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Coupling Reactions

Site-Selective (*Z*)-α-Borylalkenyl Copper Systems for Nucleophilic Stereodefined Allylic Coupling

Mireia Pujol, Ricardo J. Maza, Oriol Salvado, Jorge J. Carbó, and Elena Fernández**

Dedicated to the memory of Professor Steve A. Westcott

Abstract: 1,1-Diborylalkenes can be transformed into (*Z*)-skipped dienes through Cu^{I}-phosphine catalyzed allylic coupling reactions. The energetically preferred formation of (*Z*)-α-borylalkenyl copper (I) species and the subsequent nucleophilic attack, explains the stereoselective nucleophilic substitution with allyl bromides. The eventual treatment of (*Z*)-skipped dienes with NaO^{t}Bu promotes cyclization/aromatization patterns via enyne intermediates.

1,1-Diborylalkenes are emerging bifunctional building blocks applied in the modular synthesis of complex molecules, through boron-selective transformations.[1] Chemoselective reactions on both geminal B–C(sp^2)–B sites have attracted great research interest since they provide an efficient and flexible platform to construct molecular diversity.[2]

When the two geminal boryl moieties on 1,1-diborylalkenes are different, the transformation in a stepwise manner occurs through the more reactive boryl group while the relatively inert boryl moiety (so-called boron masked group BMG) remains intact (Scheme 1a).[3] This would then require a deprotection sequence of the masked group to become a versatile boryl group.[4] By iteration of this boron-selective coupling/deprotection sequence, several successful modular approaches towards stereoselective polyfunctionalized alkenes have recently been described.[3] However, when the geminal boryl moieties on 1,1-diborylalkenes are identical, e.g. the convenient pinacolboryl (Bpin) motifs, the boron-selective reactions become a challenge. Palladium complexes have proved to interact with the Bpin group at the less hindered position of 1,1-di(pinacolboryl)alkenes to perform a Suzuki–Miyaura cross coupling with arylhalides, but only when an aryl group is present at the C_2 position of 1,1-diborylalkene (Scheme 1b).[5] Rhodium complexes have shown to activate non-selectively both C–Bpin moieties on substituted 1,1-diborylalkenes, although the (*Z*)-α-borylalkenyl Rh complex seems to isomerize towards (*E*)-α-borylalkenyl Rh complex which undergoes faster 1,4-addition to enones generating almost exclusively the (*E*) trisubstituted alkene (Scheme 1c).[6]

Since the key for a successful boron-selective reaction is to discriminate between the boryl groups, that are exposed to the same reaction conditions, we describe here a new conceptual approach based on the generation of an α-borylalkenyl copper species. The more hindered Bpin moiety of the 1,1-di(pinacolboryl)alkene can be selectively activated to promote a nucleophilic (*Z*)-selective Cu catalyzed reaction with allyl halides (Scheme 1d). The methodology is applicable to 1,1-di(pinacolboryl)alkenes containing aryl and vinyl groups at the C_2 position.

Bearing in mind the inherent difficulty to discriminate between the two geminal Bpin-C(sp^2)–Bpin bonds in 1,1-diborylalkenes, we studied first the influence of Cu salts, bases and ligands to form the (*Z*)-selective α-borylalkenyl Cu complex, on the model substrate 2-phenyl 1,1-di(pinacolboryl)alkene (**1a**). For a total picture of the utility of this C(sp^2)–B activation, we explored the in situ selective monofunctionalization with 3-bromoprop-1-ene (Table 1). The catalyst system based on CuCl/Xantphos allowed the conversion of **1a** into the skipped diene **2** in moderate conversion, in the presence on LiO^{t}Bu as base. The protodeborylated byproduct **3** was only formed in $<1\,\%$, working at 60 °C. However, the 1,4-diene was produced in an isomeric mixture of $Z/E = 71/29$ (Table 1, entry 1). Surprisingly, the use of the alternative base LiOMe, inhibited completely the reaction (Table 1, entry 2). Both, conversion and *Z*/*E* ratio improved significantly when the ligands involved were PCy_3 and PPh_3 (Table 1, entries 3–4) with the highest steroselectivity observed on the skipped (*Z*)-diene **2** with the latter phosphine (Table 1, entry 4). Those conditions were selected as the optimized ones, despite the fact that a small amount of protodeborylated byproduct was observed (9 %). Lower temperature (30 °C) or alternative copper source $(Cu(MeCN)_4]PF_6)$ did not improve the optimized conditions (Table 1, entries 5, 6).

These optimal reaction conditions met our dual requirements for boron-selective transformations facing the challenges of site-specific C(sp^2)–B activation to control the

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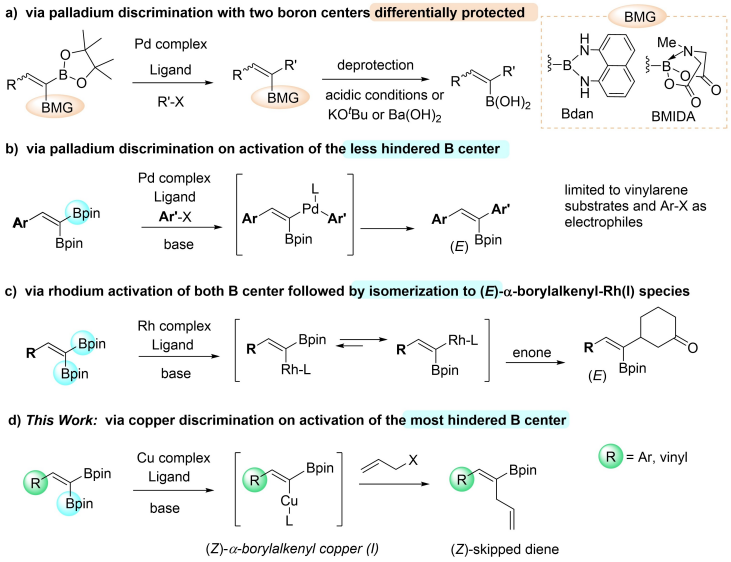
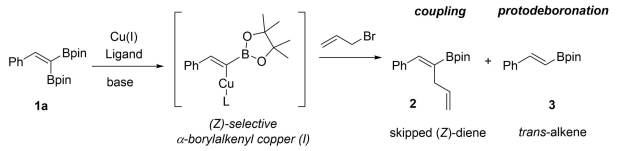


Scheme 1. Chemoselective activation of *geminal* B–C(sp^2)–B sites towards selective coupling reactions.

Table 1: Optimization conditions for nucleophilic stereodefined C–C bond formation between 1,1-diborylalkene **1a** and 3-bromoprop-1-ene.

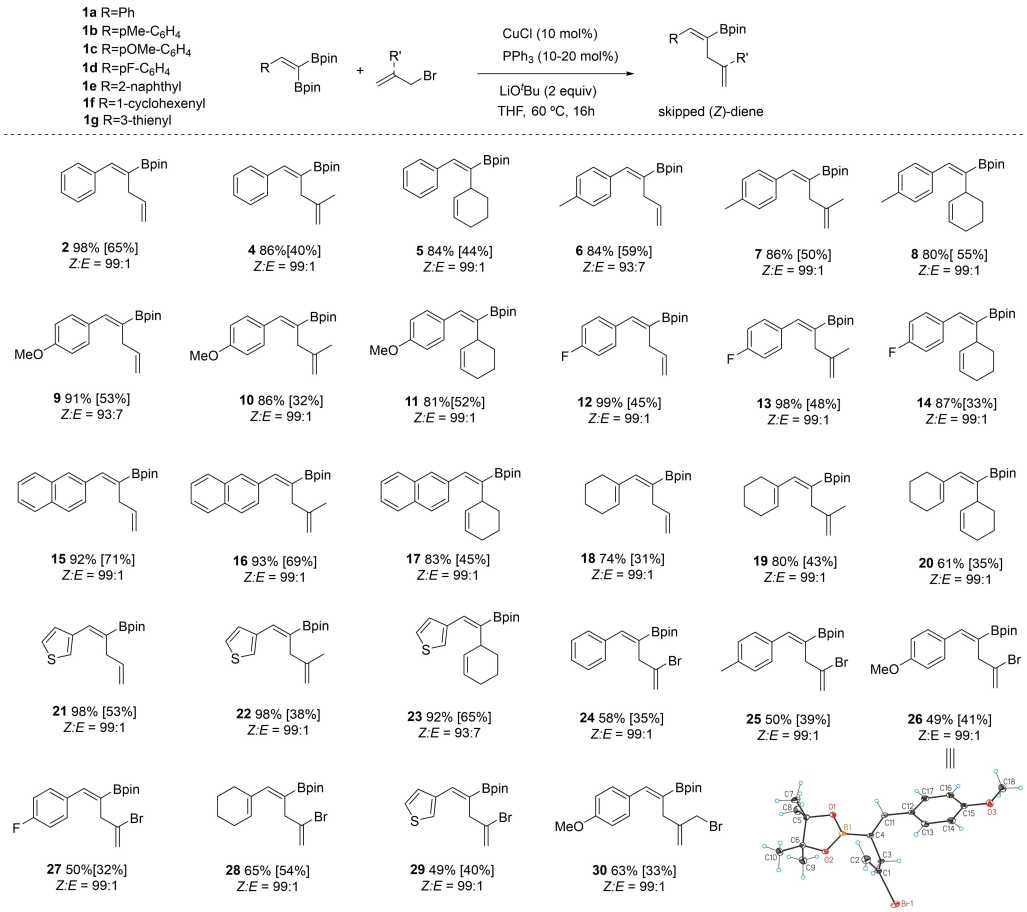


Entry[a]	Cu^I	Ligand	Base	*T* [°C]	Conv [%][b]	**2/3**	**2** (*Z*/*E*)
1	CuCl	Xantphos	LiO^{t}Bu	60	65	99:1	71:29
2	CuCl	Xantphos	LiOMe	60	–	–	–
3	CuCl	PCy_3	LiO^{t}Bu	60	91	90:10	96:4
4	CuCl	PPh_3	LiO^{t}Bu	60	98	91:9	99:1
5	CuCl	PPh_3	LiO^{t}Bu	30	72	96:4	94:6
6	[Cu]PF_6[c]	PPh_3	LiO^{t}Bu	60	50	55:45	82:18

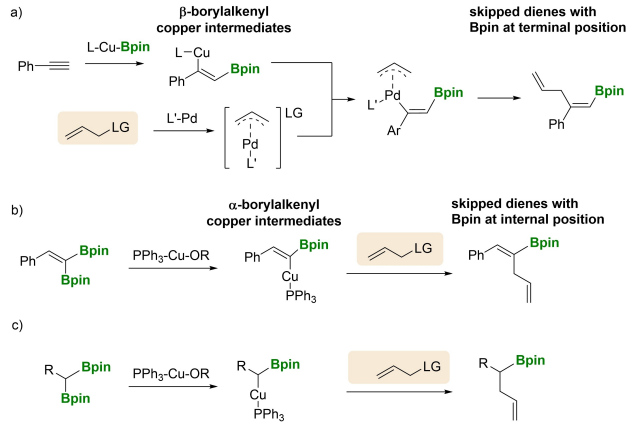
[a] General conditions: 1,1-diborylalkene (0.2 mmol), 3-bromoprop-1-ene (1.5 equiv), Cu salt (10 mol%), Xantphos (10 mol%), PR_3 (10–20 mol%), base (2 equiv), THF (2 mL), T, 16 h. [b] Conversion determined by NMR with naphthalene as internal standard. [c] [Cu(MeCN)$_4$]PF_6.

stereodefined (*Z*)-α-borylalkenyl copper (I) species while maintaining mild conditions to avoid the protodeborylative side reactions. Aimed to generalize this nucleophilic C–C bond formation at the more hindered C(sp^2)–B position we explored alternative allylic partners as well as 1,1-diborylalkenes containing an aryl or vinyl group at the C_2 position (Scheme 2). The electrophilic coupling partners 3-bromo-2-methylprop-1-ene reacted with **1a** to synthesize the skipped (*Z*)-diene **4** with exclusive stereoselectivity (Scheme 2). The (*Z*)-selectivity has been unambiguously proved by 1D NMR NOE experiments. The secondary allylic electrophile 3-bromocyclohex-1-ene also reacted with **1a** to form the cyclic 1,4-diene **5** with complete stereoselectivity (Scheme 2), however the protodeborylated byproduct **3** could be observed (up to 14%) indicating that the side-reaction becomes more competitive when the steric hindrance of the electrophile increases. 1,1-Diborylalkene substrates containing an aryl group (with electron donating or electron withdrawing substituents) or naphthyl group performed a similar stereoselective reaction outcome, generating the skipped (*Z*)-dienes **6**–**17**, in a stereodefined manner. The use of 1,1-diborylalkenes containing a cyclohexenyl or 3-thienyl group in C_2, resulted compatible with this transformation, and interesting stereodefined polyolefinic products **18**–**23** have been isolated (Scheme 2). The use of 10 or 20 mol% of PPh_3 resulted in comparable yields.

The use of 1,1-diborylalkenes containing aliphatic substituents in C_2, resulted inefficient for the allylic coupling. The electrophilic partners methyl bromide and benzyl bromide failed to react with substrate **1**. However, when we studied the allylic coupling of 1,1-diborylalkenes with 2,3-dibromoprop-1-ene, the skipped (*Z*)-dienes **24**–**29** were exclusively formed as a result of a chemoselective C–Br coupling, together with the protodeborylated byproducts (10–15%) (Scheme 2). The X-ray single-crystal diffraction analysis confirmed the geometry for the skipped (*Z*)-diene system **26** (Scheme 2).[7] Reactivity of **1c** with 3-bromo-2-(bromomethyl)prop-1-ene generated product **30** in a stereoselective manner (Scheme 2). Isolated yields are reduced due to the instability of the C(sp^2)–Bpin fragment during the separation technique, despite different treated silica were used. Interestingly, compounds **24**–**30** retained one C–Br bond becoming versatile products due to the remaining halide functionality for downstream transformations.[8] It has been described that copper-catalyzed allylboration of alkynes with 1,4-dibromo-2-butenes and diboron reagents, generate borylated dendralenes via β-borylalkenyl copper intermediates.[9] However, the trapping of the allylic partners with β-borylalkenyl copper complexes usually requires a Pd co-catalysts, to generate skipped dienes with Bpin moiety at the terminal position (Scheme 3a),[10] in sharp contrast to the straightforward allylic coupling with α-



Scheme 2. Substrate scope for nucleophilic stereodefined allylic coupling.



Scheme 3. Copper catalyzed allylic substitution reactions via a) β-borylalkenyl copper complexes, b) α-borylalkenyl copper complexes and c) α-borylalkyl copper complexes.

borylalkenyl copper systems, that we are describing in this work (Scheme 3b). The reactivity of (*Z*)-α-borylalkenyl copper (I) species resembles that of α-borylalkyl copper systems in nucleophilic substitution with allyl halides (Scheme 3c).[11]

In order to disclose the different reactivity between α-borylalkenyl and β-borylalkenyl copper systems, we analyzed here their electronic structures using the atomic charge at the carbanionic carbon (qC) and the C–B bond order ($C–B_{bo}$) as descriptors to evaluate their nucleophilicity. This would place these carbanionic species within a general reactivity map for α-boryl carbanions that we have established previously.[12] Figure 1 plots the descriptor values for α-borylalkenyl copper species **A** and the phenyl-substituted **A**-*Z* and **A**-*E* isomers, to be compared with the phenyl-substituted β-borylalkenyl copper intermediates **B**-*Z* and **B**-*E*, using in all cases Cu^{I}-PPh_3 as metal fragment. To have a total picture of the reactivity trends, we have also studied the atomic charge at carbanionic carbon and the C–B bond order of α-borylalkyl copper systems **C**.

The representation of (qC) versus ($C–B_{bo}$) for the alkenyl copper complexes shows that α-borylalkenyl copper species **A,** **A**-*Z* and **A**-*E* isomers have a stronger nucleophilic character than β-borylalkenyl copper systems (**B**-*Z* and **B**-*E*) in agreement with our experimental observations because α-borylalkenyl species conducted direct allylic coupling without the requirement of co-catalyst (Scheme 3b). For comparison, the well stablished nucleophilic α-borylalkyl copper complexes **C** (Scheme 3c) show the most negative atomic charge at the carbanionic carbon and a

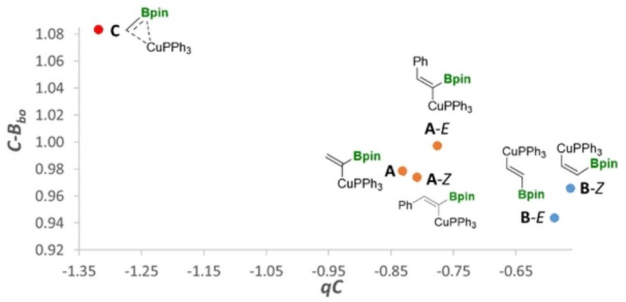


Figure 1. Representation of the C–B Wiberg bond order ($C–B_{bo}$) versus atomic charge at the carbanionic carbon (qC) for α-borylalkenyl-Cu-PPh_3 (**A**, **A**-*Z* and **A**-*E*), β-borylalkenyl-Cu-PPh_3 (**B**-*Z* and **B**-*E*), and α-borylalkyl-Cu-PPh_3 (**C**) systems.

significantly larger C–B bond order, as a consequence of the borata-alkene character of α-borylalkyl copper species due to the valence deficiency of the adjacent three coordinate boron center.[13]

Next, we conducted a DFT study[14] on the reaction mechanism for the stereodefined allylic substitution reaction described in this work with the α-borylalkenyl copper systems. Figure 2 shows the free-energy profile of the proposed mechanism for the conversion of **1a** into the skipped diene **2** catalyzed by the Cu^I/PPh_3 system, comparing the *Z* and the *E* paths (solid and dashed lines, respectively). The overall mechanism can be divided into two main stages: 1) the formation of the α-borylalkenyl copper intermediate **I2** via σ-bond metathesis between Cu-alkoxide complex and 1,1-diborylalkene substrate, and 2) the nucleophilic allylic coupling of the α-borylalkenyl moiety with the allyl bromide. The starting point of the mechanism is the formation of the phosphine copper(I) alkoxide complex (PPh_3)CuO^{t}Bu, upon mixing CuCl, the base and PPh_3 ligand. We recall that experimentally the use of 10 mol % of CuCl with 10 mol % of PPh_3 ligand resulted in comparable catalytic outcome than in the presence of 20 mol % of PPh_3, indicating that (PPh_3)CuO^{t}Bu was the model of choice for the DFT calculations.

As depicted in Figure 2, the σ-bond metathesis process takes place in two steps. First, an oxygen lone pair of the alkoxide ligand attacks to the empty p orbital of the boron atom in the 1,1-di(pinacolboryl)alkene substrate **1a**, generating the intermediates **I1**-*Z* and **I1**-*E* depending on which boryl moiety occurs the attack. In these complexes, the tertbutoxide acts as a bridging ligand between the Cu and the B atoms, while the alkene double bond of the substrate interacts with the Cu center. The formation of **I1**-*Z* and **I1**-*E* intermediates is exergonic by 14.3 and 16.1 kcal mol^{-1}, respectively, while the corresponding free-energy barriers are very low, 1.4 and 2.5 kcal mol^{-1}, respectively.

In the second step of σ-bond metathesis, the α-borylalkenyl transfer to Cu is completed (intermediates **I2**-*Z* and **I2**-*E*), and the ^{t}BuOBpin side product is released. The computed free energy barriers are relatively low (13.7 and 18.6 kcal mol^{-1} for *Z* and *E* paths, respectively), and intermediates **I2** lay at similar energy levels than the intermediates **I1**.

Overall the σ-bond metathesis is a smooth process that does not yield deep potential energy wells. Also, we note that the early alkoxide attack can occur at two different boron positions of the 1,1-diborylalkene substrate, differentiating between the *Z* and the *E* reaction paths (solid and dashed lines, respectively, in Figure 2). However, the reverse free energy barriers (ranging from 14 to 19 kcal mol^{-1}) can be easily overcome at working conditions. Consequently, these initial steps of the reaction are reversible allowing the interconversion between the *Z* and *E* isomers, and do not determine the overall stereoselectivity of the reaction.

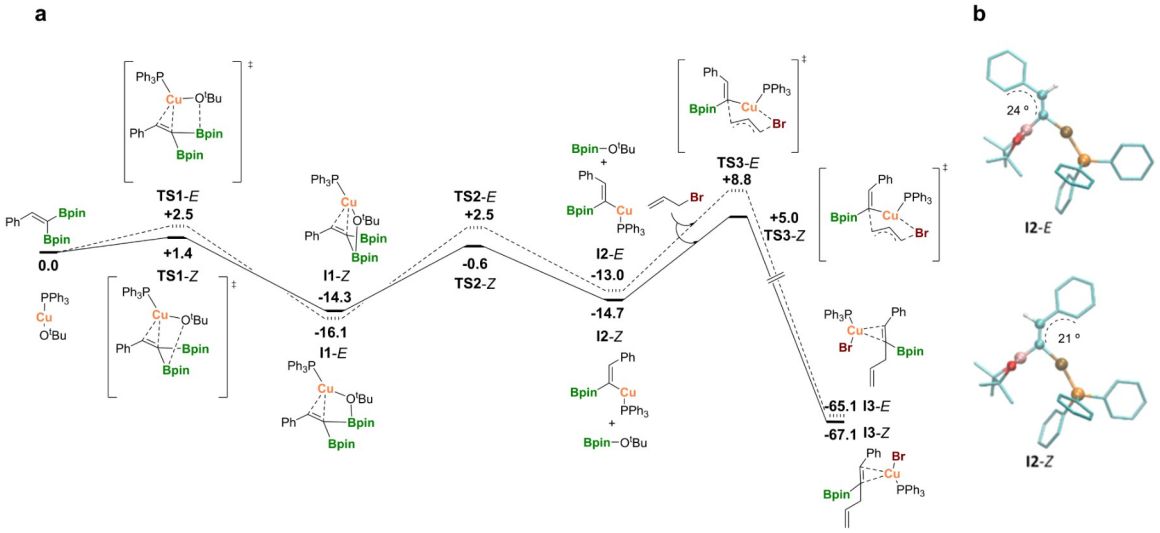


Figure 2. Free-energy profiles (kcal mol^{-1}) for the nucleophilic allylic coupling of the 1,1-di(pinacolboryl)alkene (**1a**) with allylic bromide catalysed by Cu^I/PPh_3 system. The formation of the stereoisomers *Z* and *E* are represented in solid and dashed lines, respectively (a); and 3D structures of **I2**-*E* and **I2**-*Z* (b).

From intermediate **I2**, the reaction proceeds through the nucleophilic attack of the α-borylalkenyl copper (I) species to the allyl bromide to yield the allylic coupling product **2**. We examined the attack at the allylic C(sp^2) (S_N2' mechanism) and at the C(sp^3)–Br (S_N2 mechanism). Calculations indicate that the S_N2' mechanism (19.7 kcal mol^{-1} for **I2**-*Z*→**TS3**-*Z*) is energetically preferred versus the S_N2 (24.9 kcal mol^{-1} for **I2**-*Z*→**TS3′**-*Z*), as illustrated in Figure S1. The overall barrier of the process (21.1 kcal mol^{-1}), computed as the difference between the preceding lowest-energy species (**I1**-*E*) and **TS3**-*Z*, is likely under the present experimental conditions. In the case of the electrophilic methyl bromide, for which the reaction failed, the overall free-energy barrier for the nucleophilic attack of **I2**-*Z* increases to 29.1 kcal mol^{-1} (see Figure S2 at Supporting Information). Importantly, the last step of the mechanism involving the C–C allylic coupling, has significantly higher free-energy barrier than those of previous σ-bond metathesis steps, and is largely irreversible (see Figure 2). Thus, we can assume that there is a rapid equilibrium between *Z* and *E* paths previous to the C–C allylic coupling, and that the observed stereoselectivity is determined by the relative free-energies of the corresponding transition states **TS3**-*Z* and **TS3**-*E* (Curtin–Hammett conditions). In agreement with the experimental findings, the *Z* path is kinetically preferred over the *E* path by 3.8 kcal mol^{-1}.

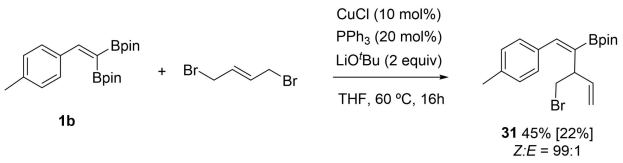
The preference for *Z* path can be attributed to the release of the steric hindrance between the phenyl substituent *cis* to the pinacolboryl moiety on **1a** substrate, that results in lower energy species along the reaction mechanism (see Figure 2a). Two illustrative species, **I2**-*Z* and **I2**-*E*, are shown in Figure 2b. In **I2**-*Z*, the Cu fragment induces less steric repulsion into the phenyl than the pinacolboryl in species **I2**-*E*, as reflected in lesser deviation of the phenyl ring out of the alkene plane for **I2**-*Z* (C_{sp2}–C_{sp2}–C_{ipso}–C_{ortho} dihedral angle of 21 and 24° for **I2**-*Z* and **I2**-*E*, respectively). These effects are translated to the key selectivity-determining transition states, resulting also in lower energy laying **TS3**-*Z* steroisomer versus the **TS3**-*E* one. A model was developed to evaluate the influence of the steric effects in the energy difference between the *Z* and the *E* paths. The replacement of the methyl groups in the pinacol borane fragment of transition states **TS3** by hydrogens significantly reduces the energy difference from 3.8 to 1.1 kcal mol^{-1}, indicating that the steric repulsions between the phenyl and the pinacolboryl substituents of the substrate govern the stereoselectivity. Alike previous discussion on steric influence, replacing the monophosphine ligands by wide bite angle Xantphos diphosphine reduces the stereoselectivity (compare entries 3 and 4 with entry 1 in Table 1). Probably, this is a consequence of the stronger repulsion between the metal Cu-Xantphos fragment and phenyl substituent of the alkene in *Z* isomers.

To prove the hypothesis of S_N2' mechanism in this nucleophilic stereodefined allylic coupling, we conducted the copper catalyzed reaction between **1b** and (*E*)-1,4-dibromobut-2-ene. Under optimized conditions, the branched skipped (*Z*)-diene product **31** was exclusively formed, although in low yield despite the fact that protodeborylated byproduct was not observed (Scheme 4).

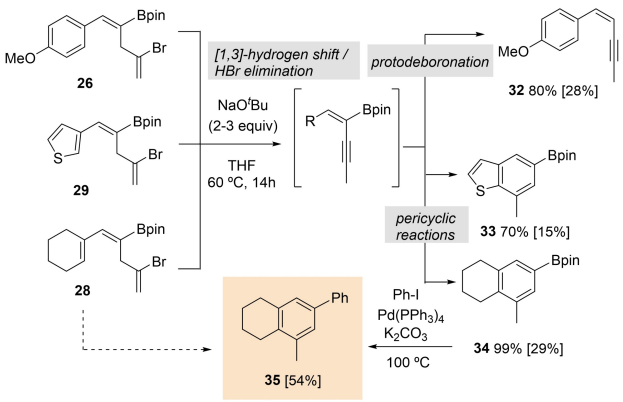
The importance of skipped diene motifs in natural products preparation has led to new strategies for the de novo synthesis.[15]

We take advantage of the straightforward access to skipped (*Z*)-dienes **26**, **28** and **29**, containing simultaneously C(sp^2)–B and C(sp^2)–Br fragments, to explore further reactivity with NaO^{t}Bu. We were intended to activate the C(sp^2)–Bpin fragment with $^-$O^{t}Bu, by forming the boron "ate" intermediate, to face a concomitant intramolecular trapping with the C(sp^2)–Br fragment and subsequent cyclopropanation. Instead we observed that compound **26** was transformed onto (*Z*)-enyne **32**, probably via domino reaction sequence [1,3]-hydrogen shift/HBr elimination/protodeboronation (Scheme 4).[16] The (*Z*)-enyne **32** has been prepared for the first time in this work, since only the corresponding (*E*) isomer was synthesized previously through Kumada coupling between (*E*)-alkenyl halide and 1-propynyl magnesium bromide.[17] Interestingly, compounds **28** and **29** were transformed, under identical conditions, into cyclic products **33** and **34**, suggesting a [1,3]-hydrogen shift/HBr elimination followed by base assisted pericyclic reaction (Scheme 5).[18]

The enyne cycloisomerization mechanism is justified by the concomitant aromatization. The protodeboronation step in products **33** and **34** seems to be precluded suggesting a more stable Bpin moiety when is coordinated to the aromatic system. Since substituted tetrahydronaphthalenes derivatives are an important class of synthons comprising key fragments of biomolecules,[19] we conducted the func-



Scheme 4. Nucleophilic stereodefined C–C bond formation between 1,1-diborylakene **1b** and (*E*)-1,4-dibromobut-2-ene.



Scheme 5. Base assisted transformations of skipped substrates towards isomerized and cyclized products.

tionalization of the C–B bond by Suzuki–Miyaura coupling with PhI, aimed to isolate product **35**. To the best of our knowledge, this substituted tetrahydronaphthalene has only been prepared before by gold-catalyzed benzannulation of 3-hydroxy-1,5-enynes.[20]

In summary, we discovered a site-selective activation of 1,1-diborylalkenes by means of Cu^{I}-phosphine catalytic system. The energetically preferred formation of (*Z*)-α-borylalkenyl copper (I) species and the subsequent coupling reaction with allyl bromides determine the stereoselectivity by releasing the steric repulsion of the *cis* pinacolboryl alkene substituent. This new methodology is applicable to 1,1-di(pinacolboryl)alkenes containing aryl and vinyl groups at the C_2 position to be efficiently coupled with different type of allyl bromides containing one or two bromides. The stereoselective nucleophilic substitution generates (*Z*)-skipped dienes which can be eventually treated with NaO^{t}Bu to promote cyclization/aromatization patterns via enyne intermediates.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Allylic Coupling · Copper · 1,1-Diborylalkenes · Skipped Dienes · Stereoselective Synthesis

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