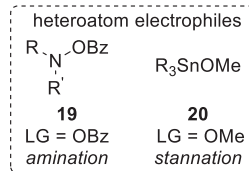
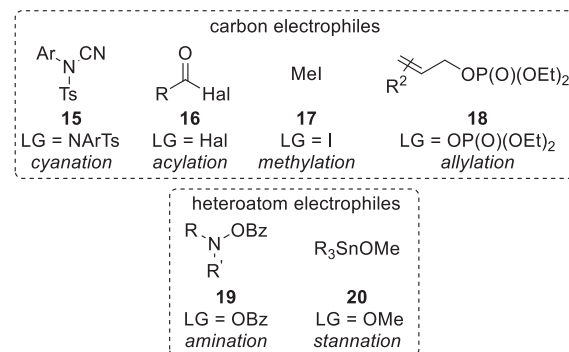
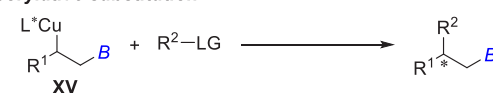
Although allylic electrophiles are capable of engaging in the palladium-based cycle, the method's advantage is to allow the use of aryl and vinyl electrophiles. The resulting overall

### Scheme 7. Various Approaches and Electrophiles in Copper-Catalyzed Asymmetric Borylative Three-Component Reactions<sup>a</sup>

borylative addition

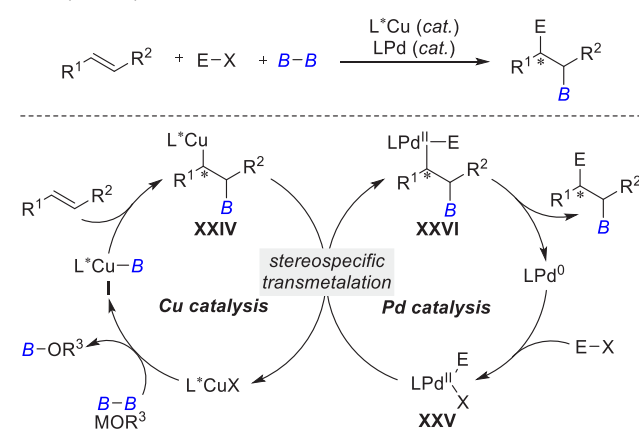


borylative substitution



<sup>a</sup>Bz = benzoyl, EWG = electron-withdrawing group, Ts = toluene-4-sulfonyl.

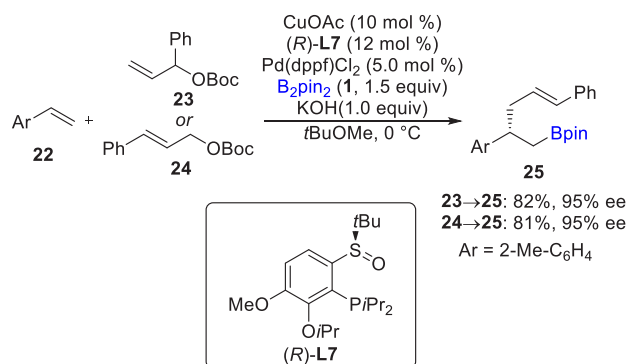
### Scheme 8. General Scheme for Cu/Pd-Catalyzed Borylative Three-Component Reactions Involving Two Synergistic Catalytic Cycles



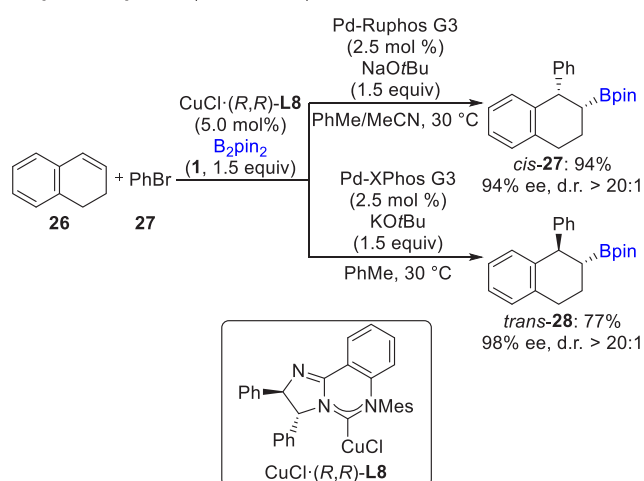
borylative arylation and vinylation are otherwise unprecedented in sole copper catalysis. Since the seminal reports by

### Scheme 9. Cu/Pd-Catalyzed Borylative Allylation and Arylation of Alkenes<sup>a</sup>

borylative allylation (Liao, 2015)<sup>129</sup>



borylative arylation (Brown, 2017)<sup>130</sup>



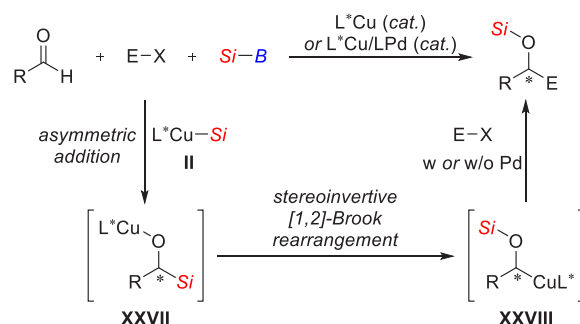
<sup>a</sup>Boc = *tert*-butoxycarbonyl.

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

**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.<sup>136,137</sup> 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).<sup>138–140</sup> The success of these reactions hinges on the generation of an  $\alpha$ -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  $\alpha$ -silylsubstituted Cu(I)–alkoxide XXVII.<sup>141,142</sup> This stereodefined complex XXVIII ensues to be intercepted with electrophiles in a stereospecific manner with the formation of enantioenriched silyl ethers.

### 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, Me<sub>2</sub>PhSiBpin (2) and NaOSiMe<sub>3</sub> in cyclooctane (Scheme 11, top).<sup>138,139</sup> In both cases, moderate to high enantiomeric excesses of the formed 1,2-diols and  $\beta$ -amino alcohols after desilylation were obtained. However, there was no diastereocontrol. Aside from the reaction of  $\alpha$ -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).<sup>129–135</sup> 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).<sup>140</sup> 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.<sup>143–149</sup> As a consequence, a library of borylative and silylative cyclization compounds that could serve as versatile building blocks are easily accessible.

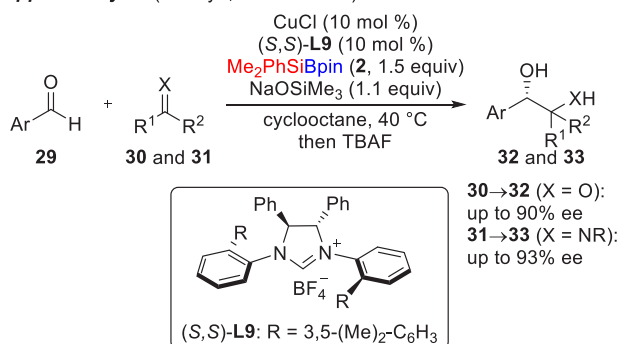
## 5. CROSS-COUPLING REACTIONS

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  $\alpha$ -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.<sup>150–153</sup>

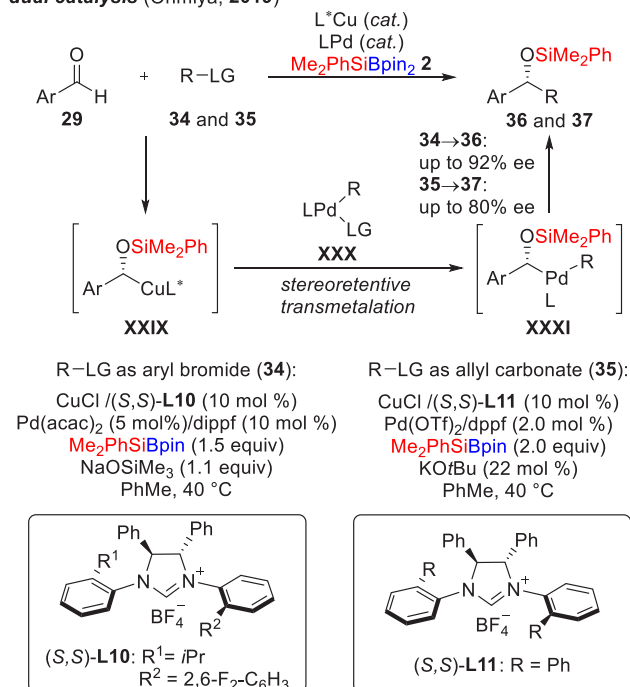
Recently, an enantioconvergent boration of racemic secondary benzyl chlorides was realized by Ito and co-workers, using a chiral copper–bisphosphine complex [Cu(MeCN)<sub>4</sub>]-BF<sub>4</sub>/(*S*)-L12 (Scheme 13).<sup>154,155</sup> The method displays good functional-group compatibility as well as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

### Scheme 11. Examples of Reductive Couplings of Aldehydes and Electrophiles.<sup>a</sup>

**copper catalysis** (Ohmiya, 2019 & 2020)<sup>138,139</sup>

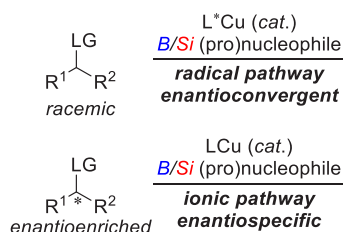


**dual catalysis** (Ohmiya, 2019)<sup>140</sup>



<sup>a</sup>TBAF = tetrabutylammonium fluoride, Tf = trifluoromethanesulfonyl.

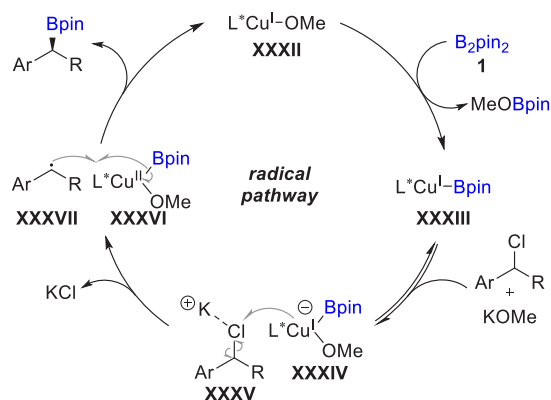
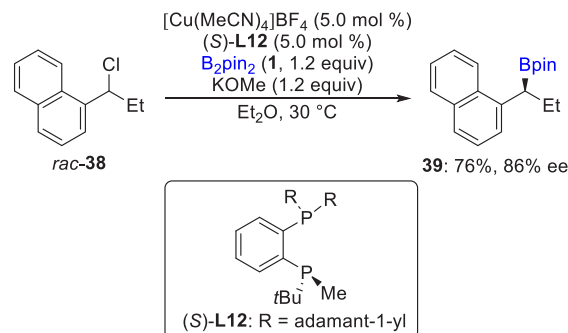
### Scheme 12. Copper-Catalyzed Enantioconvergent and Enantiospecific C(sp<sup>3</sup>)-B/Si Cross-Coupling



preliminary mechanistic studies. A borylcopper(I) intermediate XXXIII is generated from Cu(I)-alkoxide XXXII and B<sub>2</sub>pin<sub>2</sub> (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(sp<sup>3</sup>)-B coupling through radical recombination

### Scheme 13. Copper-Catalyzed Enantioconvergent Boration of Racemic Benzyl Chlorides.<sup>154</sup>

**enantioconvergent boration** (Ito, 2019)



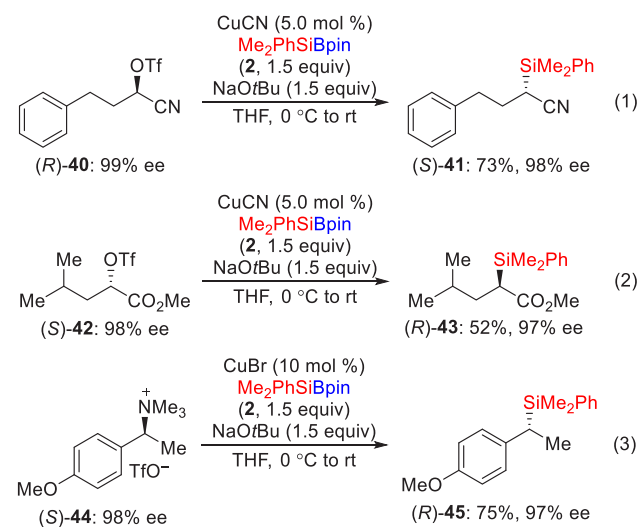
leads to the enantioenriched product associated with the regeneration of XXXII. Computational studies implied that noncovalent interactions, such as hydrogen bonding and C-H/ $\pi$  interactions, and steric repulsion between XXXVI and XXXVII account for the high enantioselectivity.

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  $\alpha$ -chiral silanes (Scheme 14).<sup>156,157</sup> The resulting Cu-Si intermediate could react with enantioenriched electrophiles such as  $\alpha$ -triflyloxy nitriles and esters as well as benzylic ammonium triflates to afford the corresponding products with high enantiospecificity. These reactions proceed through an S<sub>N</sub>2 mechanism with the inversion of configuration.

Although enantioenriched  $\alpha$ -chiral boronates and silanes can be accessed by copper-catalyzed C(sp<sup>3</sup>)-B/Si cross-coupling reactions, such chiral motifs are limited to bearing an electron-withdrawing substituent in the  $\alpha$  position. It is important to note here that  $\alpha$ -halo alkylboronates and alkylsilanes were capable of engaging in nickel-catalyzed enantioselective alkyl-alkyl Negishi coupling with alkylzinc bromides, therefore providing fully alkyl-substituted  $\alpha$ -chiral boronates and silanes that are of value but were previously unavailable.<sup>158–160</sup>

## 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.<sup>4–11</sup> The area evolved from two-

**Scheme 14. Copper-Catalyzed Enantiospecific Silylation of Enantioenriched Activated Alkyl Electrophiles<sup>156,157</sup>**


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(sp<sup>3</sup>)–H boration and silylation.<sup>161</sup>

On the other hand, the creative utilization of the resulting borylorganocopper or silylorganocopper 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.<sup>162</sup> 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.

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

The authors declare no competing financial interest.

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## REFERENCES

- (1) Harutyunyan, S. R., Ed. *Progress in Enantioselective Cu(I)-Catalyzed Formation of Stereogenic Centers*; Springer: Cham, Switzerland, 2016.
- (2) Alexakis, A.; Krause, N.; Woodward, S., Eds. *Copper-Catalyzed Asymmetric Synthesis*; Wiley-VCH: Weinheim, Germany, 2014.
- (3) Krause, N., Ed. *Modern Organocopper Chemistry*; Wiley-VCH: Weinheim, Germany, 2002.
- (4) Hemming, D.; Fritzemeier, R.; Westcott, S. A.; Santos, W. L.; Steel, P. G. Copper-Boryl Mediated Organic Synthesis. *Chem. Soc. Rev.* **2018**, 47, 7477–7494.
- (5) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. Copper-Catalyzed Borylative Transformations of Non-Polar Carbon–Carbon Unsaturated Compounds Employing Borylcopper as an Active Catalyst Species. *Tetrahedron* **2015**, 71, 2183–2197.
- (6) Takale, B. S.; Thakore, R. R.; Etemadi-Davan, E.; Lipshutz, B. H. Recent Advances in Cu-Catalyzed C(sp<sup>3</sup>)–Si and C(sp<sup>3</sup>)–B Bond Formation. *Beilstein J. Org. Chem.* **2020**, 16, 691–737.
- (7) Hensel, A.; Oestreich, M. Asymmetric Addition of Boron and Silicon Nucleophiles. In *Progress in Enantioselective Cu(I)-Catalyzed Formation of Stereogenic Centers*; Harutyunyan, S. R., Ed.; Springer: Cham, Switzerland, 2016; pp 135–167.
- (8) Sawamura, M.; Ito, H. Carbon–Boron and Carbon–Silicon Bond Formation. In *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A.; Krause, N.; Woodward, S., Eds.; Wiley-VCH: Weinheim, Germany, 2014; pp 157–177.
- (9) Kubota, K.; Ito, H. Catalytic Generation of Silicon Nucleophiles. In *Organosilicon Chemistry: Novel Approaches and Reactions*; Hiyama, T.; Oestreich, M., Eds.; Wiley-VCH: Weinheim, Germany, 2019; pp 1–31.
- (10) Wilkinson, J. R.; Nuyen, C. E.; Carpenter, T. S.; Harruff, S. R.; Van Hoveln, R. Copper-Catalyzed Carbon–Silicon Bond Formation. *ACS Catal.* **2019**, 9, 8961–8979.



- (11) Bähr, S.; Xue, W.; Oestreich, M. C(sp<sup>3</sup>)-Si Cross-Coupling. *ACS Catal.* **2019**, *9*, 16–24.
- (12) Baker, S. J.; Tomsho, J. W.; Benkovic, S. J. Boron-Containing Inhibitors of Synthetases. *Chem. Soc. Rev.* **2011**, *40*, 4279–4285.
- (13) Diaz, D. B.; Yudin, A. K. The Versatility of Boron in Biological Target Engagement. *Nat. Chem.* **2017**, *9*, 731–742.
- (14) Ramesh, R.; Reddy, D. S. Quest for Novel Chemical Entities through Incorporation of Silicon in Drug Scaffolds. *J. Med. Chem.* **2018**, *61*, 3779–3798.
- (15) Franz, A. K.; Wilson, S. O. Organosilicon Molecules with Medicinal Applications. *J. Med. Chem.* **2013**, *56*, 388–405.
- (16) Tacke, R.; Dörrich, S. Drug Design Based on the Carbon/Silicon Switch Strategy. In *Atypical Elements in Drug Design*; Schwarz, J., Ed.; Springer: Cham, Switzerland, 2016; pp 29–59.
- (17) Qiu, F.; Zhao, W.; Han, S.; Zhuang, X.; Lin, H.; Zhang, F. Recent Advances in Boron-Containing Conjugated Porous Polymers. *Polymers* **2016**, *8*, 191.
- (18) Auner, N.; Weis, J., Eds. *Organosilicon Chemistry VI: From Molecules to Materials*; Wiley-VCH: Weinheim, Germany, 2005.
- (19) Fernández, E.; Whiting, A., Eds. *Synthesis and Application of Organoboron Compounds*; Springer: Cham, Switzerland, 2015.
- (20) Hiyama, T.; Oestreich, M., Eds. *Organosilicon Chemistry: Novel Approaches and Reactions*; Wiley-VCH: Weinheim, Germany, 2019.
- (21) Cheng, Q.-Q.; Zhu, S.-F.; Zhang, Y.-Z.; Xie, X.-L.; Zhou, Q.-L. Copper-Catalyzed B–H Bond Insertion Reaction: A Highly Efficient and Enantioselective C–B Bond-Forming Reaction with Amine–Borane and Phosphine–Borane Adducts. *J. Am. Chem. Soc.* **2013**, *135*, 14094–14097.
- (22) Zhang, Y. Z.; Zhu, S. F.; Wang, L. X.; Zhou, Q. L. Copper-Catalyzed Highly Enantioselective Carbenoid Insertion into Si–H Bonds. *Angew. Chem., Int. Ed.* **2008**, *47*, 8496–8498.
- (23) Hyde, S.; Velicks, J.; Liégault, B.; Grassi, D.; Taillefer, M.; Gouverneur, V. Copper-Catalyzed Insertion into Heteroatom–Hydrogen Bonds with Trifluorodiazalkanes. *Angew. Chem., Int. Ed.* **2016**, *55*, 3785–3789.
- (24) Xi, Y.; Hartwig, J. F. Diverse Asymmetric Hydrofunctionalization of Aliphatic Internal Alkenes through Catalytic Regioselective Hydroboration. *J. Am. Chem. Soc.* **2016**, *138*, 6703–6706.
- (25) Jang, W. J.; Song, S. M.; Moon, J. H.; Lee, J. Y.; Yun, J. Copper-Catalyzed Enantioselective Hydroboration of Unactivated 1,1-Disubstituted Alkenes. *J. Am. Chem. Soc.* **2017**, *139*, 13660–13663.
- (26) Gribble, M. W.; Pirnot, M. T.; Bandar, J. S.; Liu, R. Y.; Buchwald, S. L. Asymmetric Copper Hydride-Catalyzed Markovnikov Hydrosilylation of Vinylarenes and Vinyl Heterocycles. *J. Am. Chem. Soc.* **2017**, *139*, 2192–2195.
- (27) Obligation, J. V.; Chirik, P. J. Earth-Abundant Transition Metal Catalysts For Alkene Hydrosilylation and Hydroboration. *Nat. Rev. Chem.* **2018**, *2*, 15–34.
- (28) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. Boration of an  $\alpha,\beta$ -Enone Using a Diboron Promoted by a Copper(I)–Phosphine Mixture Catalyst. *Tetrahedron Lett.* **2000**, *41*, 6821–6825.
- (29) Takahashi, K.; Ishiyama, T.; Miyaura, N. Addition and Coupling Reactions of Bis(pinacolato)diboron Mediated by CuCl in the Presence of Potassium Acetate. *Chem. Lett.* **2000**, *29*, 982–983.
- (30) Takahashi, K.; Ishiyama, T.; Miyaura, N. A Borylcopper Species Generated from Bis(pinacolato)diboron and its Additions to  $\alpha,\beta$ -Unsaturated Carbonyl Compounds and Terminal Alkynes. *J. Organomet. Chem.* **2001**, *625*, 47–53.
- (31) Ito, H.; Ishizuka, T.; Tateiwa, J.; Sonoda, M.; Hosomi, A. New Method for Introduction of a Silyl Group into  $\alpha,\beta$ -Enones Using a Disilane Catalyzed by a Copper(I) Salt. *J. Am. Chem. Soc.* **1998**, *120*, 11196–11197.
- (32) Clark, C. T.; Lake, J. F.; Scheidt, K. A. Copper(I)-Catalyzed Disilylation of Alkylidene Malonates Employing a Lewis Base Activation Strategy. *J. Am. Chem. Soc.* **2004**, *126*, 84–85.
- (33) Lee, K.-S.; Hoveyda, A. H. Enantioselective Conjugate Silyl Additions to Cyclic and Acyclic Unsaturated Carbonyls Catalyzed by Cu Complexes of Chiral N-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900.
- (34) Vyas, D. J.; Oestreich, M. Copper-Catalyzed Si–B Bond Activation in Branched-Selective Allylic Substitution of Linear Allylic Chlorides. *Angew. Chem., Int. Ed.* **2010**, *49*, 8513–8515.
- (35) Welle, A.; Petriguet, J.; Tinant, B.; Wouters, J.; Riant, O. Copper-Catalyzed Domino Silylative Aldol Reaction Leading to Stereocontrolled Chiral Quaternary Carbons. *Chem. - Eur. J.* **2010**, *16*, 10980–10983.
- (36) Ager, D. J.; Fleming, I. A Silicon-Based Protecting Group for the  $\alpha,\beta$ -Unsaturated Ketones. *J. Chem. Soc., Chem. Commun.* **1978**, 177–178.
- (37) Lipshutz, B. H.; Sclafani, J. A.; Takanami, T. Silyl Cuprate Couplings: Less Silicon, Accelerated, Yet Catalytic in Copper. *J. Am. Chem. Soc.* **1998**, *120*, 4021–4022.
- (38) Okuda, Y.; Morizawa, Y.; Oshima, K.; Nozaki, H. Intramolecular Cyclization Mediated by Silylmetalation of Acetylenes with PhMe<sub>2</sub>SiMgMe/CuI and Radical Nature of the Reagent. *Tetrahedron Lett.* **1984**, *25*, 2483–2486.
- (39) Xue, W.; Oestreich, M. Silicon Grignard Reagents as Nucleophiles in Transition-Metal-Catalyzed Allylic Substitution. *Synthesis* **2019**, *51*, 233–239.
- (40) Weickgenannt, A.; Oestreich, M. Silicon- and Tin-Based Cuprates: Now Catalytic in Copper! *Chem. - Eur. J.* **2010**, *16*, 402–412.
- (41) Neeve, E. C.; Geier, S. J.; Mkhaliid, I. A. I.; Westcott, S. A.; Marder, T. B. Diboron(4) Compounds: From Structural Curiosity to Synthetic Workhorse. *Chem. Rev.* **2016**, *116*, 9091–9161.
- (42) Oestreich, M.; Hartmann, E.; Mewald, M. Activation of the Si–B Interelement Bond: Mechanism, Catalysis, and Synthesis. *Chem. Rev.* **2013**, *113*, 402–441.
- (43) Kubota, K.; Yamamoto, E.; Ito, H. Copper(I)-Catalyzed Enantioselective Nucleophilic Borylation of Aldehydes: An Efficient Route to Enantiomerically Enriched  $\alpha$ -Alkoxyorganoboronate Esters. *J. Am. Chem. Soc.* **2015**, *137*, 420–424.
- (44) Kubota, K.; Osaki, S.; Jin, M.; Ito, H. Copper(I)-Catalyzed Enantioselective Nucleophilic Borylation of Aliphatic Ketones: Synthesis of Enantioenriched Chiral Tertiary  $\alpha$ -Hydroxyboronates. *Angew. Chem., Int. Ed.* **2017**, *56*, 6646–6650.
- (45) 1,2-Addition to aldehydes with Cu–Si intermediates: Cirriez, V.; Rasson, C.; Hermant, T.; Petriguet, J.; Díaz Álvarez, J.; Robeyns, K.; Riant, O. Copper-Catalyzed Addition of Nucleophilic Silicon to Aldehydes. *Angew. Chem., Int. Ed.* **2013**, *52*, 1785–1788.
- (46) 1,2-Addition to imines with Cu–B intermediates: Zhang, S.-S.; Zhao, Y.-S.; Tian, P.; Lin, G.-Q. Chiral NHC/Cu(I)-Catalyzed Asymmetric Hydroboration of Aldimines: Enantioselective Synthesis of  $\alpha$ -Amido Boronic Esters. *Synlett* **2013**, *24*, 437–442.
- (47) Wang, D.; Cao, P.; Wang, B.; Jia, T.; Lou, Y.; Wang, M.; Liao, J. Copper(I)-Catalyzed Asymmetric Pinacolboron Addition of N-Boc-Imines Using a Chiral Sulfoxide–Phosphine Ligand. *Org. Lett.* **2015**, *17*, 2420–2423.
- (48) Hensel, A.; Nagura, K.; Delves, L. B.; Oestreich, M. Enantioselective Addition of Silicon Nucleophiles to Aldimines Using a Preformed NHC–Copper(I) Complex as the Catalyst. *Angew. Chem., Int. Ed.* **2014**, *53*, 4964–4967.
- (49) Mita, T.; Sugawara, M.; Saito, K.; Sato, Y. Catalytic Enantioselective Silylation of N-Sulfonylimines: Asymmetric Synthesis of  $\alpha$ -Amino Acids From CO<sub>2</sub> via Stereospecific Carboxylation of  $\alpha$ -Amino Silanes. *Org. Lett.* **2014**, *16*, 3028–3031.
- (50) Zhao, C.; Jiang, C.; Wang, J.; Wu, C.; Zhang, Q. W.; He, W. Enantioselective Syntheses of  $\alpha$ -Silyl Amines via a Copper-N-Heterocyclic Carbene Catalyzed Nucleophilic Silicon Transfer to Imines. *Asian J. Org. Chem.* **2014**, *3*, 851–855.
- (51) Chen, Z.; Huo, Y.; An, P.; Wang, X.; Song, C.; Ma, Y. [2.2]Paracyclophane-Based N-Heterocyclic Carbene as Efficient Catalyst or as Ligand for Copper Catalyst for Asymmetric  $\alpha$ -Silylation of N-Tosylaldimines. *Org. Chem. Front.* **2016**, *3*, 1725–1737.
- (52) For the seminal report of asymmetric conjugate addition with Cu–B intermediates, see: Lee, J.-E.; Yun, J. Catalytic Asymmetric Boration of Acyclic  $\alpha,\beta$ -Unsaturated Esters and Nitriles. *Angew. Chem., Int. Ed.* **2008**, *47*, 145–147. For recent reviews, see refs 4–8.

(53) For the seminal report of conjugate addition with Cu–Si intermediates, see ref 33. For recent reviews, see refs 6–11.

(54) Hoveyda, A. H.; Zhou, Y.; Shi, Y.; Brown, K.; Wu, H.; Torker, S. Sulfonate N-Heterocyclic Carbene–Copper Complexes: Uniquely Effective Catalysts for Enantioselective C–C, C–B, C–H, and C–Si Bond Formation. *Angew. Chem., Int. Ed.* **2020**, DOI: 10.1002/anie.202003755.

(55) Narayan, R. Enantioselective Catalysis Using Copper(I)–Phosphine Complexes. In *Copper(I) Chemistry of Phosphines, Functionalized Phosphines and Phosphorus Heterocycles*; Balakrishna, M. S., Ed.; Elsevier: Amsterdam, The Netherlands, 2019; pp 259–313.

(56) Hoveyda, A. H.; Koh, M. J.; Lee, K.; Lee, J. Catalytic, Enantioselective, Copper–Boryl Additions to Alkenes. In *Organic Reactions*; Denmark, S. E., Ed.; Wiley: Hoboken, NJ, 2019; pp 959–1056.

(57) Corberán, R.; Mszar, N. W.; Hoveyda, A. H. NHC–Cu-Catalyzed Enantioselective Hydroboration of Acyclic and Exocyclic 1,1-Disubstituted Aryl Alkenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 7079–7082.

(58) Wang, Z.; He, X.; Zhang, R.; Zhang, G.; Xu, G.; Zhang, Q.; Xiong, T.; Zhang, Q. Copper-Catalyzed Asymmetric Hydroboration of 1,1-Disubstituted Alkenes. *Org. Lett.* **2017**, *19*, 3067–3070.

(59) Wen, L.; Cheng, F.; Li, H.; Zhang, S.; Hong, X.; Meng, F. Copper-Catalyzed Enantioselective Hydroboration of 1,1-Disubstituted Alkenes: Method Development, Applications and Mechanistic Studies. *Asian J. Org. Chem.* **2018**, *7*, 103–106.

(60) For a computational study, see: Dang, L.; Zhao, H.; Lin, Z.; Marder, T. B. DFT Studies of Alkene Insertions into Cu–B Bonds in Copper(I) Boryl Complexes. *Organometallics* **2007**, *26*, 2824–2832.

(61) Cai, Y.; Yang, X. T.; Zhang, S. Q.; Li, F.; Li, Y. Q.; Ruan, L. X.; Hong, X.; Shi, S. L. Copper-Catalyzed Enantioselective Markovnikov Protoboration of  $\alpha$ -Olefins Enabled by a Buttressed N-Heterocyclic Carbene Ligand. *Angew. Chem., Int. Ed.* **2018**, *57*, 1376–1380.

(62) Iwamoto, H.; Imamoto, T.; Ito, H. Computational Design of High-Performance Ligand for Enantioselective Markovnikov Hydroboration of Aliphatic Terminal Alkenes. *Nat. Commun.* **2018**, *9*, 2290.

(63) Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; García Ruano, J. L.; Tortosa, M. Copper-Catalyzed Diastereo- and Enantioselective Desymmetrization of Cyclopropenes: Synthesis of Cyclopropylboronates. *J. Am. Chem. Soc.* **2014**, *136*, 15833–15836.

(64) Guisán-Ceinos, M.; Parra, A.; Martín-Heras, V.; Tortosa, M. Enantioselective Synthesis of Cyclobutylboronates via a Copper-Catalyzed Desymmetrization Approach. *Angew. Chem., Int. Ed.* **2016**, *55*, 6969–6972.

(65) Zhang, L.; Oestreich, M. Copper-Catalyzed Enantio- and Diastereoselective Addition of Silicon Nucleophiles to 3,3-Disubstituted Cyclopropenes. *Chem. - Eur. J.* **2019**, *25*, 14304–14307.

(66) Cui, M.; Oestreich, M. Copper-Catalyzed Enantioselective and Exo-Selective Addition of Silicon Nucleophiles to 7-Oxa- and 7-Azabenzonorbornadiene Derivatives. *Org. Lett.* **2020**, *22*, 3684–3687.

(67) Lee, Y.; Hoveyda, A. H. Efficient Boron–Copper Additions to Aryl-Substituted Alkenes Promoted by NHC–Based Catalysts. Enantioselective Cu-Catalyzed Hydroboration Reactions. *J. Am. Chem. Soc.* **2009**, *131*, 3160–3161.

(68) Lee, Y.; Jang, H.; Hoveyda, A. H. Vicinal Diboronates in High Enantiomeric Purity through Tandem Site-Selective NHC–Cu-Catalyzed Boron–Copper Additions to Terminal Alkynes. *J. Am. Chem. Soc.* **2009**, *131*, 18234–18235.

(69) Kubota, K.; Yamamoto, E.; Ito, H. Regio- and Enantioselective Monoborylation of Alkenylsilanes Catalyzed by an Electron-Donating Chiral Phosphine–Copper(I) Complex. *Adv. Synth. Catal.* **2013**, *355*, 3527–3531.

(70) Tobisch, S. Copper-Catalyzed Aminoboration of Vinylarenes with Hydroxylamine Esters—A Computational Mechanistic Study. *Chem. - Eur. J.* **2017**, *23*, 17800–17809.

(71) Ito, H.; Kawakami, C.; Sawamura, M. Copper-Catalyzed  $\gamma$ -Selective and Stereospecific Substitution Reaction of Allylic

Carbonates with Diboron: Efficient Route to Chiral Allylboron Compounds. *J. Am. Chem. Soc.* **2005**, *127*, 16034–16035.

(72) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. Copper-catalyzed Enantioselective Substitution of Allylic Carbonates with Diboron: An Efficient Route to Optically Active  $\alpha$ -Chiral Allylboronates. *J. Am. Chem. Soc.* **2007**, *129*, 14856–14857.

(73) Guzman-Martinez, A.; Hoveyda, A. H. Enantioselective Synthesis of Allylboronates Bearing a Tertiary or Quaternary B-Substituted Stereogenic Carbon by NHC–Cu-Catalyzed Substitution Reactions. *J. Am. Chem. Soc.* **2010**, *132*, 10634–10637.

(74) Park, J. K.; Lackey, H. H.; Ondrusek, B. A.; McQuade, D. T. Stereoconvergent Synthesis of Chiral Allylboronates from an *E/Z* Mixture of Allylic Aryl Ethers Using a 6-NHC–Cu(I) Catalyst. *J. Am. Chem. Soc.* **2011**, *133*, 2410–2413.

(75) Yamamoto, E.; Takenouchi, Y.; Ozaki, T.; Miya, T.; Ito, H. Copper(I)-Catalyzed Enantioselective Synthesis of  $\alpha$ -Chiral Linear or Carbocyclic (*E*)-( $\gamma$ -Alkoxyallyl)boronates. *J. Am. Chem. Soc.* **2014**, *136*, 16515–16521.

(76) Delvos, L. B.; Vyas, D. J.; Oestreich, M. Asymmetric Synthesis of  $\alpha$ -Chiral Allylic Silanes by Enantioconvergent  $\gamma$ -Selective Copper(I)-Catalyzed Allylic Silylation. *Angew. Chem., Int. Ed.* **2013**, *52*, 4650–4653.

(77) Takeda, M.; Shintani, R.; Hayashi, T. Enantioselective Synthesis of  $\alpha$ -Tri- and  $\alpha$ -Tetrasubstituted Allylsilanes by Copper-Catalyzed Asymmetric Allylic Substitution of Allyl Phosphates with Silylboronates. *J. Org. Chem.* **2013**, *78*, 5007–5017.

(78) Hensel, A.; Oestreich, M. Asymmetric Catalysis with Silicon-Based Cuprates: Enantio- and Regioselective Allylic Substitution of Linear Precursors. *Chem. - Eur. J.* **2015**, *21*, 9062–9065.

(79) Ito, H.; Kunii, S.; Sawamura, M. Direct enantio-convergent transformation of racemic substrates without racemization or symmetrization. *Nat. Chem.* **2010**, *2*, 972–976.

(80) Delvos, L. B.; Oestreich, M. Temperature-Dependent Direct Enantioconvergent Silylation of a Racemic Cyclic Allylic Phosphate by Copper(I)-Catalyzed Allylic Substitution. *Synthesis* **2015**, *47*, 924–933.

(81) Ge, Y.; Cui, X. Y.; Tan, S. M.; Jiang, H.; Ren, J.; Lee, N.; Lee, R.; Tan, C. H. Guanidine–Copper Complex Catalyzed Allylic Borylation for the Enantioconvergent Synthesis of Tertiary Cyclic Allylboronates. *Angew. Chem., Int. Ed.* **2019**, *58*, 2382–2386.

(82) Kojima, R.; Akiyama, S.; Ito, H. A Copper(I)-Catalyzed Enantioselective  $\gamma$ -Boryl Substitution of Trifluoromethyl-Substituted Alkenes: Synthesis of Enantioenriched  $\gamma,\gamma$ -gem-Difluoroallylboronates. *Angew. Chem., Int. Ed.* **2018**, *57*, 7196–7199.

(83) Gao, P.; Yuan, C.; Zhao, Y.; Shi, Z. Copper-Catalyzed Asymmetric Defluoroborylation of 1-(Trifluoromethyl)Alkenes. *Chem.* **2018**, *4*, 2201–2211.

(84) Paioti, P. H.; del Pozo, J.; Mikus, M. S.; Lee, J.; Koh, M. J.; Romiti, F.; Torker, S.; Hoveyda, A. H. Catalytic Enantioselective Boryl and Silyl Substitution with Trifluoromethyl Alkenes: Scope, Utility, and Mechanistic Nuances of Cu–F  $\beta$ -Elimination. *J. Am. Chem. Soc.* **2019**, *141*, 19917–19934.

(85) Akiyama, S.; Kubota, K.; Mikus, M. S.; Paioti, P. H.; Romiti, F.; Liu, Q.; Zhou, Y.; Hoveyda, A. H.; Ito, H. Catalytic Enantioselective Synthesis of Allylic Boronates Bearing a Trisubstituted Alkenyl Fluoride and Related Derivatives. *Angew. Chem., Int. Ed.* **2019**, *58*, 11998–12003.

(86) Pulis, A. P.; Yeung, K.; Procter, D. J. Enantioselective Copper Catalysed, Direct Functionalisation of Allenes via Allyl Copper Intermediates. *Chem. Sci.* **2017**, *8*, 5240–5247.

(87) Holmes, M.; Schwartz, L. A.; Krische, M. J. Intermolecular Metal-Catalyzed Reductive Coupling of Dienes, Allenes, and Enynes with Carbonyl Compounds and Imines. *Chem. Rev.* **2018**, *118*, 6026–6052.

(88) Perry, G. J.; Jia, T.; Procter, D. J. Copper-Catalyzed Functionalization of 1,3-Dienes: Hydrofunctionalization, Borofunctionalization and Difunctionalization. *ACS Catal.* **2020**, *10*, 1485–1499.

- (89) Li, X.; Wu, H.; Wu, Z.; Huang, G. Mechanism and Origins of Regioselectivity of Copper-Catalyzed Borocyanation of 2-Aryl-Substituted 1,3-Dienes: A Computational Study. *J. Org. Chem.* **2019**, *84*, 5514–5523.
- (90) Guo, X.; Wang, T.; Zheng, Y.; Zhou, L.; Li, J. Computational Study of Regiodivergent Pathways in the Copper-Catalyzed Borocyanation of 1,3-Dienes: Mechanism and Origin of Regioselectivity. *J. Organomet. Chem.* **2019**, *904*, 121014.
- (91) Mejuch, T.; Gilboa, N.; Gayon, E.; Wang, H.; Houk, K. N.; Marek, I. Axial Preferences in Allylation Reactions via the Zimmerman–Traxler Transition State. *Acc. Chem. Res.* **2013**, *46*, 1659–1669.
- (92) For computational studies supporting the 6-membered Zimmerman–Traxler-type transition state, see refs **89**, **90**, and **104**.
- (93) There is also evidence for other transition states. See ref **108** for a 4-membered transition state and ref **109** for an 8-membered transition state.
- (94) Meng, F.; Jang, H.; Jung, B.; Hoveyda, A. H. Cu-Catalyzed Chemoselective Preparation of 2-(Pinacolato)boron-Substituted Allylcopper Complexes and Their *In Situ* Site-, Diastereo-, and Enantioselective Additions to Aldehydes and Ketones. *Angew. Chem., Int. Ed.* **2013**, *52*, S046–S051.
- (95) Meng, F.; Haefner, F.; Hoveyda, A. H. Diastereo- and Enantioselective Reactions of Bis(pinacolato)diboron, 1,3-Enynes, and Aldehydes Catalyzed by an Easily Accessible Bisphosphine–Cu Complex. *J. Am. Chem. Soc.* **2014**, *136*, 11304–11307.
- (96) Green, J. C.; Joannou, M. V.; Murray, S. A.; Zanghi, J. M.; Meek, S. J. Enantio- and Diastereoselective Synthesis of Hydroxy Bis(boronates) via Cu-Catalyzed Tandem Borylation/1,2-Addition. *ACS Catal.* **2017**, *7*, 4441–4445.
- (97) Cheng, F.; Lu, W.; Huang, W.; Wen, L.; Li, M.; Meng, F. Cu-Catalyzed Enantioselective Synthesis of Tertiary Benzylic Copper Complexes and Their *in situ* Addition to Carbonyl Compounds. *Chem. Sci.* **2018**, *9*, 4992–4998.
- (98) Gan, X.-C.; Zhang, Q.; Jia, X.-S.; Yin, L. Asymmetric Construction of Fluoroalkyl Tertiary Alcohols through a Three-Component Reaction of (Bpin)<sub>2</sub>, 1,3-Enynes, and Fluoroalkyl Ketones Catalyzed by a Copper(I) Complex. *Org. Lett.* **2018**, *20*, 1070–1073.
- (99) Gan, X.-C.; Yin, L. Asymmetric Borylative Propargylation of Ketones Catalyzed by a Copper(I) Complex. *Org. Lett.* **2019**, *21*, 931–936.
- (100) Feng, J. J.; Oestreich, M. Tertiary  $\alpha$ -Silyl Alcohols by Diastereoselective Coupling of 1,3-Dienes and Acylsilanes Initiated by Enantioselective Copper-Catalyzed Borylation. *Angew. Chem., Int. Ed.* **2019**, *58*, 8211–8215.
- (101) Feng, J.-J.; Xu, Y.; Oestreich, M. Ligand-Controlled Diastereodivergent, Enantio- and Regioselective Copper-Catalyzed Hydroxyalkylboration of 1,3-Dienes with Ketones. *Chem. Sci.* **2019**, *10*, 9679–9683.
- (102) Yeung, K.; Ruscoe, R. E.; Rae, J.; Pulis, A. P.; Procter, D. J. Enantioselective Generation of Adjacent Stereocenters in a Copper-Catalyzed Three-Component Coupling of Imines, Allenes, and Diboranes. *Angew. Chem., Int. Ed.* **2016**, *55*, 11912–11916.
- (103) Jiang, L.; Cao, P.; Wang, M.; Chen, B.; Wang, B.; Liao, J. Highly Diastereo- and Enantioselective Cu-Catalyzed Borylative Coupling of 1,3-Dienes and Aldimines. *Angew. Chem., Int. Ed.* **2016**, *55*, 13854–13858.
- (104) Jang, H.; Romiti, F.; Torker, S.; Hoveyda, A. H. Catalytic Diastereo- and Enantioselective Additions of Versatile Allyl Groups to N–H Ketimines. *Nat. Chem.* **2017**, *9*, 1269–1275.
- (105) Itoh, T.; Kanzaki, Y.; Shimizu, Y.; Kanai, M. Copper(I)-Catalyzed Enantio- and Diastereodivergent Borylative Coupling of Styrenes and Imines. *Angew. Chem., Int. Ed.* **2018**, *57*, 8265–8269.
- (106) Manna, S.; Dherbassy, Q.; Perry, G. J.; Procter, D. J. Enantio- and Diastereoselective Synthesis of Homopropargyl Amines by Copper-Catalyzed Coupling of Imines, 1,3-Enynes, and Diboranes. *Angew. Chem., Int. Ed.* **2020**, *59*, 4879–4882.
- (107) Fiorito, D.; Liu, Y.; Besnard, C.; Mazet, C. Direct Access to Chiral Secondary Amides by Copper-Catalyzed Borylative Carboxamidation of Vinylarenes with Isocyanates. *J. Am. Chem. Soc.* **2020**, *142*, 623–632.
- (108) Li, X.; Meng, F.; Torker, S.; Shi, Y.; Hoveyda, A. H. Catalytic Enantioselective Conjugate Additions of (pin)B-Substituted Allylcopper Compounds Generated *in situ* from Butadiene or Isoprene. *Angew. Chem., Int. Ed.* **2016**, *55*, 9997–10002.
- (109) Meng, F.; Li, X.; Torker, S.; Shi, Y.; Shen, X.; Hoveyda, A. H. Catalytic Enantioselective 1,6-Conjugate Additions of Propargyl and Allyl Groups. *Nature* **2016**, *537*, 387–393.
- (110) Jia, T.; Smith, M. J.; Pulis, A. P.; Perry, G. J.; Procter, D. J. Enantioselective and Regioselective Copper-Catalyzed Borocyanation of 1-Aryl-1,3-Butadienes. *ACS Catal.* **2019**, *9*, 6744–36750.
- (111) For mechanistic investigations of borylative cyanation, see refs **89** and **90**.
- (112) Huang, Y.; Smith, K. B.; Brown, M. K. Copper-Catalyzed Borylacylation of Activated Alkenes with Acid Chlorides. *Angew. Chem., Int. Ed.* **2017**, *56*, 13314–13318.
- (113) Han, J.; Zhou, W.; Zhang, P.-C.; Wang, H.; Zhang, R.; Wu, H.-H.; Zhang, J. Design and Synthesis of WJ-Phos, and Application in Cu-Catalyzed Enantioselective Boroacylation of 1,1-Disubstituted Allenes. *ACS Catal.* **2019**, *9*, 6890–6895.
- (114) Chen, B.; Cao, P.; Liao, Y.; Wang, M.; Liao, J. Enantioselective Copper-Catalyzed Methylboration of Alkenes. *Org. Lett.* **2018**, *20*, 1346–1349.
- (115) Meng, F.; McGrath, K. P.; Hoveyda, A. H. Multifunctional Organoboron Compounds for Scalable Natural Product Synthesis. *Nature* **2014**, *513*, 367–374.
- (116) Lee, J.; Radomkit, S.; Torker, S.; Del Pozo, J.; Hoveyda, A. H. Mechanism-Based Enhancement of Scope and Enantioselectivity for Reactions Involving a Copper-Substituted Stereogenic Carbon Centre. *Nat. Chem.* **2018**, *10*, 99–108.
- (117) Kim, N.; Han, J. T.; Ryu, D. H.; Yun, J. Copper-Catalyzed Asymmetric Borylallylation of Vinyl Arenes. *Org. Lett.* **2017**, *19*, 6144–6147.
- (118) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. Regioselective and Stereospecific Copper-Catalyzed Aminoboration of Styrenes with Bis(pinacolato)diboron and *O*-Benzoyl-*N,N*-dialkylhydroxyl-amines. *J. Am. Chem. Soc.* **2013**, *135*, 4934–4937.
- (119) Sakae, R.; Hirano, K.; Satoh, T.; Miura, M. Copper-Catalyzed Stereoselective Aminoboration of Bicyclic Alkenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 613–617.
- (120) Nishikawa, D.; Hirano, K.; Miura, M. Copper-Catalyzed Regio- and Stereoselective Aminoboration of Alkenylboronates. *Org. Lett.* **2016**, *18*, 4856–4859.
- (121) Jiang, H.-C.; Tang, X.-Y.; Shi, M. Copper-Catalyzed Regio- and Enantioselective Aminoboration of Alkylidenecyclopropanes: The Synthesis of Cyclopropane-Containing  $\beta$ -Aminoalkylboranes. *Chem. Commun.* **2016**, *52*, 5273–5276.
- (122) Kato, K.; Hirano, K.; Miura, M. Copper-Catalyzed Regio- and Enantioselective Aminoboration of Unactivated Terminal Alkenes. *Chem. - Eur. J.* **2018**, *24*, 5775–5778.
- (123) Wu, L.; Zatulochyna, O.; Qu, B.; Wu, L.; Wells, L. A.; Kozłowski, M. C.; Senanayake, C. H.; Song, J. J.; Zhang, Y. Cu-Catalyzed Asymmetric Aminoboration of *E*-Vinylarenes with <sup>ptiv</sup>ZPhos as the Ligand. *Org. Lett.* **2019**, *21*, 8952–8956.
- (124) For a mechanistic investigation of borylative amination, see ref **70**.
- (125) Jia, T.; Cao, P.; Wang, D.; Lou, Y.; Liao, J. Copper-Catalyzed Asymmetric Three-Component Borylstannation: Enantioselective Formation of C–Sn Bond. *Chem. - Eur. J.* **2015**, *21*, 4918–4922.
- (126) Allen, A. E.; Macmillan, D. W. C. Synergistic Catalysis: A Powerful Synthetic Strategy for New Reaction Development. *Chem. Sci.* **2012**, *3*, 633–658.
- (127) Liu, Z.; Gao, Y.; Zeng, T.; Engle, K. M. Transition-Metal-Catalyzed 1,2-Carboboration of Alkenes: Strategies, Mechanisms, and Stereocontrol. *Isr. J. Chem.* **2020**, *60*, 219–229.
- (128) Logan, K. M.; Smith, K. B.; Brown, M. K. Copper/Palladium Synergistic Catalysis for the *syn*- and *anti*-Selective Carboboration of Alkenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 5228–5231.



- (129) Jia, T.; Cao, P.; Wang, B.; Lou, Y.; Yin, X.; Wang, M.; Liao, J. A Cu/Pd Cooperative Catalysis for Enantioselective Allylboration of Alkenes. *J. Am. Chem. Soc.* **2015**, *137*, 13760–13763.
- (130) Logan, K. M.; Brown, M. K. Catalytic Enantioselective Arylboration of Alkenylarenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 851–855.
- (131) Bergmann, A. M.; Dorn, S. K.; Smith, K. B.; Logan, K. M.; Brown, M. K. Catalyst-Controlled 1,2- and 1,1-Arylboration of  $\alpha$ -Alkyl Alkenyl Arenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 1719–1723.
- (132) Lee, H.; Lee, S.; Yun, J. Pd-Catalyzed Stereospecific Cross-Coupling of Chiral  $\alpha$ -Borylalkylcopper Species with Aryl Bromides. *ACS Catal.* **2020**, *10*, 2069–2073.
- (133) Huang, Y.; Brown, M. K. Synthesis of Bisheteroarylalkanes by Heteroarylboration: Development and Application of a Pyridylidene-Copper Complex. *Angew. Chem., Int. Ed.* **2019**, *58*, 6048–6052.
- (134) Sardini, S. R.; Brown, M. K. Catalyst Controlled Regiodivergent Arylboration of Dienes. *J. Am. Chem. Soc.* **2017**, *139*, 9823–9826.
- (135) Liao, Y.; Yin, X.; Wang, X.; Yu, W.; Fang, D.; Hu, L.; Wang, M.; Liao, J. Enantioselective Synthesis of Multisubstituted Allenes by Cooperative Cu/Pd-Catalyzed 1,4-Arylboration of 1,3-Enynes. *Angew. Chem., Int. Ed.* **2020**, *59*, 1176–1180.
- (136) Fleming, I.; Rowley, M.; Cuadrado, P.; González-Nogal, A. M.; Pulido, F. J. The Silyl-Cupration and Stannyl-Cupration of Allenes. *Tetrahedron* **1989**, *45*, 413–424.
- (137) Barbero, A.; Pulido, F. J. Allylsilanes and Vinylsilanes from Silylcupration of Carbon–Carbon Multiple Bonds: Scope and Synthetic Applications. *Acc. Chem. Res.* **2004**, *37*, 817–825.
- (138) Takeda, M.; Mitsui, A.; Nagao, K.; Ohmiya, H. Reductive Coupling between Aromatic Aldehydes and Ketones or Imines by Copper Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 3664–3669.
- (139) Mitsui, A.; Nagao, K.; Ohmiya, H. Copper-Catalyzed Enantioselective Reductive Cross-Coupling of Aldehydes and Imines. *Org. Lett.* **2020**, *22*, 800–803.
- (140) Yabushita, K.; Yuasa, A.; Nagao, K.; Ohmiya, H. Asymmetric Catalysis Using Aromatic Aldehydes as Chiral  $\alpha$ -Alkoxyalkyl Anions. *J. Am. Chem. Soc.* **2019**, *141*, 113–117.
- (141) Brook, A. G. Isomerism of Some  $\alpha$ -Hydroxysilanes to Silyl Ethers. *J. Am. Chem. Soc.* **1958**, *80*, 1886–1889.
- (142) Brook, A. G. Molecular Rearrangements of Organosilicon Compounds. *Acc. Chem. Res.* **1974**, *7*, 77–84.
- (143) Zhong, C.; Kunii, S.; Kosaka, Y.; Sawamura, M.; Ito, H. Enantioselective Synthesis of *trans*-Aryl- and -Heteroaryl-Substituted Cyclopropylboronates by Copper(I)-Catalyzed Reactions of Allylic Phosphates with a Diboron Derivative. *J. Am. Chem. Soc.* **2010**, *132*, 11440–11442.
- (144) Burns, A. R.; Solana González, J.; Lam, H. W. Enantioselective Copper (I)-Catalyzed Borylative Aldol Cyclizations of Enone Diones. *Angew. Chem., Int. Ed.* **2012**, *51*, 10827–10831.
- (145) Whyte, A.; Burton, K. I.; Zhang, J.; Lautens, M. Enantioselective Intramolecular Copper-Catalyzed Borylacylation. *Angew. Chem., Int. Ed.* **2018**, *57*, 13927–13930.
- (146) Whyte, A.; Mirabi, B.; Torelli, A.; Prieto, L.; Bajohr, J.; Lautens, M. Asymmetric Synthesis of Boryl-Functionalized Cyclobutanols. *ACS Catal.* **2019**, *9*, 9253–9258.
- (147) Whyte, A.; Torelli, A.; Mirabi, B.; Lautens, M. Enantioselective Copper-Catalyzed Borylative Cyclization with Cyclic Imides. *Org. Lett.* **2019**, *21*, 8373–8377.
- (148) Larin, E. M.; Loup, J.; Polishchuk, I.; Ross, R. J.; Whyte, A.; Lautens, M. Enantio- and Diastereoselective Conjugate Borylation/Mannich Cyclization. *Chem. Sci.* **2020**, *11*, 5716–5723.
- (149) He, Z. T.; Tang, X. Q.; Xie, L. B.; Cheng, M.; Tian, P.; Lin, G. Q. Efficient Access to Bicyclo[4.3.0]nonanes: Copper-Catalyzed Asymmetric Silylative Cyclization of Cyclohexadienone-Tethered Allenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 14815–14818.
- (150) Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. Alkylboronic Esters from Copper-Catalyzed Borylation of Primary and Secondary Alkyl Halides and Pseudohalides. *Angew. Chem., Int. Ed.* **2012**, *51*, 528–532.
- (151) Ito, H.; Kubota, K. Copper(I)-Catalyzed Boryl Substitution of Unactivated Alkyl Halides. *Org. Lett.* **2012**, *14*, 890–893.
- (152) Scharfbier, J.; Oestreich, M. Copper-Catalyzed Si–B Bond Activation in the Nucleophilic Substitution of Primary Aliphatic Triflates. *Synlett* **2016**, *27*, 1274–1276.
- (153) Xue, W.; Qu, Z.-W.; Grimme, S.; Oestreich, M. Copper-Catalyzed Cross-Coupling of Silicon Pronucleophiles with Unactivated Alkyl Electrophiles Coupled with Radical Cyclization. *J. Am. Chem. Soc.* **2016**, *138*, 14222–14225.
- (154) Iwamoto, H.; Endo, K.; Ozawa, Y.; Watanabe, Y.; Kubota, K.; Imamoto, T.; Ito, H. Copper(I)-Catalyzed Enantioconvergent Borylation of Racemic Benzyl Chlorides Enabled by Quadrant-by-Quadrant Structure Modification of Chiral Bisphosphine Ligands. *Angew. Chem., Int. Ed.* **2019**, *58*, 11112–11117.
- (155) For a nickel-catalyzed approach, see: Wang, Z.; Bachman, S.; Dudnik, A. S.; Fu, G. C. Nickel-Catalyzed Enantioconvergent Borylation of Racemic Secondary Benzylic Electrophiles. *Angew. Chem., Int. Ed.* **2018**, *57*, 14529–14532.
- (156) Scharfbier, J.; Hazrati, H.; Irran, E.; Oestreich, M. Copper-Catalyzed Substitution of  $\alpha$ -Triflyloxy Nitriles and Esters with Silicon Nucleophiles under Inversion of the Configuration. *Org. Lett.* **2017**, *19*, 6562–6565.
- (157) Scharfbier, J.; Gross, B. M.; Oestreich, M. Stereospecific and Chemoselective Copper-Catalyzed Deaminative Silylation of Benzylic Ammonium Triflates. *Angew. Chem., Int. Ed.* **2020**, *59*, 1577–1580.
- (158) Schmidt, J.; Choi, J.; Liu, A. T.; Slusarczyk, M.; Fu, G. C. A General, Modular Method for the Catalytic Asymmetric Synthesis of Alkylboronate Esters. *Science* **2016**, *354*, 1265–1269.
- (159) Schwarzwald, G. M.; Matier, C. D.; Fu, G. C. Enantioconvergent Cross-Couplings of Alkyl Electrophiles: The Catalytic Asymmetric Synthesis of Organosilanes. *Angew. Chem., Int. Ed.* **2019**, *58*, 3571–3574.
- (160) Yi, H.; Mao, W.; Oestreich, M. Enantioselective Construction of  $\alpha$ -Chiral Silanes by Nickel-Catalyzed  $C(sp^3)–C(sp^3)$  Cross-Coupling. *Angew. Chem., Int. Ed.* **2019**, *58*, 3575–3578.
- (161) Wang, F.; Chen, P.; Liu, G. Copper-Catalyzed Radical Relay for Asymmetric Radical Transformations. *Acc. Chem. Res.* **2018**, *51*, 2036–2046.
- (162) Lei, A.; Shi, W.; Liu, C.; Liu, W.; Zhang, H.; He, C., Eds. *Oxidative Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 2017.