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Reactivity Trends with Borylalkyl Copper(I) Species

Macarena Corro,[a] Oriol Salvado,[a] Sara González,[a] Paula Dominguez-Molano,[a] and Elena Fernández*[a]

The renaissance on the application of *gem*-diborylalkanes from 2010, has allowed the conquest of new synthetic application towards C–C and C–N bond formation. The activation of *gem*-diborylalkanes by Cu(I) catalysts, generates active borylalky copper(I) species that are able to trap several electrophilic reagents, in an efficient way. In addition, the modification of Cu(I) complexes with chiral ligands, induces asymmetric platforms towards the synthesis of enantioenriched organoboron compounds.

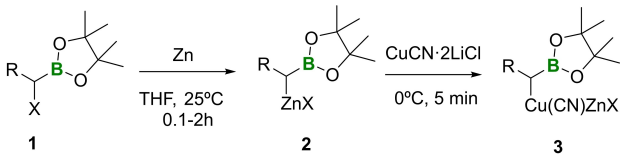
1. Introduction

Boron-stabilized carbanions can be considered versatile reagents that have found numerous synthetic applications in advanced synthetic protocols.[1–4]

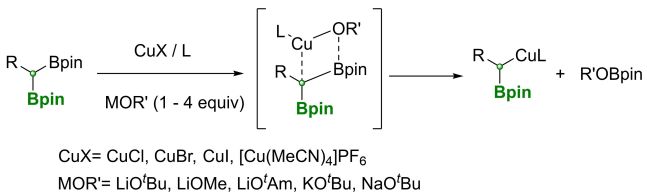
Copper(I) is one of the most reliable counter cation of α-borylcarbanions and the synthesis of borylalkyl copper(I) can be performed via complementary methods. Original work by Knochel[5] in 1990 showed that the insertion of zinc dust to the readily available halo pinacolboronic esters (**1** Bpin = pinacolboryl), in THF, proceeds smoothly towards the corresponding α-(dialkoxyboryl)alkyl)zinc halides (**2**) (Scheme 1). However, since these organometallic compounds did not show significant reactivity, the subsequent addition of soluble copper salt CuCN-2LiCl converted the zinc compounds **2** into the more reactive borylalkyl copper(I) derivatives **3** (Scheme 1).[5]

Cu (I) salts are involved in the deborylation of 1,1-diborylalkanes to deliver the corresponding α-boryl carbanions (Scheme 2).[6,7] Normally, alkoxy groups (-OR') favour the σ-bond metathesis pathway and consequently deborylation is essentially established with the concomitant formation of R_2B-OR' as byproduct. The deborylation of 1,1-diborylalkanes is essentially performed *in situ*, with standard reagents (CuX and MOR'), together with the addition of stabilizing ligands, such as mono and diphosphines, which contribute to the steric and electronic tuning of the borylalkyl copper(I) catalyst (Scheme 2).

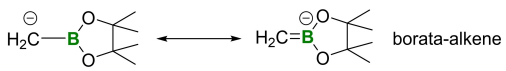
The relative stability of the corresponding α-boryl carbanions formed is due to the adjacent remaining B atom. In fact, α-boryl carbanions can also be expressed as stable borata-alkene species ($[R_2B{=}CH_2]^-$) (Scheme 3).[8] This pronounced α-boryl carbanion stabilization represents an extra advantage to explore the potential reactivity of borylalkyl copper(I) species in front of electrophilic reagents.



Scheme 1. Synthesis of (Bpin)CHRCu(CN)ZnX species.



Scheme 2. *In situ* preparation of borylalkyl copper(I) species.



Scheme 3. Resonance expression of α-boryl carbanions and borata-alkene species ($[R_2B{=}CH_2]^-$).

The generation of α-borylcarbanions and their electrophilic trapping in a transition metal-free context, has recently been reviewed by Cho and co-workers.[9] Therefore, the present review is focused on the complementary study about the Cu(I) catalyzed borylalkyl reactivity, with a special emphasis on the steroselectivity provided in the new C–C bond formation, as a consequence of the influence of the ligands coordinated to Cu(I) catalysts.

1.1. Borylalkyl copper(I) addition to Aldehydes

The boron-Wittig olefination is conceptually based on the addition of borylmethide reagents to aldehydes or ketones.[10] The corresponding 1,2-oxaboretaninide intermediate[11] easily

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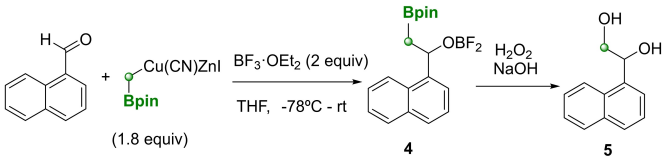
performs the B–O elimination to generate the corresponding *E*- or *Z*-alkenes, or a mixture of the two stereoisomers.

Pioneer work by Knochel,[5] demonstrated that α-boryl carbanion from (Bpin)CH_2Cu(CN)ZnI can react with 1-naphthaldehyde to form the corresponding 1,2-oxaboretaninide (**4**), which in presence of BF_3·OEt_2 can be partially stabilized and after *in situ* oxidation generates the corresponding 1,2-diol **5** (Scheme 4).

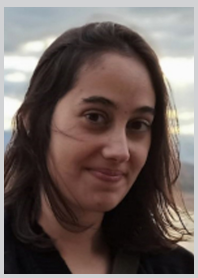


Scheme 4. Reactivity of (Bpin)CH_2Cu(CN)ZnI with aldehydes in the presence of BF_3·OEt_2.

Miyaura and co-workers, developed a simple procedure for the olefination of aldehydes using borylmethyl copper reagents.[12] The *in situ* preparation of (Bpin)CH_2Cu(CN)ZnI, in THF, followed by addition to aldehydes, in the presence of boron trifluoride etherate, yields the corresponding β-hydroxyalkylboronate that can be further transformed into the stable alkenes by thermal dehydroxyboronation. The optimized reaction conditions for the boron-Wittig methylenation of representative aldehydes was conducted with 2 equiv. of (Bpin)CH_2Cu(CN)ZnI and 4 equiv. of BF_3·OEt_2. The reaction proceeds smoothly for aromatic aldehydes and α,β-unsaturated aldehydes (Scheme 5), however lower yields result for the homologation of aliphatic aldehydes. The reaction is compatible with esters, but ketones are quite inert to the reaction.

Dr. Macarena Corro obtained her degree in chemistry at University of Huelva-Spain, in 2013. Afterwards, she completed her Master's Degree in Synthesis, Catalysis and Molecular Design at URV working on "Kinetic resolution of non-terminal aziridines promoted by chiral phosphoric acid". She did a PhD in organic chemistry focused on "Novel Strategies for the Syntheses of Sphingosine Kinase Inhibitors and β-Fluoroamines" under the supervision of Prof. S. Castillón and Dr. Y. Díaz (2014-2018). She enjoyed a predoctoral stay at Max-Planck-Institut für Kohlenforschung in the group of Prof. Alois Fürstner. As doctor, she joined the R&D Department at Instituto Español in Huelva, followed by postdoctoral researcher position at University Rovira i Virgili in Tarragona.

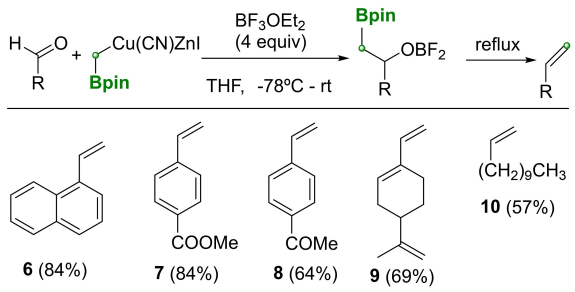
Mr. Oriol Salvado received the B.S in chemistry from the Universitat Rovira i Virgili (URV) in 2018. Subsequently, he was granted to study the Master in Synthesis, Catalysis and Molecular Design at University Rovira i Virgili and ICIQ, working under the project "Diborylmethylation/ring opening of vinyl aziridines and vinyl epoxides". He has got a grant from URV-Martí Franques programme and he is currently developing the PhD studies under the supervision of Prof. Elena Fernández.



Ms. Sara González received the B.S in chemistry from Universidad de Salamanca in 2019. In her Bachelor's project, she worked in the degradation of the pollutant 4-nitrophenol in water using birnessites as photocatalysts. Afterwards, she was granted to study the Master in Synthesis, Catalysis and Molecular Design at University Rovira i Virgili and ICIQ. The Master's project was based on the synthesis and characterization of Pt-Sn nanoparticles under the project 'Transition Metal catalysts for selective and sustainable processes'. She has got a grant to develop PhD studies under the supervision of Prof. Elena Fernández.

Ms. Paula Dominguez-Molano received her B. Sc. in Chemistry from the Universitat Rovira i Virgili (URV) in 2020. Her Bachelor's project was based on the study of cobalt catalyzed trifluoromethylthiolation functionalization reactions at Institut Català d'Investigació Química (ICIQ). Currently she is doing the URV-ICIQ Master Synthesis, Catalysis and Molecular Design working on the project "Alpha-Boryl Carbanions for C–C coupling" under supervision of Prof. Elena Fernández.

Dr. Elena Fernández received her degree in chemistry at the University of Barcelona in 1991. She did PhD studies in catalytic hydroformylation of sugars with Prof. S. Castillón (1991-1995) and she moved to Oxford University (UK) (1995-1997) for a postdoctoral position with Prof. J. M. Brown where her studies culminated with an approach towards the first catalytic asymmetric hydroboration-amination reaction. Elena accepted in 1997 a lecturer position at the University Rovira i Virgili (URV), becoming part of the permanent staff in 2000 and Full Professor in 2019. She is Distinguished Professor at the URV from 2018. Her current scientific campaign is aimed to generate knowledge and awareness about activation modes of organoboron reagents to be used in selective synthesis of multifunctional compounds.

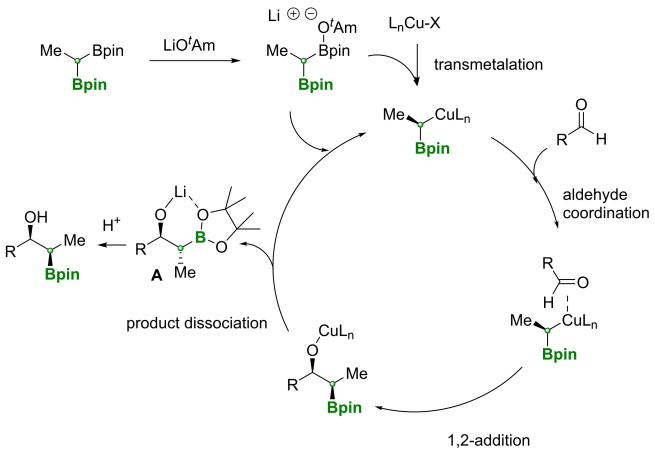


Scheme 5. (Bpin)CH_2Cu(CN)ZnI catalyzes boron-Wittig methylenation of representative aryl, vinyl and alkyl aldehydes.

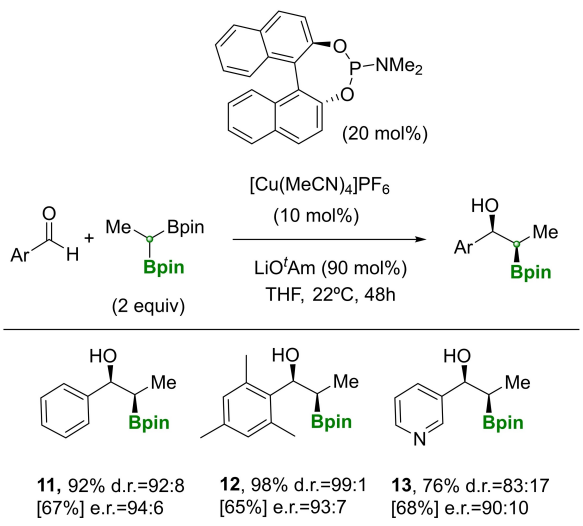
The copper mediated borylmethide addition to aldehydes has been revisited in 2015 by Meek and co-workers who demonstrated that copper can catalyze the C–C bond formation in the presence of chiral ligands to conduct an enantio- and diastereoselective synthesis of 1,2-hydroxyboronates (Scheme 6).[13] Both, aryl and vinyl aldehydes can be transformed by a readily available chiral monodentate phosphoramidite-copper complex in the presence of 1,1-diborylethane reagent. The 1,2-hydroxyboronates prepared contain two contiguous stereogenic centers and are obtained in remarkably high diastereo- and enantioselectivity. The optimized reaction conditions shown in Scheme 6 demonstrated that the use of almost stoichiometric amount of lithium *tert*-amylate (LiO^{t}Am) resulted not only efficient, but also more stereoselective in its role as activator. Alkenyl aldehydes can also be used, but are formed in slightly reduced yields and diastereoselectivities. This reaction manifold is currently limited to only diborylethane, as other more highly substituted *gem*-diboronates are formed in reduced yields, although in high -diastereo- and enantioselectivity.

Meek and co-workers proposed a catalytic cycle for the 1,2-addition reaction between diborylethane and aldehydes (Scheme 7). Initial activation of the *gem*-diboron reagent forms a borate complex, which transmetallates to the copper precatalyst to form a α-boryl alkyl copper species. This complex can coordinate the aldehyde and undergo further 1,2-addition into Cu–C bond. Product dissociation takes place in the presence of α-boryl alkyl copper species, and the structure **A** has been suggested to prevent olefination through the Boron-Wittig mechanism. The regeneration of the copper catalyst, occurs through the transmetalation step.

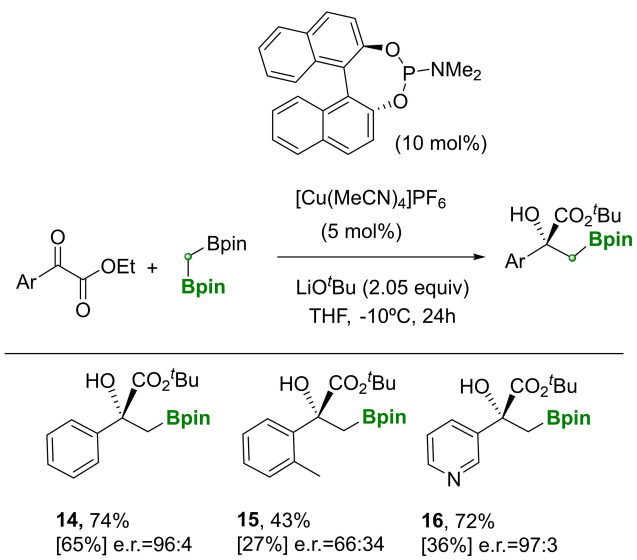
The same authors have studied a similar strategy for the synthesis of tertiary alcohols containing 1,2-hydroxyboronates by addition of α-boryl alkyl copper species to α-ketoesters (Scheme 8).[14] The difficulty involved in this catalytic method



Scheme 7. Suggested mechanism for 1,2-addition reaction netween diborylethane and aldehydes.

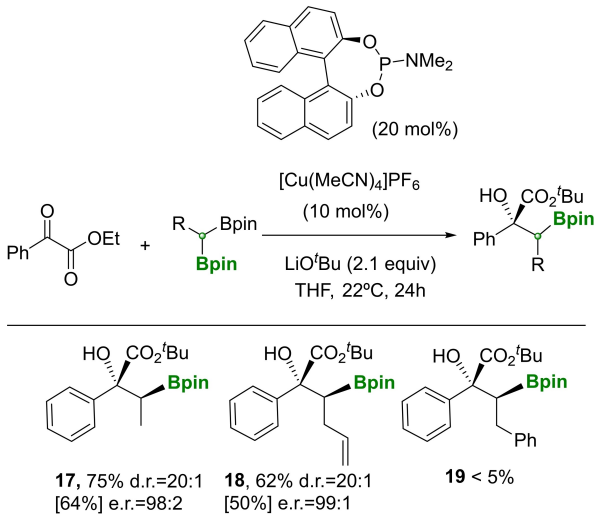


Scheme 6. [Cu(MeCN)$_4$]PF$_6$ / phosphoramidite catalyzes the diborylethane addition to representative aryl aldehydes. Conversion and diastereoselectivity are given for 1,2-hydroxyboronates, and the yield and enantioselectivity on the corresponding diol prepared by oxidation of 1,2-hydroxyboronates with $NaBO_3$.

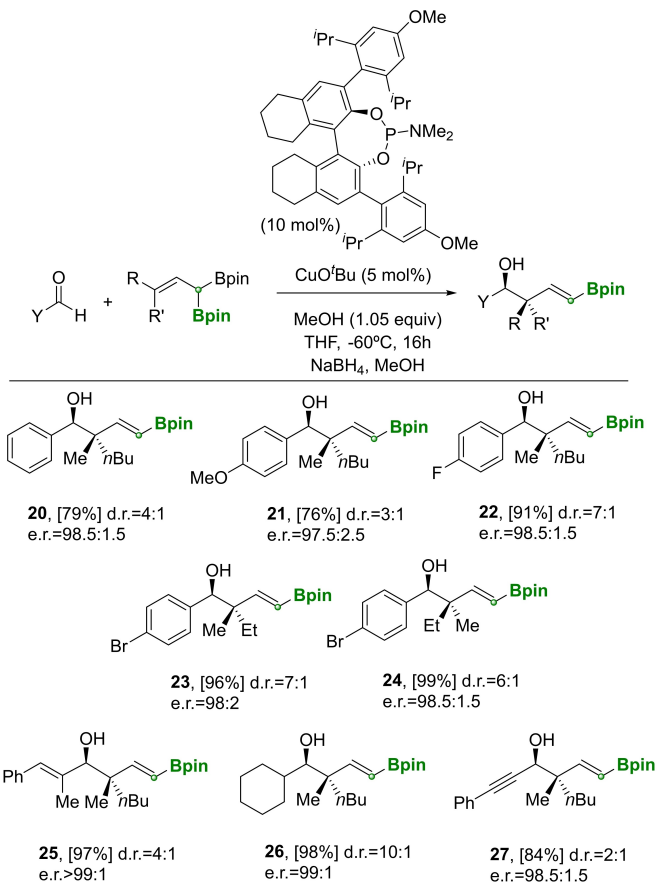


Scheme 8. [Cu(MeCN)$_4$]PF$_6$ / phosphoramidite catalyzes borylmethide addition to representative α-ketoesters. Yield is given for 1,2-hydroxyboronates, and in brackets is the yield and enantioselectivity on the corresponding diol prepared by oxidation of 1,2-hydroxyboronates with $NaBO_3$.

arises from the sterically congested vicinal C(sp^3) stereogenic centre formed. The copper-catalyzed protocol can be extended to more challenging processes which utilize substituted alkyl



Scheme 9. $[Cu(MeCN)_4]PF_6$ / phosphoramidite catalyzes the alkyl borylmethide addition to representative α-ketoesters. Conversion is given for 1,2-hydroxyboronates, and the yield and enantioselectivity on the corresponding diol prepared by oxidation of 1,2-hydroxyboronates with $NaBO_3$.



Scheme 10. CuO^{t}Bu / phosphoramidite catalyzes the additions of B-substituted allyl nucleophiles to aldehydes.

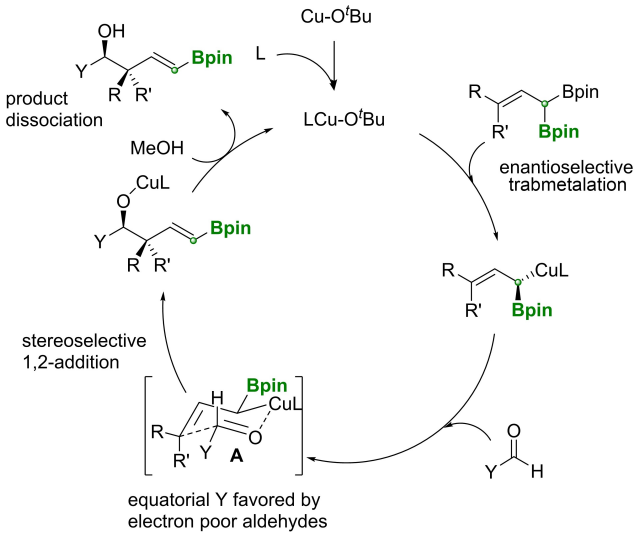
1,1- diboron reagents to afford congested contiguous tertiary and secondary stereogenic centers. Reactions require 5–10 mol% of the copper catalyst to proceed to good conversion and high enantioselectivity (Scheme 9). The stereochemical assignment concludes an *anti* conformation between the hydroxy and Bpin units, thus corresponding to the addition of an B-alkyl copper species to the Si face of the α-ketoester.

1,1-Allylic diboronic esters can be activated by chiral copper catalysts to generate the corresponding enantioenriched boron-stabilized allylic copper nucleophile that react with accessible aldehydes to promote the γ-addition (Scheme 10).[15] This strategy generates secondary homoallylic alcohols containing α-quaternary stereogenic carbon in high diastereo- and enantioselectivity (up to $>20:1$ dr and $>99:1$ er). The catalytic protocol is general for a wide variety of aldehydes and Hammett studies disclosed that diastereoselectivity of the reaction is correlated to the electronic nature of the aldehyde, with dr increasing as aldehydes become more electron poor. The reaction is also general for a variety of 1,1-allylic diboronic esters and notably, diastereomers **23** and **24** could be synthesized stereospecifically by subjecting either *E*- or *Z*-allyldiboronates to the reaction conditions (Scheme 10). The catalytic protocol also extends to alkenyl, alkynyl, and alkyl aldehydes, although reactions of alkynyl aldehydes provides a significant decrease in diastereoselectivity. Additionally, no adverse effects arising from a pendant alkene moiety have been observed (Scheme 10).

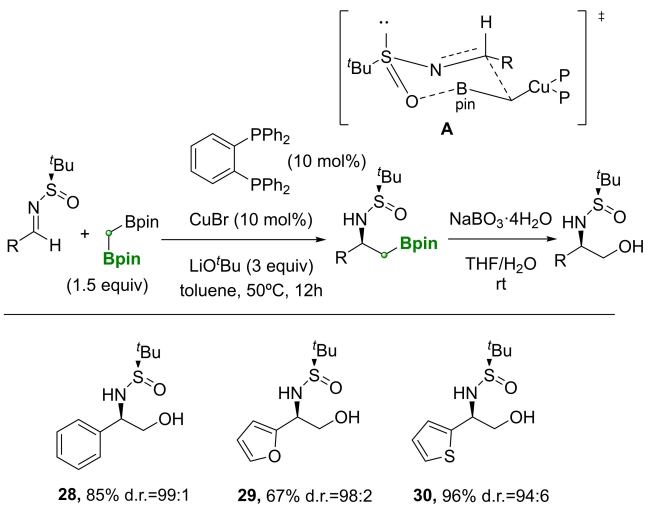
A catalytic cycle has been suggested to justify the CuO^{t}Bu / phosphoramidite catalyzed additions of B-substituted allyl nucleophiles to aldehydes. In parallel, a stereochemical model has been proposed to rationalize the diastereo-, enantio-, and *anti*-selective formation of secondary alcohol and quaternary carbon stereocenters.[15] Authors suggest that the reaction likely proceeds via S_E2' transmetalation of (L)Cu–OMe with 1,1-allylic diboronic esters followed by a rapid 1,3-suprafacial shift to the less sterically encumbered boron-stabilized allyl copper species (Scheme 11). This sequence might be faster than C–C bond rotation to prevent isomerization of alkene geometry. Coordination of aldehyde results in cyclization affording Cu-bound product. It has been proved that the large substituent occupies the pseudoequatorial position in **A**, resulting in the observed diastereoselectivity. Finally, protonation of the intermediate with MeOH releases the desired product and regenerates the Cu(I) catalyst (Scheme 11).

1.2. Borylalkyl copper(I) addition to Aldimines and Ketimines

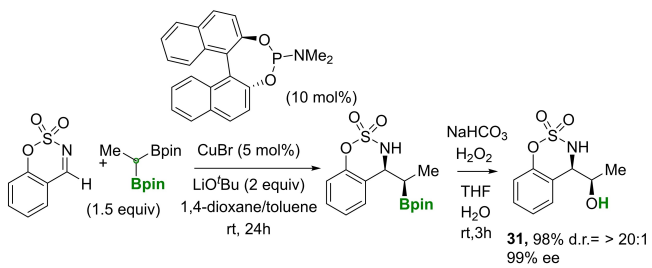
The first chemo- and diastereoselective alkylation of *N*-tert-butanesulfinyl aldimines with diborylmethane, catalyzed by a copper salt and an achiral bidentate phosphine ligand, was conducted by Cho and co-workers.[16] The reaction provides β-aminoboronates, which can be further functionalized to generate synthetically valuable intermediates. CuBr and the ligand 1,2-bis(diphenylphosphino)benzene were considered the optimized catalytic system. On the basis of the diastereoselectivity observed, the authors suggested that the reaction proceeds via



Scheme 11. Proposed catalytic cycle and stereochemical model in the addition of allyl nucleophiles to aldehydes.



Scheme 12. Copper-catalyzed diastereoselective addition of diborylmethane to *N-tert*-butanesulfinyl aldimines: synthesis of β-aminoboronates.



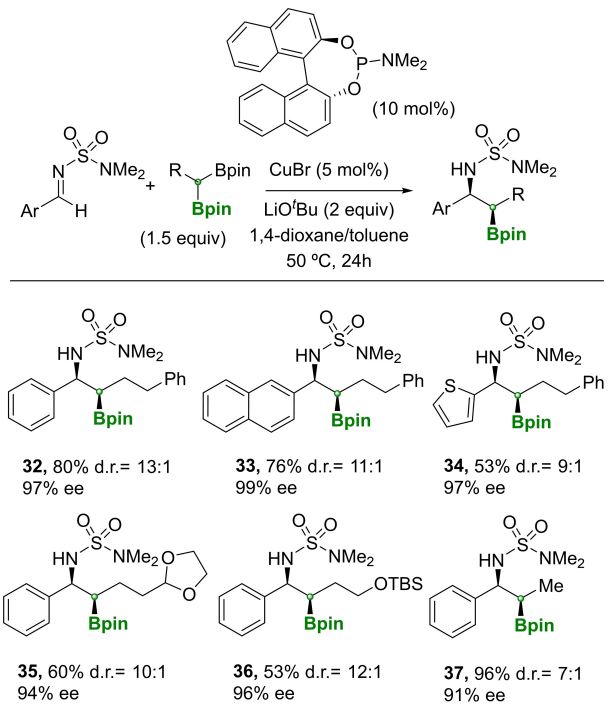
Scheme 13. Copper-catalyzed diastereo- and enantioselective 1,2-addition of 1,1-diborylalkanes to protected cyclic imines.

a chairlike six-membered cyclic transition state **A**, in which the boron species was coordinated to the oxygen atom of the sulfinyl moiety (Scheme 12).

The same authors have developed an efficient copper(I)-catalytic system for the diastereo- and enantioselective 1,2-addition of 1,1-diborylalkanes to protected imines in order to afford synthetically valuable enantioenriched β-aminoboron compounds bearing contiguous stereogenic centers.[17] In the presence of CuBr (5 mol%), an (R)-BINOL-derived phosphoramidite ligand (10 mol%) and LiO^{t}Bu in 1,4-dioxane at room temperature, the reactions proceed to generate a broad range of β-aminoboronate esters with contiguous stereocenters in high yields (Scheme 13).

Cho and co-workers extended the efficient copper-catalyzed 1,2-addition of 1,1-diborylalkanes to N-protected acyclic arylaldimines.[18] Remarkably, the installation of an *N,N*-dimethylsulfamoyl group as protecting group in acyclic arylaldimines allows the 1,2-addition reaction to proceed with good to excellent diastereoselectivity and enantioselectivity, thus providing β-aminoboronate esters bearing vicinal chiral secondary amines and secondary boronate esters in good yields (Scheme 14).[18]

Cho and co-workers reported that allylic- *gem*-diboronates undergo the crotylation with cyclic aldimines forming (*E*)-δ-boryl-*anti*-homoallylic amines in high efficiency, despite the fact that copper(I) complexes were not catalyzing the reaction.[19] However, Meek and co-workers found that a (phosphoramidite)-Cu complex facilitates the catalytic reaction between allyldiboronates and aldimines towards the enantio- and diastereoselective formation of homoallylic amines. Signifi-

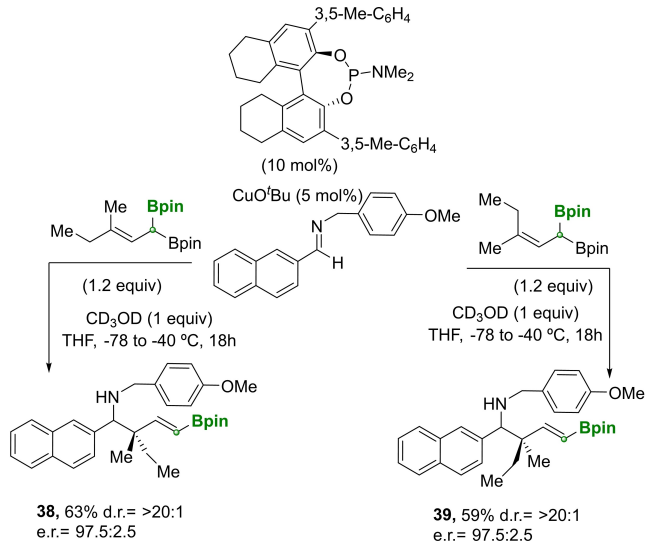


Scheme 14. Copper-Catalyzed diastereo- and enantioselective 1,2-addition of 1,1-diborylalkanes to N-protected acyclic imines.

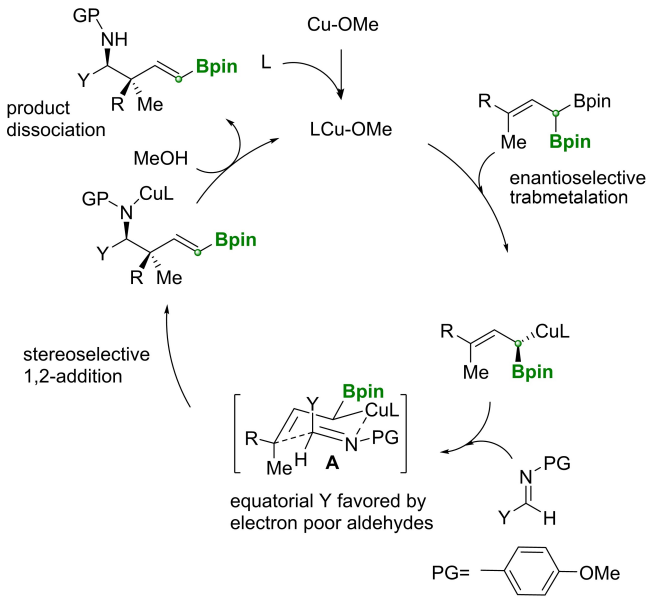
cantly, both diastereoisomeric products can be formed by choice of *E*- or *Z*-allyldiboron stereoisomer (Scheme 15).[20]

The same authors have suggested that the copper catalyst promotes, initially, an enantioselective transmetalation step, generating a highly reactive α-boryl-Cu-allyl species (Scheme 16). The orientation of the Bpin units seems to be positioned to minimize allylic (1,3)-strain. Isomerization to the less congested and boron-stabilized allylic Cu species is followed by reaction with the protected aldimine via 6-membered cyclic transition state **A**. Authors have postulated that in order to minimize additional 1,3-diaxial interactions, the Bpin motif is presumably placed in the equatorial position. The last steps include allyl transfer in a highly diastereoselective manner, followed by release of the homoallylic amine and regeneration of (L)-Cu-OMe, in presence of MeOH (Scheme 16).[20]

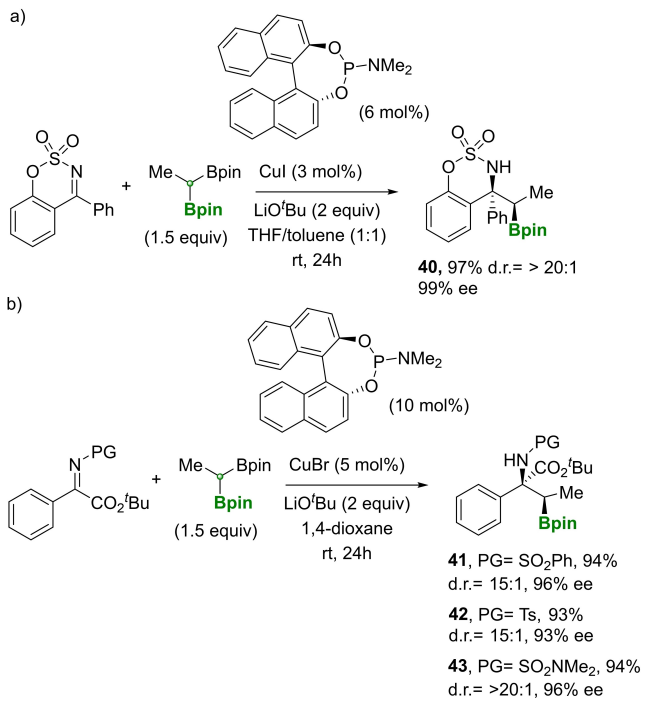
The common features of the copper catalyzed addition of α-boryl carbanions on aldimines is based on the enantioselective transmetalation of 1,1-diborylalkanes with a chiral copper complex to generate enantioenriched α-boryl-alkyl-copper species that undergo addition reaction to prochiral electrophiles. Cho and co-workers also envisaged that the reaction of chiral α-boryl-alkyl-copper species with ketimines would provide β-aminoboronate esters containing contiguous tetrasubstituted and trisubstituted stereocenters.[21] Despite the fact that ketimines proved to be intrinsically less reactive than aldimines the copper-catalyzed 1,2-addition of 1,1-diborylalkanes to cyclic ketimines and α-imino esters was performed with high diastereoselectivity and enantioselectivity. Scheme 17a shows the reactivity of 4-phenyl-1,2,3-benzoxathiazine-2,2-dioxide with 1,1-diborylethane as a coupling reagent in the presence of catalytic amounts of CuI /phosphoramidite ligand, and LiO^{t}Bu in THF/toluene at room temperature. Notably, the corresponding β-aminoboronate ester **40** was obtained in high yield and diastereoselectivity. Enantioselectivity values were also remarkably (Scheme 17a). The same authors also studied the copper-catalyzed 1,2-addition of 1,1-diborylalkanes to imino esters as electrophiles because the coordination of chiral copper species with nitrogen and oxygen atoms of the imino and ester group could facilitate the transfer of the α-boryl-alkyl moiety to the adjacent electrophilic C=N bond. Interestingly, the reaction provided β-boryl-α-amino acid derivatives, as versatile synthons



Scheme 15. Copper-catalyzed stereospecific additions with *E* and *Z*-methyl / ethyl allyldiborons.



Scheme 16. Proposed catalytic cycle and stereochemical model in the addition of allyl nucleophiles to aldimines.



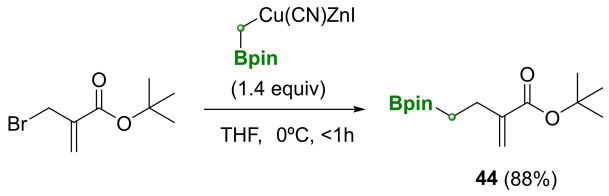
Scheme 17. Copper-catalyzed diastereo- and enantioselective 1,2-addition of 1,1-diborylethane to cyclic ketimines and α-imino esters.

in the preparation of unnatural peptides. Substrates such as phenylsulfonyl-protected α-imino ester, N–Ts-protected α-imino ester and *N,N*-dimethylsulfamoyl- protected α-imino ester were efficiently transformed into the desired β-boryl-α-amino acid derivative in high yield. Diastereoselectivity and enantioselectivity was also efficiently achieved when CuBr/phosphoramidite and LiO^{t}Bu were used as catalytic system (Scheme 17b). However, the use of Boc-protected α-imino ester did not facilitated the coupled product.

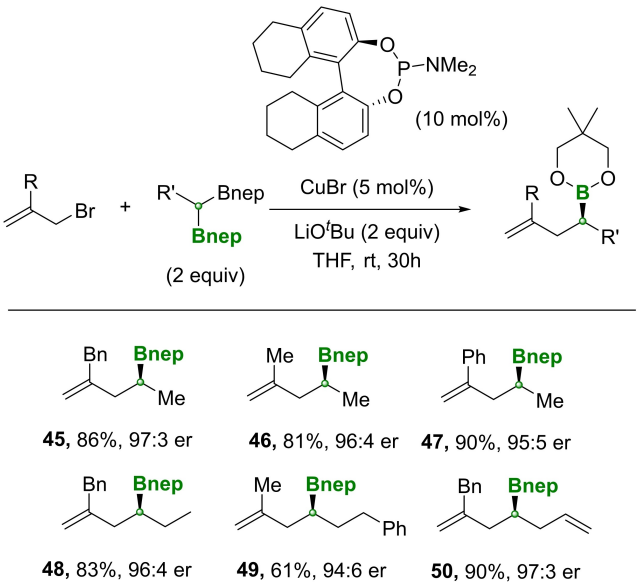
1.3. Borylalkyl copper(I) reactivity with allyl halides

Early experiments by Knochel, demonstrated that the α-boryl carbanion involved in (Bpin)CH$_2$Cu(CN)ZnI shows excellent reactivity toward allyl halides, as it can be seen in the model reaction between *tert*-butyl α-(bromomethyl)-acrylate with (Bpin)CH$_2$Cu(CN)ZnI, at low temperatures (Scheme 18).[5] There is an impressive control on the chemoselectivity of the process since the α,β-unsaturated ester remains inert, whereas the alkyl bromide substitution takes place efficiently.

Cho and co-workers have recently developed a copper-catalyzed enantiotopic-group selective allylation of *gem*-diborylalkanes with a series of allyl bromides.[22] A significant range of



Scheme 18. Copper catalyzed allylation between *tert*-butyl α-(bromomethyl)-acrylate with (Bpin)CH$_2$Cu(CN)ZnI.



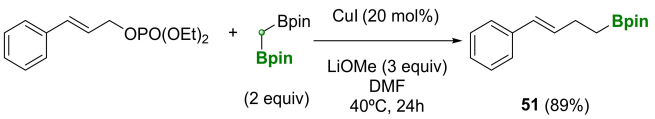
Scheme 19. Copper-catalyzed enantioselective allylation of *gem*-diborylalkanes and allyl bromides.

gem-diborylalkanes and allyl bromides undergoes the coupling, thereby providing various enantioenriched homoallylic boronates (Scheme 19). Mechanistic studies have revealed a enantiotopic-group selective transmetalation between *gem*-diborylalkanes and chiral copper complex to generate a chiral α-borylalkyl-copper species, which subsequently undergoes C–C bond formation with allyl bromides.

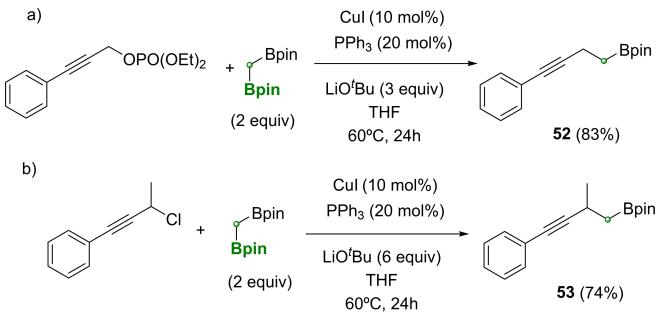
Fu, Marder and co-workers have reported that cinnamyl phosphate and diborylmethane can be coupled in the presence of 10 mol% CuI and 3 equiv. of LiOMe as base, under 40 °C. This copper-catalyzed allylic alkylation reaction allows to form linear alkylboronate **51** through a S$_N$2 mechanism (Scheme 20).[23]

Xiao, Fu and co-workers explored next the Cu/PPh$_3$-catalyzed propargylic substitution reaction with diborylmethane.[24] The optimal conditions for this reaction involve 10 mol% of CuI modified with PPh$_3$ as the catalytic system, in the presence of 3 equiv. of LiO^{t}Bu as base and THF as solvent, at 60 °C (Scheme 21a). This reaction can be successfully applied to aryl and alkyl propargyl electrophiles and various synthetic valuable functional groups can be tolerated. For homologation of secondary propargyl with diborylmethane, reactions conditions had to be re-optimized since authors noticed that a Cl leaving group is the most productive, albeit the formation of byproducts. Interestingly, simply increasing the base loading of LiO^{t}Bu to 6 equivalents, the formation of by products can be avoided and the total yield about 74% on product **53** indicates that the main reaction might proceed in a strong basic environment (Scheme 21b).

Moving from the S$_N$2 to S$_N$2′ substitution reactions, Cho and co-workers have reported a Cu-catalyzed allylic alkylation reaction of allylic electrophiles with diborylmethane in the presence of the N-heterocyclic carbene ligand IMes.[25] In fact, negligible amount of product was formed when phosphine ligands were used instead. The optimized reaction was conducted in toluene, at 50 °C, with 3 equiv. of LiO^{t}Bu. Under



Scheme 20. Copper-catalyzed allylation of cinnamyl phosphate and diborylmethane.



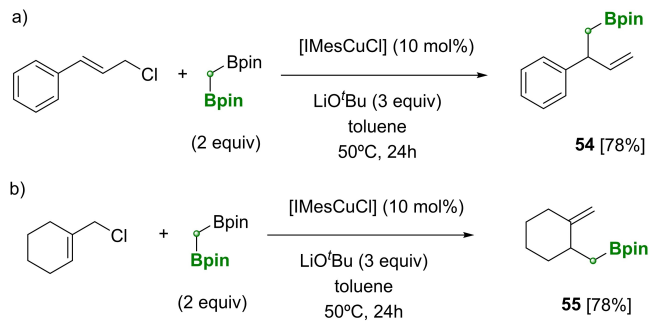
Scheme 21. Cu/PPh$_3$-catalyzed primary and secondary propargylic substitution reaction with diborylmethane.

these reaction conditions, cinnamyl acetate and *tert*-butyl cinnamyl carbamate do not react, although the use of methyl cinnamyl carbamate as substrate affords an almost 1:1 mixture of the S_N2' and S_N2 products. However, when cinnamyl ethyl phosphate is used, the S_N2' reaction is preferentially formed, and the highest selectivity ($S_N2'/S_N2 = 92:8$) is obtained when cinnamyl chloride is used as the allylic electrophile (Scheme 22a). This method has a wide substrate scope including both aromatic and aliphatic allylic chlorides. Scheme 22b shows the efficient transformation of 1-(chloromethyl)cyclohex-1-ene into the corresponding S_N2' product **55** with exclusive selectivity. Interestingly, the developed catalytic conditions are also applicable to secondary allylic chlorides.

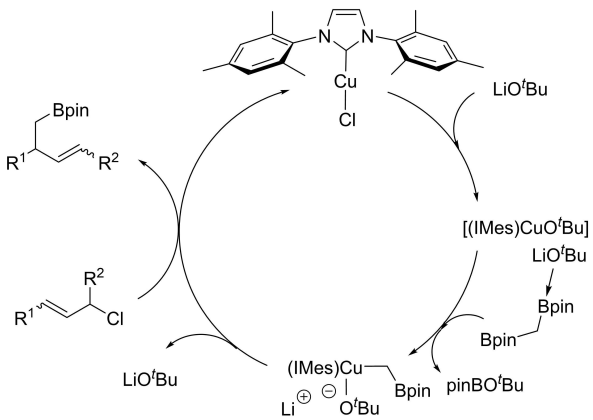
From a mechanistic point of view it has been suggested that copper alkoxide complex [Cu(IMes)O^{t}Bu] can be generated from [Cu(IMes)Cl] in the presence of LiO^{t}Bu. The copper(I) complex undergoes transmetalation with the activated diborylmethane to afford the heterocuprate that promotes the subsequent S_N2' substitution of the allylic chloride (Scheme 23).[25] The branched alkylboronates are formed in good yields and with a high functional-group compatibility.

Alternatively, Xiao, Fu and co-workers reported the Cu/(NHC)-catalyzed S_N2'-selective substitution reaction of both aromatic and aliphatic allylic phosphates with diborylmethane, conducting the reaction with 3 equiv. of LiOMe at 60 °C, in 1,4-dioxane.[26] A variety of halogen-substituted cinnamyl phosphates can successfully afford the corresponding products in good yields and complete S_N2' selectivity, demonstrating the compatibility of the reaction. Many important functional groups are also compatible, such as NO_2, CF_3, CN, and vinyl groups. Both (*Z*)- and (*E*)-allylic phosphates have similar reactivity and afford the same branched product with high selectivity (Scheme 24). Under these optimized reaction conditions, the homologative allylic substitution of allylic phosphates can also afford quaternary carbon centre, although with moderate yield.

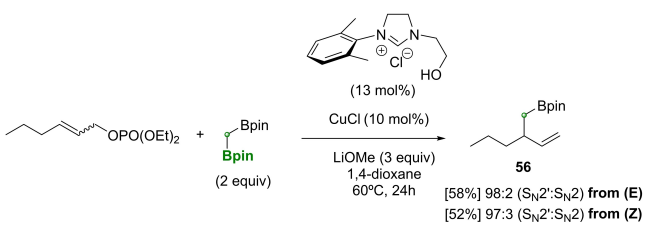
Surprisingly, Xiao, Fu and co-workers found a divergent selectivity depending on the solvent and ligand involved in the reaction when CuCl is used as catalyst. In the presence of LiOMe as base, the γ-alkylation products can be principally obtained being 1,4-dioxane the solvent of choice. The γ-selectivity increased (from 83:17 to 97:3) when NHC ligand is added.[26] However, when the solvent 1,4-dioxane is changed to DMF in the absence of NHC, α-alkylation products are mainly obtained.[23] To find some justification to this divergent selectivity on the homologative allylic substitution of allylic phosphates, the Liu and Fu's group investigated the mechanism of the Cu-catalyzed allyl substitution reaction through density functional theory calculations.[27] The study concluded that γ-alkylation of allylic phosphates with Cu–CH_2Bpin undergoes oxidative addition and direct Cγ–C reductive elimination (Scheme 25). The α-alkylation is found to undergo oxidative addition, isomerization, and Cα–C reductive elimination. The



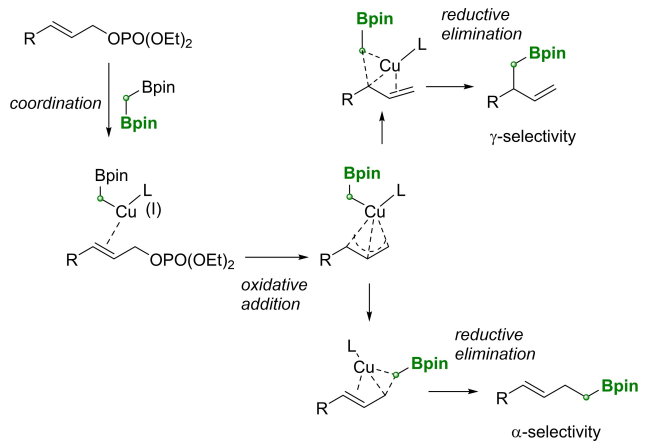
Scheme 22. Cu-catalyzed S_N2'allylic alkylation reaction of allylic electrophiles with diborylmethane.



Scheme 23. Proposed catalytic cycle for Cu-NHC catalyzed S_N2' allylic alkylation reaction.



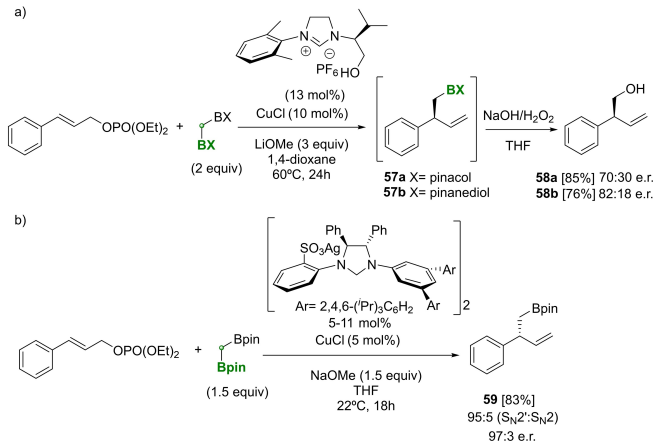
Scheme 24. Cu-NHC catalyzed S_N2' allylic alkylation reaction of allylic phosphates with diborylmethane.



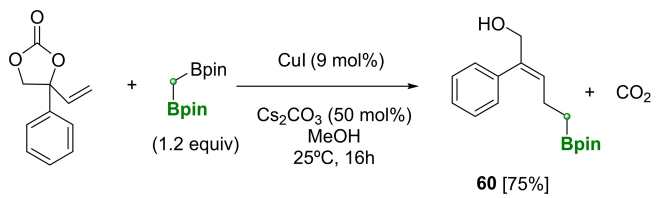
Scheme 25. Proposed rationalization for divergent selectivity observed in Cu-catalyzed allylic alkylation reaction depending on the solvent and ligand involved in the reaction.

stronger electron-donating ability of DMF than 1,4-dioxane promotes the isomerization to facilitate α-alkylation.

The asymmetric version of this reaction was initially investigated by Xiao, Fu and co-workers, using a chiral N-heterocyclic carbene (NHC) ligand.[26] The branched boronate product was oxidated *in situ* to provide the corresponding branched alcohol. The authors found that the enantioselectivity can be controlled by the steric hindrance at the boryl moiety (40% ee with pinacolboryl and 64% ee with pinanediolboryl) (Scheme 26a). Similar enantioselective Cu-catalyzed S_N2' substitution of allylic electrophiles with diborylmethane was developed by Hoveyda and co-workers.[28] They focussed the study on allylic phosphates as substrates because the Lewis basic phosphate could bind to a chiral Cu complex, to favour high S_N2' selectivity as well as enantioselectivity. The base NaOMe seems to be the most beneficial for the branch selectivity of the product formation, in comparison with LiOMe and KOMe. The chiral ligand used is a N-heterocyclic carbene ligand with a sulfonate functional group stabilized with Ag^+. This asymmetric methodology is general for various aryl-substituted substrates, including those with electron donating or electron withdrawing substituents, generating the desired S_N2' products with high yields as well as selectivity, and e.r. up to 99:1 (Scheme 26b).



Scheme 26. Enantioselective Cu-NHC catalyzed S_N2'allylic alkylation reaction of allylic phosphates with diborylmethane.

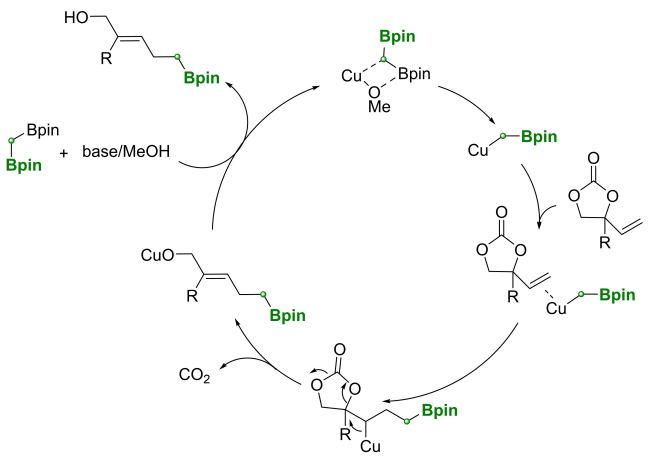


Scheme 27. Ligand-free Cu(I)-catalyzed S_N2'allylic alkylation reaction of vinyl cyclic carbonates with diborylmethane.

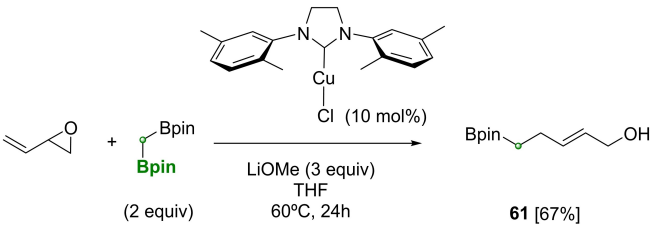
1.4. Borylalkyl copper(I) reactivity with vinyl carbonates and vinyl epoxides

Fernández, Kleij and co-workers explored the nucleophilic borylmethylation reaction through copper(I)-catalyzed S_N2' allylic alkylation of vinyl cyclic carbonates with diborylmethane (Scheme 27).[29] This new approach allows additional functionality to be retained in the homoallylic borylated product since a hydroxyl group is generated with the concomitant loss of CO_2, providing access to scaffolds that are not easily prepared through other routes. This reaction is conducted in the presence of 9 mol% of CuCl and only 0.5 equiv. of Cs_2CO_3 as base, in MeOH at rt (Scheme 27). The global sequence represents a carbonate ring opening reaction under favoured stereocontrol on the *E* isomer formation. A plausible mechanism is suggested involving first the activation of the diborylmethane reagent by Cu(I) alkoxide to form Cu – CH_2Bpin fragment. The mechanism suggests that Cu–CH_2Bpin might coordinates the terminal alkene of the vinyl cyclic carbonate followed by regioselective addition producing a new alkyl – Cu intermediate. Hereafter, elimination of the product in a formal *anti*-S_N2' pathway releases CO_2 and regenerates the copper(I) complex (Scheme 28).

Vinyl epoxides have been used as allylic electrophiles for copper catalyzed addition of CH_2Bpin moiety on the terminal position of the vinyl epoxide to generate S_N2'-selective products with the concomitant ring opening.[26] Scheme 29 illustrates the



Scheme 28. Suggested ligand-free Cu(I)-catalyzed S_N2' allylic alkylation reaction of vinyl cyclic carbonates with diborylmethane.



Scheme 29. Enantioselective Cu-NHC catalyzed S_N2'allylic alkylation/ring opening reaction of allylic epoxides with diborylmethane.

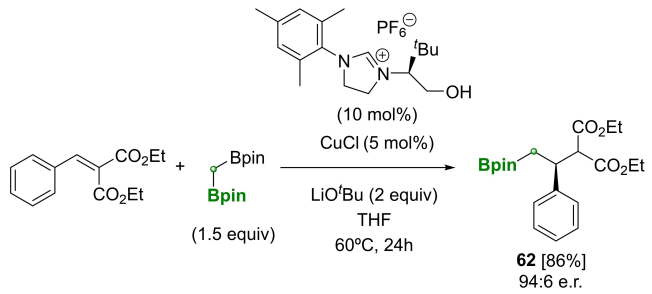
strategy developed by Xiao, Fu and co-workers towards the selective formation of the (*E*)-isomer, whereas the S_N2 attack on the ring was never observed.

1.5. Borylalkyl copper(I) reactivity with α,β-unsaturated carbonyl compounds

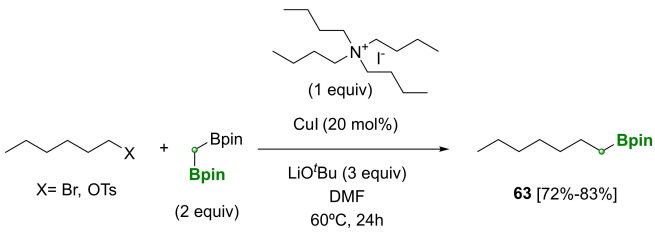
Yun and co-workers have described the copper-catalyzed conjugate addition of diborylmethane to α,β-unsaturated diesters.[30] The use of chiral N-heterocyclic carbene in combination with CuCl catalyst and LiO^{t}Bu allows the synthesis of enantiomerically enriched β-alkylboronates in good yields and high enantioselectivity through the incorporation of a CH_2Bpin moiety at the β-position of the diesters. The conjugate addition results efficient for β-aryl-substituted diesters (Scheme 30) but also for diesters with primary and secondary alkyl substituents. The versatility of this catalytic method has been demonstrated by stereospecific transformation of the resulting homologated chiral organoboron compounds into various functionalized organic molecules.

1.6. Borylalkyl copper(I) reactivity with alkyl or aryl halides

Fu, Marder and co-workers developed the homologation of a variety of alkyl bromides with diborylmethane in the presence of 10 – 20 mol% CuI as catalyst.[23] The reaction can proceed smoothly in the presence of 3 equiv. of LiO^{t}Bu and DMF, at 60 °C (Scheme 31). Under the optimized conditions it was found that the activity of alkyl bromide and tosylate is higher than that of aryl bromide, and the activity of alkyl bromide is higher than that of aryl and alkyl chloride. Interestingly, functional groups including acetal, terminal olefin and TBS-protected alcohol are tolerated. In addition, alkyl esters and aryl esters are good substrates for this homologation reaction. A S_N2 mechanism has been suggested as the most plausible for the homologation of the alkyl bromides. The addition of tetrabutylammonium iodide contributes to increase slightly the yields as it can be seen on the homologation of *n*-hexyl bromide and diborylmethane (Scheme 31).[23]



Scheme 30. Enantioselective Cu-NHC catalyzed conjugate addition of diborylmethane to α,β-unsaturated diesters.



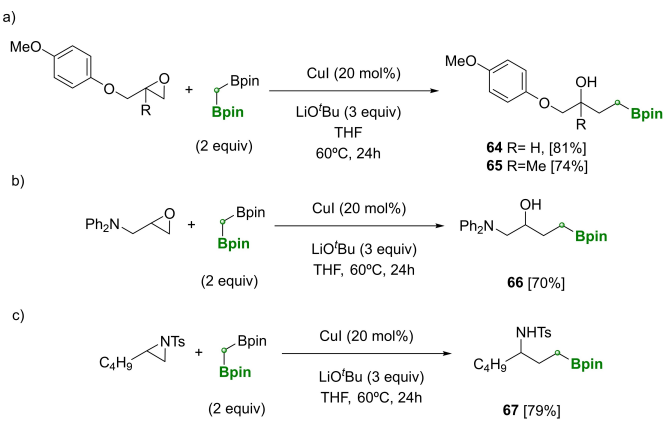
Scheme 31. Cu catalyzed conjugate addition of diborylmethane to alkyl halides.

1.7. Borylalkyl copper(I) reactivity with epoxides and aziridines

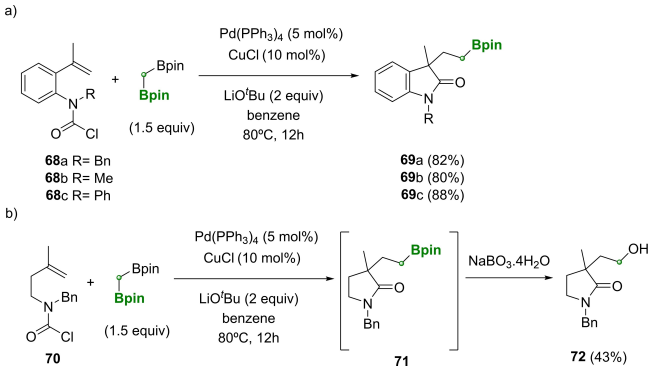
Aliphatic and aromatic epoxides have been converted to the corresponding secondary or tertiary γ-hydroxyl boronic esters when react with diborylmethane in the presence of CuI catalyst and LiO^{t}Bu (3 quiv) conducting the reaction at 60 °C (Scheme 32a).[31] This methodology has a limitation since 1,2-disubstituted epoxides do not afford the desired homologative-ring opening product. Interestingly, 1,4-pinacolboronate amines (**66**) can be easily prepared from reaction of diborylmethane with *N*-(oxiran-2-ylmethyl)-*N*-phenylaniline under standard reaction conditions (Scheme 32b) whereas 2-butyl-1-tosylaziridine can be converted smoothly to the corresponding 1,3-pinacolboronate amine **67** (Scheme 32c).

1.8. Cooperative effect of copper and palladium in the borylmethide reaction with electrophiles

Qu, Cheng and co-workers have described a Pd/Cu cooperative catalyzed domino carbamoylative alkylation of alkenes to form oxindole derivatives containing a C(sp^3) – B bond. Based on the model reaction of carbamoyl chloride **68** with diborylmethane in the presence of 5 mol% $Pd(PPh_3)_4$ / 10 mol% of CuCl, and 2.0 equiv. of LiO^{t}Bu as the base, it is possible to obtain the borylated 3,3-disubstituted oxindole skeleton **69** in high yield (Scheme 33a).[32] The high temperature required (80 °C) effec-



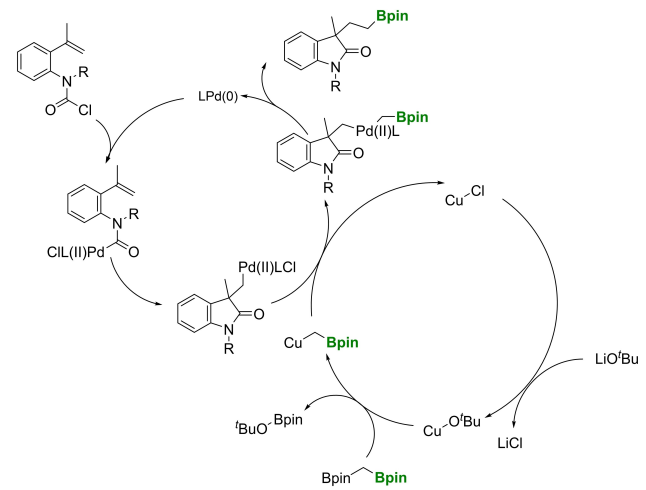
Scheme 32. Cu-catalyzed borylmethide addition to epoxides and aziridines with the concomitant ring opening.



Scheme 33. Pd/Cu cooperative catalyzed domino carbamoylative alkylation of alkenes.

tively promote this cascade reaction, whereas the yield dropped to 38% when the reaction was performed at room temperature. The reaction has been generalized for a large number of substrates with electron and steric modifications and notably, non-aromatic-ring-tethered carbamoyl chloride **70** can also be successfully applied to this strategy, although the corresponding product **71** is not stable upon various workup procedures. The oxidized hydroxyl-substituted γ-lactam **72** can be synthetized in 43% isolated yield when the reaction mixture was directly treated with $NaBO_3 \cdot 4H_2O$ (Scheme 33b).[32]

Mechanistically, the reaction has been suggested to be initiated by oxidative addition of substrate to Pd(0) to generate the carbamoyl-palladium species followed by an intramolecular migratory insertion to deliver the cyclic palladium(II) intermediate. The monoalkyl cuprate is generated *in situ* by a copper catalyst and diborylmethane in the presence of LiO^{t}Bu. Presumably, $CuCH_2Bpin$ system undergoes facile transmetalation with the alkyl-palladium species that eventually promote the reductive elimination towards the desired product with the regeneration of the Pd(0) species (Scheme 34).

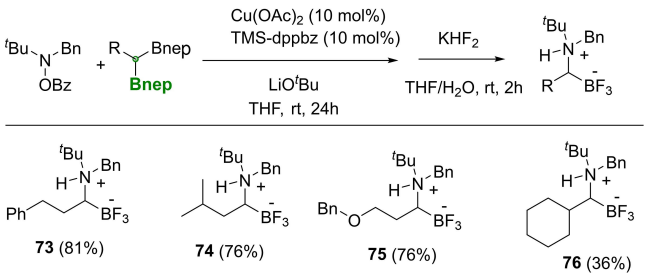


Scheme 34. Suggested mechanism for Pd/Cu cooperative catalyzed domino carbamoylative alkylation of alkenes.

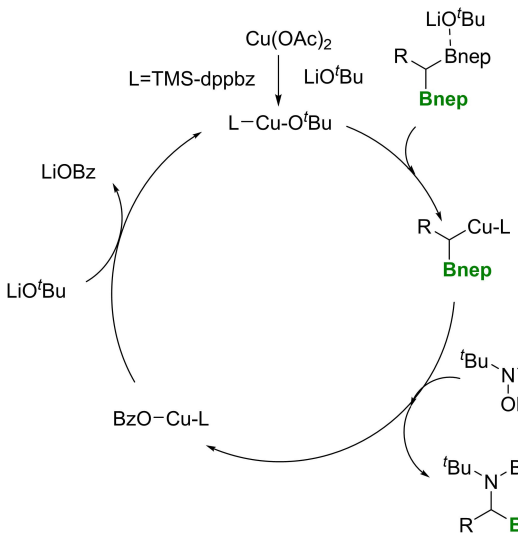
1.9. Borylalkyl copper(I) reactivity with amines

Alternatively to the copper activation of *gem*-diborylalkanes to generate new C–C bonds, it is also possible to promote a new C–N bond by electrophilic amination of borylalkyl copper(I) with hydroxilamines. In fact, Hirano and Miura have been pioneer demonstrating the first successful catalytic substitution reaction of *gem*-diborylalkanes with heteroatom coupling partners.[33] They demonstrated that copper-catalyzed electrophilic amination of *gem*-diborylalkanes with the hydroxylamines proceeds with high chemoselectivity under mild conditions, giving access to α-aminoborates (Scheme 35). Additionally, they found that neopentylglycol-derived diborylalkanes show higher reactivity than those of the more common pinacol-derived ones.

Mechanistically, authors suggest an initial reduction and salt metathesis of $Cu(OAc)_2$ with LiO^{t}Bu and coordination with the TMS-dppbz ligand form the starting copper alkoxide species. On the other hand, the organoborate might be generated *in situ* from the *gem*-diborylalkane and LiO^{t}Bu (Scheme 36). Transmetalation can be followed by the electrophilic amination with the hydroxylamine to afford the targeted α-aminoboronic acid derivative. The ligand exchange of concurrently formed



Scheme 35. Copper-catalyzed electrophilic amination of *gem*-diborylalkanes with the hydroxylamines.



Scheme 36. Mechanism for copper-catalyzed electrophilic amination of *gem*-diborylalkanes with the hydroxylamines.

CuOBz with LiO^{t}Bu has been suggested to regenerate the copper alkoxide and complete the catalytic cycle.[33] The less congested neopentylglycol-derived (Bneo) can undergo the transmetalation step, much more readily than the pinacol-derived.

2. Conclusions

We have collected, here, several *in situ* prepared borylalkyl copper(I) species that have shown a tremendous impact in new strategic C–C and C–N bond formation. Those reactivity trends can be summarized as electrophilic trapping of copper α-boryl carbanions. Reactivity with carbonyl substrates, such as aldehydes, provides the expected Boron-Witting pathway towards olefination protocols, together with the corresponding β-hydroxyboronate species that can be isolated, even in high levels of diastereo- and enantioselectivity. The roles of Cu(I) and the chiral phosphoramidites, in the catalytic process, are disclosed through suggested catalytic cycles. Analogously, it has been highlighted the addition of borylalkyl copper(I) species to aldimines and ketimines to form the corresponding β-aminoboronates through selective chairlike six-membered cyclic intermediates. The influence of the amine protecting groups is also remarkable to guarantee significant enantioselectivity. Allyl halides have been extensively studied to react with borylalkyl copper(I) species, and in this minireview we present the optimized conditions to control both, the S_N2 and the S_N2' substitution reactions, allowing to obtain enantioenriched branched organoboron compounds, when specific chiral ligands are employed. Alkyl or aryl halides react smoothly with α-borylcarbanions through S_N2 mechanism, as a new methodology for homologation reactions. Copper catalyzed addition of borylalkyl to vinyl carbonates and vinyl epoxides, proceeds through allylic alkylation with concomitant ring opening. Similarly, epoxides and aziridines also suffered ring opening procedures when react with borylalkyl copper(I) species. Electrophilic amination of borylalkyl copper species has been recently discovered by reactivity with hydroxylamines, proceeding with high chemoselectivity. Eventually, we highlight here the cooperative effect between copper and palladium complexes in domino carbamoylative borylalkylation of alkenes, in order to generate 3,3-disubstituted oxindole skeletons.

This is, indeed, an emerging area that benefits from the current accessibility to a huge palette of *gem*-diborylalkanes. Since they can be easily activated with copper(I) salts, new synthetic nucleophilic protocols have been elaborated, and the examples showed here represent a growing trend that will be the germ of future new synthetic applications.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: α-Boryl carbanions · Copper · Electrophilic trapping · Diastereoselectivity · Enantioselectivity

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MINIREVIEWS

Borylalkyl copper(I) species have shown a tremendous impact in new strategic C–C and C–N bond formation. Those reactivity trends can be summarized as nucleophilic addition to aldehydes, aldimines or ketimines. Analogously, the electrophilic trapping of α-boryl carbanions with allyl halides has been extensively studied to control both, the S_N2 and the S_N2' substitution reactions. Alkyl or aryl halides also react smoothly with α-borylcarbanions through S_N2 mechanism, as a new methodology for homologation reactions. Copper catalyzed addition of borylalkyl to vinyl carbonates and vinyl epoxides proceeds through allylic alkylation with concomitant ring opening. Electrophilic amination of borylalkyl copper species has been recently discovered by reactivity with hydroxylamines, proceeding with high chemoselectivity. We also highlight here the cooperative effect between copper and palladium complexes in domino carbamoylative borylalkylation of alkenes, in order to generate 3,3-disubstituted oxindole skeletons.

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