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Rationalizing the Role of NaO^{t}Bu in Copper-Catalyzed Carboboration of Alkynes: Assembly of Allylic All-Carbon Quaternary Stereocenters

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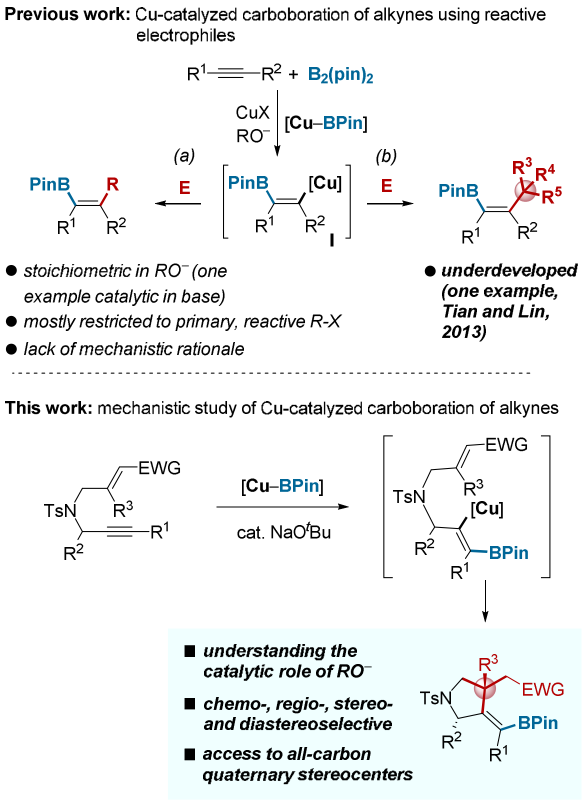
ABSTRACT: A preliminary mechanistic approach to the Cu-catalyzed carboboration of alkynes using $B_2(pin)_2$ was used as a blueprint for the rational design and development of a regiocontrolled, stereoselective caboborylation of internal alkynes by reaction with a β,β-disubstituted acrylate fragment to provide synthetically versatile and densely functionalized pyrrolidines. Experimental observations and computational analysis relevant to understanding the activation role of the alkoxide functionality in this type of carboboration process were instrumental in developing a synthetic method broad in scope and functional group tolerance. Compounds obtained by this strategy feature a stereochemically defined tetrasubstituted vinylboronate, together with an all-carbon quaternary stereocenter. This procedure involves a tandem regio-, chemo-, and diastereoselective borylcupration of unsymmetrical dialkyl alkynes followed by migratory insertion of an activated olefin to a carbon–Cu bond.

Keywords: Carboboration · Internal alkynes · Copper-catalyzed · Bis(pinacolato)diboron · Tetrasubstituted alkenylboronate · All-carbon quaternary stereocenter · Pyrrolidines · Role of alkoxide

INTRODUCTION

The ability to impart chemo-, regio-, and stereoselective control in the assembly of alkenes with four different substituents is a key challenge in Organic Synthesis.[1] Catalytic carboboration of internal alkynes, where C–C and C–B bonds are constructed in a single operation, represents a powerful tool for the construction of tetrasubstitued vinyl boronates, which are ideal precursors for fully substituted olefins.[2] Among the methods reported to synthesize this structural motif, the copper-catalyzed carboboration pioneered by Tortosa and Yoshida[3] via reaction of alkynes with bis(pinacolato)diboron [$B_2(pin)_2$] and subsequent interception of the putative β-boryl alkenyl-copper intermediate species (species **I**, generated by *syn* addition of nucleophilic Cu^I–BPin complexes across the C≡C bond, Scheme 1) with carbon-based electrophiles is receiving increasing interest.[4] Despite its synthetic relevance and the elegant efforts reported to date, the Cu-catalyzed alkyne carboboration is more challenging and remains underdeveloped when compared to the parent hydroboration processes.[4] In this regard, trapping of boryl-copper intermediate **I** with alkyl halides is arguably the most explored strategy for the rapid access to tetrasubstituted vinylboronates.[5] The alkenyl-Cu species **I** has also been reacted with aryl iodides (boryl-arylation),[6] allyl phosphates (boryl-allylation),[7] and CO_2 (boryl-carboxylation).[8] In all of these procedures (Scheme 1) stoichiometric quantities of an alkoxide salt -typically NaO^{t}Bu, a rather strong base with potentially low functional group tolerance- are required for the reactions to proceed. While it is generally accepted that the stoichiometric alkoxide is needed to promote the regeneration of the catalytically active CuOR species from the CuX formed after reaction of the vinylcopper intermediate with R–X, to our knowledge no experimental or theoretical study on the overall role of the base has been published.[9] A notable exception to this general behavior is the report by Lin and Tian,[10] in which a properly designed *O*-tethered 1,6-enyne undergoes borylcupration of the alkyne and subsequent cyclization with an enone via intramolecular conjugate addition.[11] In contrast to previous studies, this catalyst system is the only one that works efficiently with substoichiometric amounts of alkoxide (NaO^{t}Bu, 15 mol %), which was ascribed to the formation of a Cu-enolate intermediate whose protonation with MeOH regenerates the active CuOR species.

Despite these advances, limitations still remain. Firstly, the majority of the examples reported thus far are restricted to the use of higly reactive alkyl halides, quite likely due to the inherent limitations imposed by a S_N-type mechanism. As a direct consequence, this strategy is not amenable to the formation of actively sought for all-carbon quaternary stereocenters,[12] with the exception of a single example described.[10a] Secondly, and perhaps more importantly, the carboboration mechanism and the role played by the stoichiometric alkoxide remain so far poorly understood; also, no computational study on this subject has been reported.[13] This lack of mechanistic information prevents further development of this valuable transformation.



Scheme 1. Cu-catalyzed carboboration of alkynes

In addition to the proposed role of NaO^{t}Bu in CuX→CuOR catalyst regeneration, Ito has recently speculated that an interaction between the alkoxide and the copper center could result in formation of a heterocuprate complex [RCu(O^{t}Bu)Na, Figure 1a][5c] that would then evolve through the typical mechanism proposed for S$_N$2 alkylation of organocuprates on sp^3 carbons (oxidative addition to R–X to provide a Cu^{III} intermediate and reductive elimination).[14] Elegant work by Negishi, Matteson, Levy, Aggarwal, Morken, and others[15] prompted us to consider an alternative activation scenario that would involve reaction of the alkoxide with the electrophilic boron center, in which the resulting hypervalent alkenyl-boron "ate" species could provide increased nucleophilicity at the reactive carbon of the vinyl cuprate, thereby triggering nucleophilic attack to the electrophile.

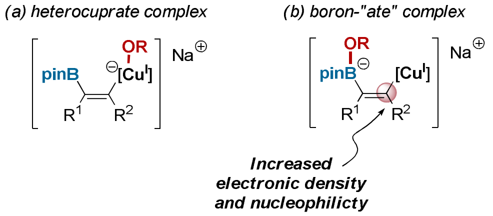


Figure 1. Possible activation modes of the vinyl-Cu intermediate by the alkoxide additive: (a) copper-activation or (b) boron-activation.

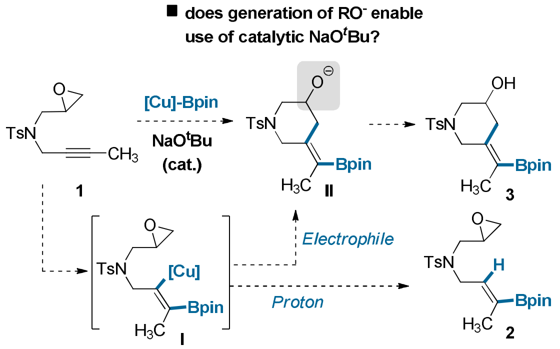
In this report, we describe insights into these aspects of the chemistry of vinylboronates, gathered from a combination of theoretical and experimental studies. These observations substantiate a proposal for an activation mode based on a boron/alcoxide interaction. Additionally, these mechanistic investigations provide basis for the rational design of a regio- and stereocontrolled Cu-catalyzed procedure for the (Bpin)$_2$-carboboration of alkynes. This transformation comprises the following distinct features (Scheme 1): *i) operates under a catalytic amount of alkoxide additive, ii) displays excellent levels of selectivity (including chemo- and regioselectivity), and iii) concurrently generates a breadth of molecules which contain allylic all-carbon quaternary centers.*

RESULTS AND DISCUSSION

1. Formulation of a working hypothesis

1.1. Experimental studies on epoxide substrates

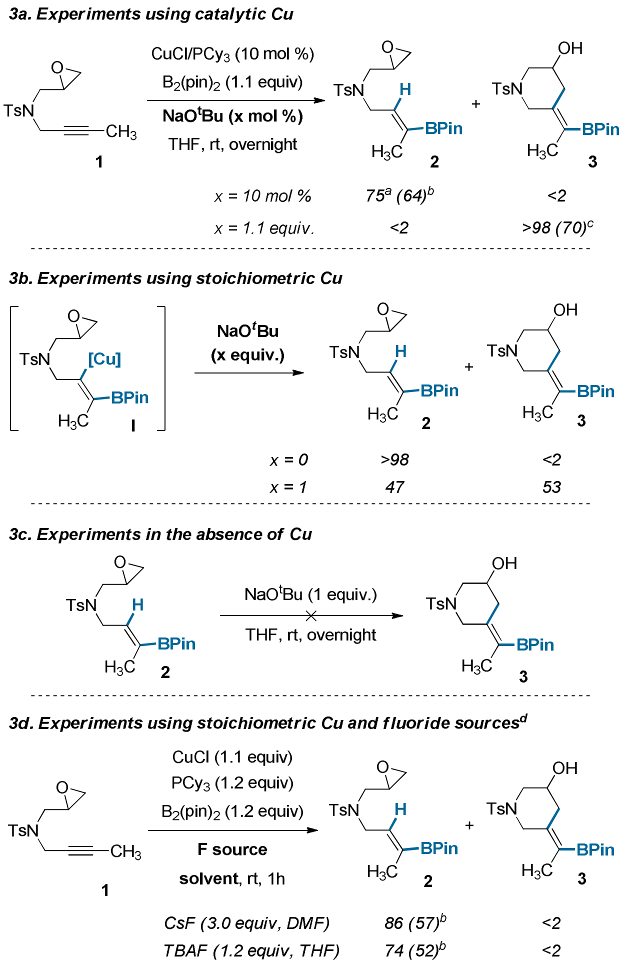
At the outset of our studies, we reasoned that the reaction of the intermediate organocopper species with a halide-free electrophile such as an epoxide would result in formation of an alkoxide, thus enabling a S$_N$2-type borylalkylation without the need for a stoichiometric amount of alkoxide (Scheme 2).[16,17] In light of the lack of precedence on carboboration with epoxides, we decided to test this reaction in an intramolecular manifold. Our previous studies on boryl-cupration of dialkyl internal alkynes showed that the presence of an heteroatom (e.g. O-, S- or N-based functionality) at the propargylic position serves as a tool for highly regioselective borylation at the acetylenic carbon distal to the heteroatom.[13a,18] This knowledge guided us to choose propargylamine **1** as model substrate, in which an epoxide moiety is placed in the appropriate position to satisfy the geometrical requirements of an intramolecular nucleophilic attack by the putative vinylcopper intermediate **I**, thereby facilitating a cyclization step to afford piperidine **3**.



Scheme 2. First working hypothesis

A first set of experiments performed on substrate **1** using catalytic amounts of CuCl and PCy$_3$ showed that the use of 10 mol % NaO^{t}Bu resulted in sole formation of the corresponding hydroborylated product **2** (64%, Scheme

3a).[19,20] In turn, performing the reaction in the presence of a 1.1 equivalent of alkoxide allowed the reaction to give the carboborylated alcohol **3** as the only product detected in the reaction mixture (70%). If the base were necessary only for the second step of the reaction, a base-free scenario in which a stoichiometric amount of the corresponding boryl-vinyl-copper complex **I** were formed should afford the hydroborylated epoxide **2** exclusively. In principle, **I** should be generated by addition of the boryl-copper species Cy$_3$PCu-Bpin to alkyne **1**: however, this compound has been reported to be highly unstable,[21] and all our attempts to isolate it were unsuccessful. To address this issue, we added 1 equivalent of Cy$_3$PCuO^{t}Bu to a mixture of B$_2$pin$_2$ and **1**, in hopes forming a stoichiometric amount of Cy$_3$PCu-Bpin which would immediately react with **1** to yield **I**. In agreement with this assumption, direct hydrolysis of intermediate **I** resulted again in exclusive formation of **2** (Scheme 3b), while **3** was not detected by ^{1}H NMR analysis of the reaction mixture. However, immediate addition of a second equivalent of NaO^{t}Bu to **I** showed that products **2** and **3** were formed in a 1:1 ratio.[22] This observation, along with the fact that compound **2** does not form **3** upon addition of NaO^{t}Bu (Scheme 3c), supports the hypothesis that **3** is originated from intermediate **I**.



Scheme 3. Initial experiments: influence of the base on product ratio

[a] In the absence of MeOH. 100% conv (80% yield) in the presence of 2 equivalents of MeOH. [b] Isolated yield. Compound **2** was found to decompose slightly on silica. [c] Isolated yield. [d] Ratios determined by ^{1}H NMR using an internal standard.

Next, we explored the possibility of performing a borylcupration of **1** using a source of fluoride instead of NaO^{t}Bu (Scheme 3d). This very weak base is capable of promoting the initial [B–B/Cu–F] → [B–Cu/B–F] σ-bond metathesis,[23] and its behavior would ideally help us to establish firmly the need for an alkoxide base in the carboboration process. We observed that the the reaction of **1** with 3 equivalents of CsF in DMF as solvent[23b,c] afforded compound **2** as sole product. An analogous result was observed when the reaction was run in THF using TBAF as fluoride source. These results suggest that although the fluoride anion is capable of promoting the initial [B–B/Cu–F]→[B–Cu/B–F] σ-bond metathesis, it fails at promoting the reactivity of the putative vinyl-Cu intermediate towards carboboration.

Two conclusions can be drawn from the results detailed in Scheme 3: 1. Intermediate **I**, generated as a result of a regioselective insertion of a B-Cu complex onto an alkyne, cannot react further with an epoxide in the absence of a full equivalent of an external alkoxide base. 2. Although stoichiometric amounts of fluoride salts are capable of promoting the catalytic borylation of the alkyne (formation of product **2** is observed), this weaker base is not effective at promoting the carboboration step.

1.2. Computational studies on epoxide substrates

As mentioned in the introduction, we were intrigued by the possibility of an alternative explanation for the need of stoichiometric amounts of alkoxide that would involve interaction of O^{t}Bu with the electrophilic boron atom. At this point, we performed a preliminary computational study[24] on the cyclization step to evaluate possible activation modes from the vinyl-Cu intermediate model **IA** (Figure 2, where Tol, PCy$_3$ and O^{t}Bu were replaced by Ph, P^{i}Pr$_3$ and OMe, respectively). In the absence of a OMe anion, a high energy barrier was found for the reaction to proceed (**TS(I-II)A**, drawn in black, 25.2 kcal·mol^{-1}). When an interaction with an alkoxide ion was considered, the energy profile involving coordination of methoxide with boron (**IAa**, -9.9 kcal·mol^{-1}, drawn in blue, route a) was found to be much more favorable than that involving coordination with copper (**IAb**, -2.4 kcal·mol^{-1}, drawn in red, route b). Attempts directed at locating any other type of intermediates along the reaction coordinate failed. From this point forward, the barrier to reach the corresponding TS in each case is notably higher in the case of coordination with Cu (27.6 kcalmol^{-1}) than it is with boron (19.3 kcalmol^{-1}). NBO analysis of the TSs found reveals important differences in the polarization of the alkenyl moiety (values indicated within dashed squares in Figure 2). In the case of **TS(I-II)A** the difference in natural charge for both atoms is quite small (Δq = 0.04, compare q$_1$ and q$_2$). However, in **TS(I-II)Aa** (with OMe bound to B), or (**TS(I-II)Ab** (with OMe bound to Cu), the alkenyl moiety is strongly polarized ($\Delta q \approx 0.2$, compare q$_1$ and q$_2$), although in the opposite direction. This switch results in a reversal of the naturally occurring electrostatic polarization of the vinyl boronate unit. Notably, it is only in **TS(I-II)Aa** in which this negative charge buildup is located at the reactive carbon 2. *This increase in electronic density at the carbon moiety would result in an increase in its nucleophilicity, an effect that might well be at the origin of the activation mode by stoichiometric alkoxide additives*. Additionally, according to the structure of products **IIA**, the presence of the alkoxide ion seems to strongly increase their stability (compare the energy of **IIA** to that of **IIAa** and **IIAb**) by coordination to the leaving Cu atom.

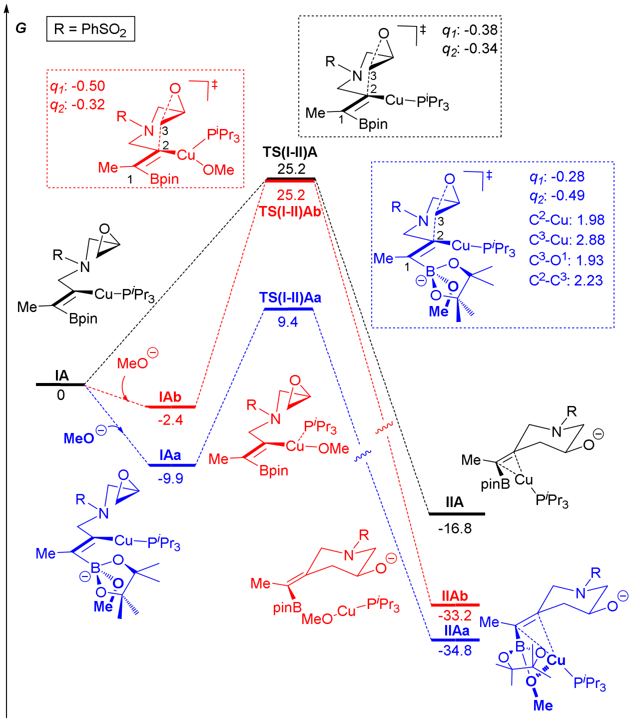


Figure 2. Energy profile for the C-C bond-forming step considering the possible activation modes of the vinyl-Cu intermediate model **IA**. Calculated relative free energies at 298 K (kcalmol^{-1}) include single point solvation energy corrections [SMD$_{THF}$/M06/6-311+G(2df,2p) (B, C, H, N, O, P, S), LANL2TZ(f) (Cu)//B3LYP/6-31G(d) (B, C, H, N, O, P, S), LANL2DZ (Cu)]. Natural charges (q_i, in a.u.) of alkenyl carbons in TSs and relevant distances in **TS(I-II)Aa** (Å) are also indicated.

We also evaluated the role of Cu in this transformation by studying the C-C bond-forming step from intermediate model **IB** (Figure 3), in which only boron (and not Cu) was present. The coordination of a OMe anion with boron resulted again in formation of a very stable complex (**IBa**). From this point, the barrier that should be overcome for the reaction to proceed (**TS(I-II)Ba**) was found to be higher than the barrier found when Cu is present (compare **TS(I-II)Aa** in Figure 2 and **TS(I-II)Ba** in Figure 3, with barriers of 19.3 kcalmol^{-1} and 26.6 kcalmol^{-1}, respectively). Moreover, the geometry of **TS(I-II)Ba** was found to be analogous to those described in for the TSs in Figure 2, which supports the hypothesis that Cu is not involved in the C-C bond-forming event. From that point forward, **TS(I-II)Ba** did not evolve in the absence of Cu into a stable cyclization product: instead, an endothermic and likely reversible step was found to form the carbocationic intermediate **IIBA**. These findings provide a rationale for the role of Cu in the second part of the process (regeneration of double bond and active catalyst), and are in good agreement with the experimental observation that product **2** does not evolve into **3** upon treatment with 1 equivalent of NaO^{t}Bu (Scheme 3c).

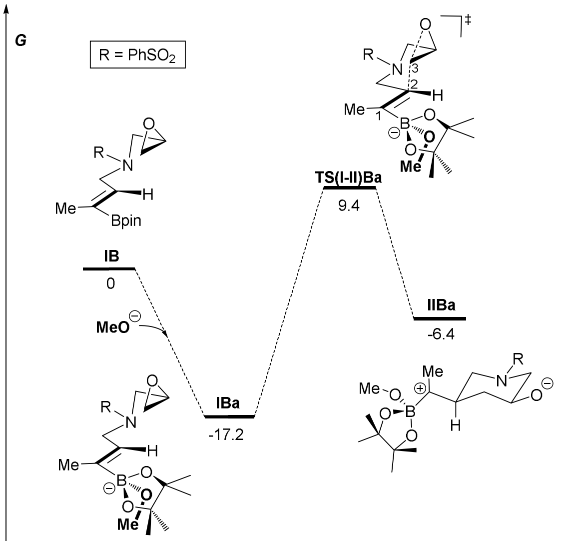
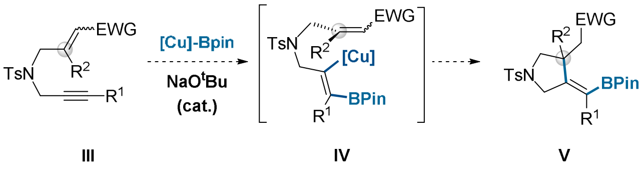


Figure 3. Energy profile for the C-C bond-forming step for vinyl-H intermediate model **IB**. Calculated relative free energies at 298 K (kcalmol^{-1}) include single point solvation energy corrections [SMD$_{THF}$/M06/6-311+G(2df,2p)//B3LYP/6-31G(d)].

A particularly relevant conclusion from this theoretical study is that for the three pathways found the process involves an S_N2-type reaction that takes place *via* chair-like TS by nucleophilic attack of the β-carbon in the vinylcopper (C2) to the electrophilic carbon of the epoxide. *As a direct consequence of this mechanistic manifold, formation of a quaternary stereocenter at the allylic position would not be viable.*

2. Revised working hypothesis: Development of a method for the preparation of tetrasubstituted vinyl boronates bearing allylic quaternary stereocenters

We reasoned that a viable solution to the challenge posed above might come from a distinct mechanistic approach that would not rely on a S_N2-type pathway. Specifically, we envisaged that a distinct carboboration approach exploiting a migratory insertion across an activated β,β-disubstituted olefin *would override any a priori limitation imposed by an S_N2-type approach in terms of substitution at the electrophile, hence setting the stage for the preparation of quaternary stereocenters at the allylic position* (Scheme 4).



Scheme 4. Revised working hypothesis

Propargylamine-type substrates **III**, in which a β,β-disubstituted Michael acceptor fragment replaces the epoxide moiety in model substrate **1**, should provide a unique opportunity to explore this hypothesis (Scheme 4). We anticipated, however, three conceptual/synthetic challenges: Firstly, controlling chemoselectivity is an immediate issue, as the well-known conjugate boration of activated olefins is a possible competing side reaction. Secondly, carboboration via boryl-cupration of an alkyne and subsequent conjugate addition to β,β-disubstituted activated alkenes is, to the best of our knowledge, heretofore unknown and would require the vinyl-Cu intermediate **IV** to react with the sterically congested alkene faster than it undergoes protonolysis to afford the hydroboration byproduct. Lastly, the configuration of the alkene might also have an influence on catalytic activity and selectivity control.

2.1. Computational studies on ester substrates

We next conducted a preliminary computational study in order to obtain insights into the viability of a migratory insertion of a vinyl-Cu bond (model **IC** in Figure 3) across a trisubstituted olefin (Figure 4). This study shows how both the barrier and the geometry of all species completely agrees with those expected for a nucleophilic organocopper(I) conjugate addition reaction[13] that follows a typical transition metal/olefin reaction. Model **IC** shows the geometry of a Cu(III) π-complex from which the reductive elimination through **TS(I-II)C** takes place. During the process, Cu(III) recovers its d-electrons from the Cu-C$_\beta$ bond, developing a slightly positive charge at C^3 while the bond is being cleaved, and staying bonded to C^4 in which a strong negative charge is developed. In this way a stereochemically controlled quaternary center is formed in the Cu-enolate intermediate **IIC**.

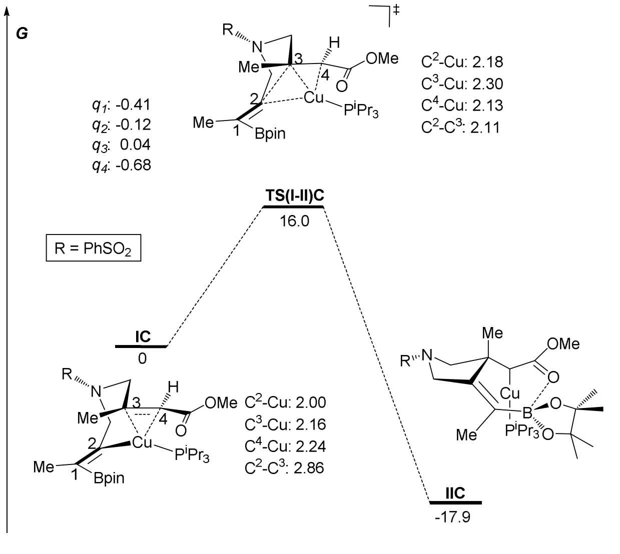
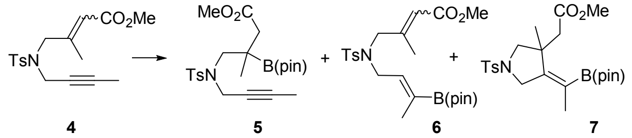


Figure 4. Energy profile for the C-C bond-forming step of intermediate model **IC**. Calculated relative free energies at 298 ºK (kcal/mol) include single point solvation energy corrections [SMD$_{THF}$/M06/6-311+G(2df,2p) (B, C, H, N, O, P, S), LANL2TZ(f) (Cu)//B3LYP/6-31G(d) (B, C, H, N, O, P, S), LANL2DZ (Cu)]. Natural charges (q_i) of alkenyl carbons and relevant distances (Å) in **TS(I-II)C** are also indicated.

2.2. First experimental studies on ester substrates

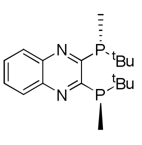
Impact of ligand structure on chemoselectivity. To test our revised hypothesis, we synthesized model substrate **4**, containing a β-substituted methyl acrylate moiety, initially obtained as a 3:2 mixture of *E*/*Z* isomers. With substrate **4** in our hands, we conducted a brief initial study on the effect that ancillary ligands would have in the borylation process. Our results, collected in Table 1, show a marked impact on the chemoselectivity of the process: Use of bidentate phosphines **L1-L3** (entries 1-3; (*R*)-QuinoxP, (*R*,*R*)-Me-DUPHOS, and (*R*)-DTBMSegphos, respectively) resulted in smooth borylation of the vinyl ester fragment (product **5**). However, switching to monodentate phosphite **L4** (entry 4, (*R*)-Monophos) almost completely suppressed the conjugate borylation pathway (conversion to **5** decreased to 10%). Instead, we observed 60% of compound **6**, generated by regioselective hydroborylation of the alkyne in substrate **4**. Along with **6**, we detected formation of pyrrolidine **7** (30%),[25] the result of the boryl-cupration/migratory insertion sequence (**6**/**7** = 2:1). Finally, use of more electron rich ligands helped in increasing formation of **7**; for example, when we used the SPhos ligand the ratio was improved notably (entry 5, **6**/**7** = 1:4), while use of PCy$_3$ translated into a highly chemoselective reaction to form product **7** in 85% yield (entry 6, **6**/**7** = 1:19).

Table 1. Ligand effects on chemoselectivity

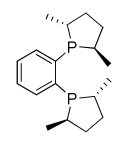


#[a]	Ligand	Conv. (%)[b]	**5** (%)[b]	**6** (%)[b]	**7** (%)[b]
1	**L1**	>98 (86)	>98 (86)	<2	<2
2	**L2**	>98	>98	<2	<2
3	**L3**	71	82	18	<2
4	**L4**	28	10	60	30
5	**L5**	47	<2	20	80
6	PCy$_3$	90	<2	5	95 (85)

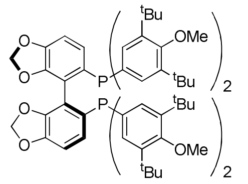
[a] Reaction conditions: B$_2$(pin)$_2$ (1.1 equiv.), CuCl (10 mol %), Ligand (12 mol %), NaO^{t}Bu (15 mol %), MeOH (2.0 equiv), THF, overnight. [b] Ratios determined by ^{1}H NMR analysis of the crude reaction mixtures.



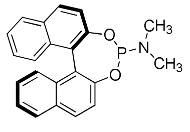
L1, (*R*)-QuinoxP



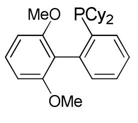
L2, (*R*,*R*)-Me-DUPHOS



L3, (*R*)-DTBMSegphos

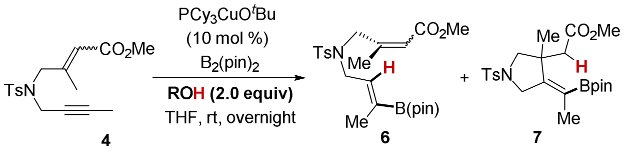


L4, (*R*)-Monophos



L5, SPhos

Influence of the pK_a of the proton donor. In an effort to improve the conversion and product ratio of the carboboration, we next considered the possibility of altering the pK_a value of the proton source used in the reaction. Specifically, we reasoned that use of a slightly less acidic alcohol would slow down the protonation of the intermediate vinyl-Cu species generated after the first borylation step, and consequently improve the ratio of product **7**.[26] In good agreement with this hypothesis, switching from MeOH to the less acidic ^{i}PrOH resulted in complete conversion and selectivity towards **7** (Scheme 5), affording the carbocyclic product in 93% yield (similar yields were also obtained from the stereochemically pure olefins *E*-**4** and *Z*-**4**). Conversely, use of the more acidic hexafluoroisopropanol (HFIP) translated into a reverse effect: while the conversion was still high (91%), protonation of the intermediate vinyl-Cu species was too fast for the carboboration to take place (**6**:**7** = 93:7).



ROH	pK_a		6/7^a	conversion^a
(CF$_3$)$_2$CHOH	9.3	**4** (*E*/*Z* = 2:1)	93:7	*91%*
MeOH	15.5	**4** (*E*/*Z* = 2:1)	5:95	*90%*
^{i}PrOH	16.5	**4** (*E*/*Z* = 2:1)	<2:>98	*>98% (93% yield)*
		from *E*-**4**	<2:>98	*>98% (93% yield)*
		from *Z*-**4**	<2:>98	*>98% (95% yield)*

^{a}Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard

Scheme 5. Influence of the alcohol on product ratio

It should be noted that, despite extensive progress in this field, in virtually all reports described thus far MeOH has been used as the proton source additive to secure turnover when the borylated acceptor needs to be liberated through protonolysis (along with the copper(I) methoxide complex). However, we anticipate that this study is of relevant importance because it provides a more pronounced beneficial impact in the case of substrates where the coordination of the metal to the π-system (needed to initiate 1,2-migration of the C-Cu bond across the alkene) is hindered, and might be beneficial by slowing down the terminating alcoholysis (vide infra).

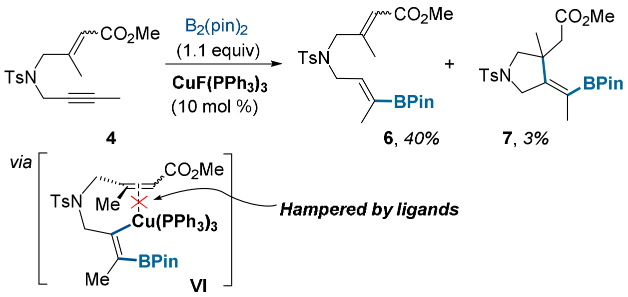
3. Mechanistic considerations: Cu- *vs.* B-activation.

Although the two processes described in the previous sections follow similar reaction patterns (catalytic borylcupration of an alkyne followed by reaction of the vinyl-Cu intermediate with an electrophile), the theoretical and experimental data gathered thus far suggest subtle mechanistic differences. The role of NaO^{t}Bu appears to be crucial in this regard, as evidenced by the different amounts of this additive required for both transformations to take place. In an attempt to gain understanding on the important role of the alkoxide, and to address the question of whether it is the copper (as proposed in the literature) or the boron atom (as suggested by our DFT studies) that undergoes activation by the stoichiometric NaO^{t}Bu to enhance reactivity, we designed two different and complementary strategies: First, hampering the reactivity of the copper atom by modulating its coordination sphere, in order to analyze the reactivity of the vinylboronate fragment. Second, performing the reaction in the absence of boron to isolate the reactivity of the alkenylcopper moiety.

3.1. Inhibition of Cu reactivity

As a first step, we sought to analyze the system in a scenario in which the reactivity of Cu were hampered. For that purpose, we reasoned that saturating the coordination sphere of the transition metal with ancillary ligands would result in temporal inhibition of the reactivity associated to Cu. We chose commercially available CuF(PPh$_3$)$_3$ as pre-catalyst for two reasons: 1. It possessed three PPh$_3$ ligands in its coordination sphere. 2. As shown in Scheme 3d, the fluoride anion is effective at promoting the required initial σ-bond metathesis that results in formation of the B-Cu complex.

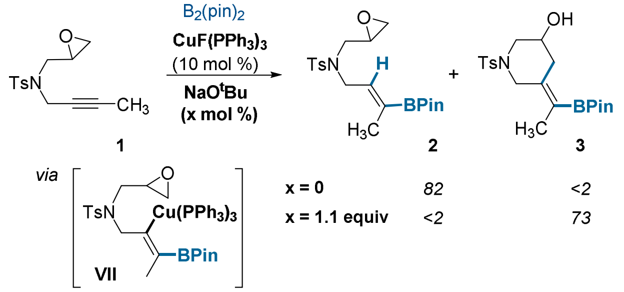
Use of CuF(PPh$_3$)$_3$ (10 mol %) in the reaction of substrate **4** with B$_2$(pin)$_2$ under the standard conditions resulted in poorer catalytic efficiency (43% conversion after 12 hours) and, more importantly, the reaction virtually stopped at the hydroborylation stage (Scheme 6). The hydroborylated product **6** was almost exclusively formed (40%) and only traces of the carboboration product **7** were detected in the reaction mixture (3%).[27] This observation suggests that the crowded environment created by the ancillary ligands prevents the necessary interaction with the olefin prior to the migratory insertion step. This result is thus indicative of the involvement of Cu in the C–C bond-forming event.



Conditions: B$_2$(pin)$_2$ (1.1 equiv), **CuF(PPh$_3$)$_3$** (10 mol %), MeOH (2.0 equiv), THF, rt, overnight. Ratios determined by ^{1}H NMR using an internal standard.

Scheme 6. Reactivity of acrylate **4** with coordinatively saturated CuF(PPh$_3$)$_3$ complex

In sharp contrast, the reaction of alkynyl epoxide **1** with B$_2$(pin)$_2$ in the presence of CuF(PPh$_3$)$_3$ (10 mol %) led to results comparable to those previously obtained with the combination CuCl/PPh$_3$ and a metal to phosphine ligand ratio of 1:1 (Scheme 3a). Thus, as shown in Scheme 7, hydroborylated product **2** was the only one detected in the absence of NaO^{t}Bu, while carboborylated product **3** was the only product detected in the presence of 1.1 equivalent of this additive. This observation suggests that the number of ancillary ligands around Cu does not alter the reaction course. Therefore, it would follow that Cu is not involved in the rate-determining step of the reaction between alkenylcopper and epoxide.

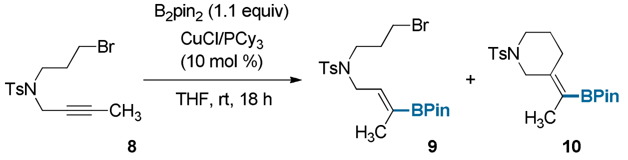


Conditions: $B_2(pin)_2$ (1.1 equiv), **$CuF(PPh_3)_3$** (10 mol %), **NaO^{t}Bu (x mol %),** THF, rt, overnight. Ratios determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Scheme 7. Reactivity of epoxide **1** with coordinatively saturated $CuF(PPh_3)_3$ complex

We next sought to complete our study with a brief look at alkyl halides. The purpose of this extension was twofold: Primary alkyl halides have been widely used as reaction partners in Cu-catalyzed carboborations of alkynes, and it would be logical to explore the validity of our findings in this context. In addition, since the oxidative addition of alkyl halides to the intermediate alkenyl-Cu species is the most accepted pathway for the C–C bond-forming event, we reasoned that analyzing the reactivity of these substrates in the presence of $CuF(PPh_3)_3$ would provide us with valuable information.

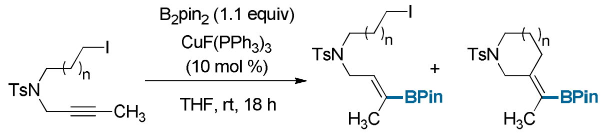
8a. Alkyl bromides/CuCl



	9	10
NaO^{t}Bu (0,15 mol %)	*71%*^{a}	*<2%*
NaO^{t}Bu (1,1 equiv)	*<2%*	*91%*
NaO^{t}Bu (1,1 equiv), **TEMPO (1 equiv.)**	*<2%*	*81%*

^{a}Isolated yield in the absence of MeOH. 84% in the presence of MeOH (2 equiv).

8b. Alkyl iodides/CuF(PPh$_3$)$_3$



NaO^{t}Bu (0 equiv)	**11**, n=0	**13**, *56%*^{a,c}	*<2%*
	12, n=1	**14**, *59%*^{b,c}	*<2%*
NaO^{t}Bu (1.2 equiv)	**11**, n=0	*<2%*	**15**, *69%*
	12, n=1	*<2%*	**16**, *74%*

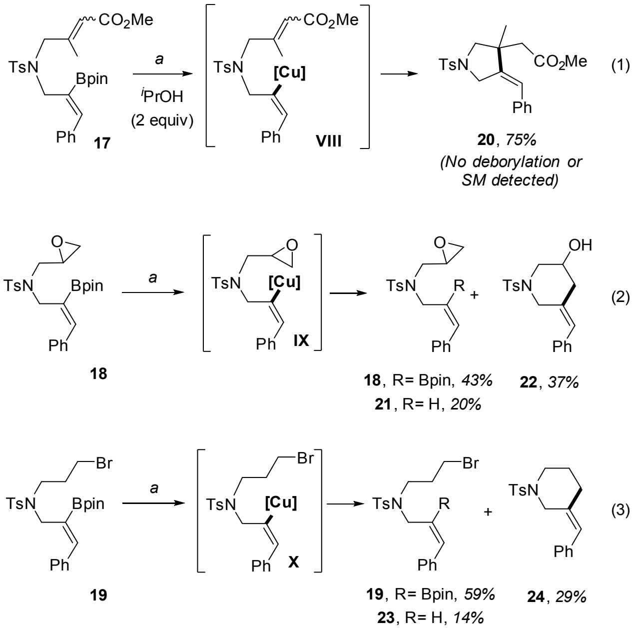
^{a}Conversion in the absence of MeOH. 70% in the presence of MeOH (2 equiv).
^{b}Conversion in the absence of MeOH. 72% in the presence of MeOH (2 equiv).
^{c}Compounds **13** and **14** were found to decompose on silica.

Scheme 8. Reactivity of alkyl halides

A first study conducted on alkyl bromide **8** (Scheme 8a) quickly showed an analogous behavior to epoxide **1**: whereas the reaction in the absence of NaO^{t}Bu led exclusively to alkyl bromide **9**, the addition of 1 equivalent of additional base resulted in formation of the corresponding carbocycle **10** as sole reaction product. In addition, a reaction conducted in the presence of 1 equivalent of TEMPO led to full formation of carbocycle **10**. This result, along with the observation that the C-Br bond is preserved in the hydroborylated product **9**, points against an oxidative addition by a radical mechanism. Additionally, it rules out formation of a primary radical intermediate as first step in the carboboration sequence, which is an alternative mechanism previously suggested to be operative in some cases.[28] A second part of this study, conducted on alkyl iodides **11** and **12**, and using $CuF(PPh_3)_3$ to evaluate the involvement of Cu in the carboboration process, showed that reactions conducted in the absence of NaO^{t-}Bu led exclusively to the hydroboration products **13** and **14**, whereas no appreciable amounts of the corresponding carbocycles were observed by ^{1}H NMR. However, the addition of 1 equivalent of additional base cleanly afforded the corresponding carbocycles **15** and **16** as sole reaction product. As in the case of model substrate **1**, which bears an epoxide as electrophilic partner, these results point against the involvement of Cu in the C–C bond-forming event.

3.2. Study of the reactivity of vinyl-Cu in the absence of the boron moiety

At this point, we designed a system that would help explore the reactivity of the alkenyl copper intermediates in the absence of boron. Although the additions of alkenylcopper species to epoxides[29] and α,β-unsaturated systems[30] are known, we reasoned that appreciable differences in reactivity when compared to the systems that incorporate the Bpin fragment could be interpreted as indirect evidence of the involvement of boron in the cyclization step. Based on this assumption, and taking advantage of the facile transmetalation between vinylboronates and Cu-X (X = OAc or OMe), we set out to prepare alkenyl boronates **17**, **18**, and **19**, shown in Scheme 9.[31] Upon treatment with catalytic amounts of CuCl, cleavage of the C–B bond in these compounds would generate the corresponding alkenyl-Cu species we required (**VIII**, **IX**, and **X** respectively).[32]



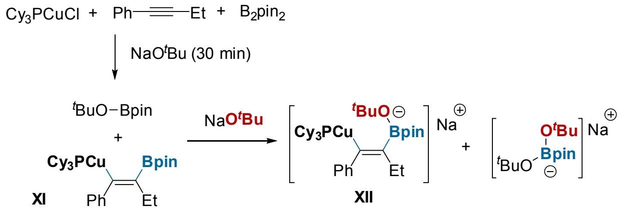
a) CuCl (10 mol %), PCy_3 (12 mol %), NaO^{t}Bu (1.1 equiv), toluene, rt, 12 h. Ratios determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

Scheme 9. Alkenyl-Cu reactivity in the absence of boron

In good correlation with the experiments described in the paragraphs above, we observed that the alkenylcopper species **VIII** generated from **17** reacted smoothly with the α,β-unsaturated ester to generate exclusively carbocycle **20** (75% yield). In turn, the reactivity of intermediates **IX** and **X** was found to be only modest (37% for the epoxide and 29% for the alkyl bromide), leading in both cases to mixtures of unreacted material and protonated products. Our interpretation of these observations is as follows: the reaction of alkenylcopper intermediate **VIII** takes place via coordination of the olefin to Cu followed by migratory insertion, and the reactivity of the system is unaltered by the presence or absence of boron. However, the fact that the reaction of alkenylcopper with either an epoxide or an alkyl halide works poorly when compared to substrates **1** and **8** (and **11-12**) suggests that in the presence of a boron moiety in the alkyne, activation via boron-"ate" formation could be the preferred reaction pathway.[33]

3.3. NMR analysis of reaction intermediates

In hopes of gathering tangible evidence on the proposed interaction between B and O^{t}Bu, we next considered the possibility of conducting NMR experiments aimed at identifying formation of a B-O bond in the reaction intermediates. Although initial attempts at isolating intermediate **I** (Scheme 2) were unsuccessful, we considered the system found by Brown and coworkers[6] as an alternative model for our studies, in which the reaction of 1-phenyl-1-butyne with $Cy_3PCuBpin$ led to the preparation and full characterization of the boryl-vinyl-Cu species **XI** (Scheme 10). As opposed to dialkyl substituted substrate **1**, 1-phenyl-1-butyne bears an aromatic group directly bound to the alkyne fragment, which presumably increases the stability and lifetime of the organometallic species **XI**. This compound was prepared by mixing equimolar amounts of Cy_3PCuO^tBu and B_2pin_2. Subsequent treatment with 1 equivalent of 1-phenyl-1-butyne resulted in formation of **XI**, along with ^{t}BuOBpin.[34] Then, **XI** was treated with NaO^{t}Bu (2 equivalents added in two portions of 1 equivalent) and the results were analyzed by ^{11}B NMR (Figure 5). We observed that the first equivalent of base reacted rapidly with both **XI** and ^{t}BuOBpin, as evidenced by a shift of both peaks to the 4-6 ppm region (spectra marked in green, Figure 5). This shift was attributed to formation of **XII** along with the "ate" complex of ^{t}BuO-Bpin. In addition, no significant shift was observed in the ^{31}P NMR spectra of species **XI** and **XII**. In this first experiment, we observed that the peak corresponding to ^{t}BuO-Bpin disappeared completely, whereas a portion of **XI** remained unreacted. This led us to reason that, presumably, the B atom in **XI** is less Lewis acidic than the B atom in ^{t}BuOBpin. Finally, the addition of a second equivalent of the alkoxide led to complete disappearance of **XI** (spectra marked in blue, Figure 5).



Scheme 10. Stoichiometric experiments aimed at identifying formation of a B-O bond.

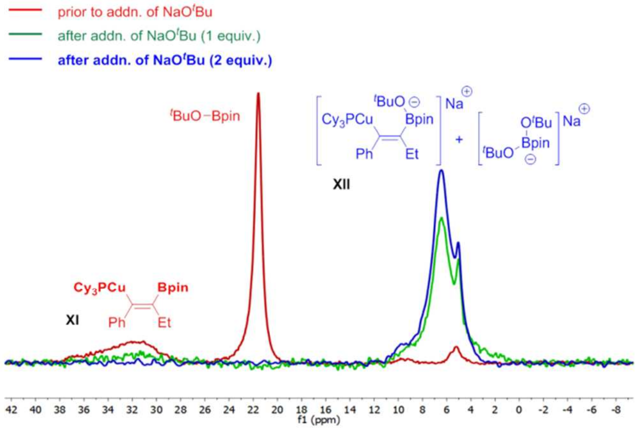
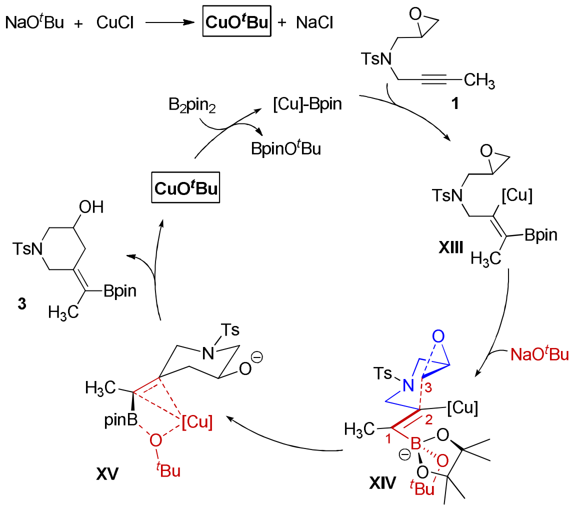


Figure 5. ^{11}B NMR experiments conducted on boryl-vinyl-Cu species **XI**.

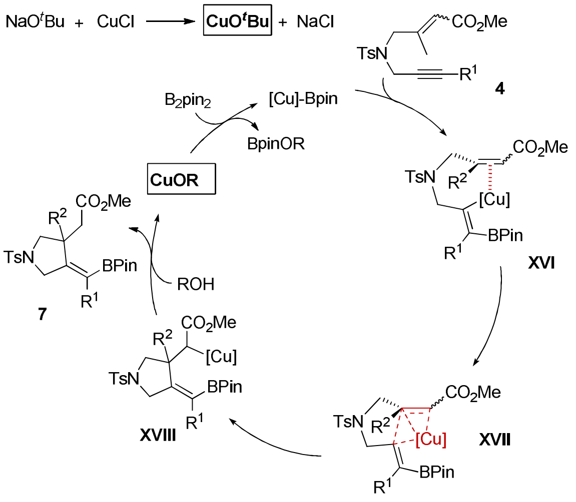
4. Mechanistic hypothesis

Scheme 11 is intended as an overall mechanistic proposal that incorporates all the aspects explored throughout our studies, and highlights the differences between the two substrates in our case study. Both systems begin with the well-established generation of a boryl-copper species by σ-bond metathesis between B_2pin_2 and CuO^t-Bu. Subsequent reaction of the [Cu]Bpin complex with the alkyne moiety on either substrate (1 or 4) results in formation of an alkenylcopper species (**XIII** and **XVI**, from **1** and **4**, respectively), which is generated in a regio- and stereoselective fashion. In the first scenario (outlined in Scheme 11a), the addition of one equivalent of NaO^{t}Bu to the mixture forms an "ate" complex with boron, and as a result the electron density at C_2 is significantly enhanced. A nucleophilic attack from C_2 to C_3 via six-membered transition state **XIV** results in formation of a new C-C σ-bond with concomitant cleavage of a C-O σ-bond. An interaction between copper and oxygen in intermediate **XV**, both located on the same side, leads to simultaneous cleavage of a C-Cu and B-O bonds, and regeneration of CuO^{t}Bu. The second scenario is presented in Scheme 11b. In it, the copper atom in intermediate **XVI** coordinates to the olefin (an interaction which is prevented in the presence of three phosphine ligands) prior to migratory insertion of the olefin to the C-Cu σ-bond. *This interaction does not require the help of an additional molecule of NaO^{t}Bu, and therefore the overall process takes place under catalytic conditions*. Subsequent reaction with a suitable proton source (ROH) yields carbocycle **7**, and generates CuOR.

11a. First scenario: Akyne/epoxide, stoichiometric NaO^{t}Bu



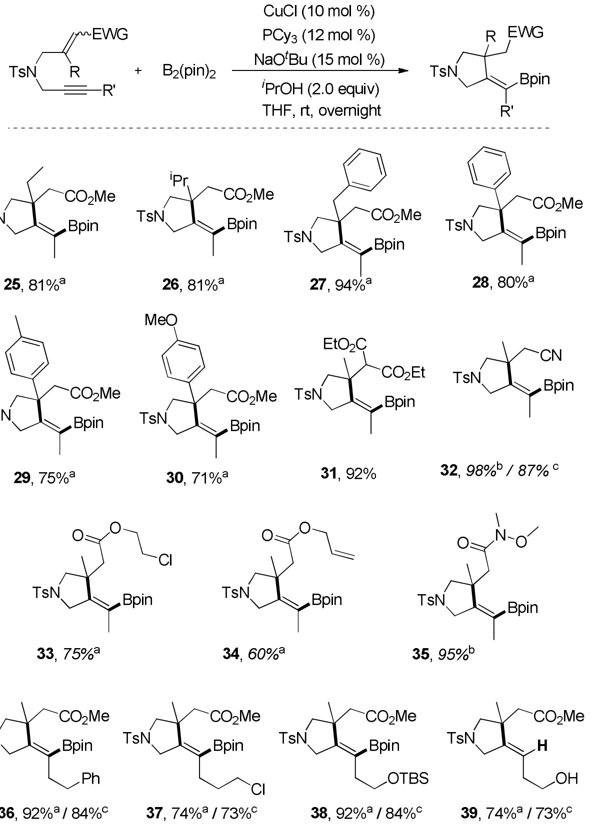
11b. Second scenario: Akyne/alkenyl ester, catalytic NaO^{t}Bu



Scheme 11. Proposed catalytic cycle

5. Generality of the carboboration via insertion across activated β,β-disubstituted olefins.

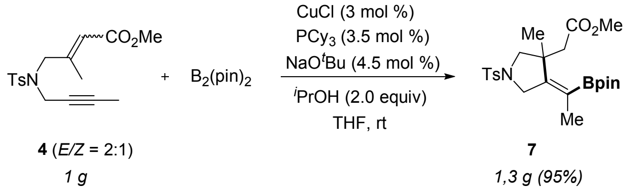
A study on the generality of the transformation is shown in Scheme 12. Using the typical conditions reported for borylations of alkynes in combination with ^{i}PrOH, we quickly observed that the reaction tolerated a number of substituents at the β position of the olefin. In addition to the methyl group in model substrate **4**, we observed good reactivity when alkyl groups such as Et (**25**), or the bulkier ^{i}Pr and Bn groups (**26** and **27**, respectively) were introduced, affording the corresponding cycloadducts in 81-94% yield. Remarkably, the presence of aryl groups did not constitute a problem, and products **28**, **29**, and **30** (bearing Ph, 4-$CH_3C_6H_4$ and 4-$CH_3OC_6H_4$ groups, respectively) were also obtained in good yields. It should be noted that in the case of β-aryl substitution, the use of ^{i}PrOH as source of protons had a marked influence on the reaction selectivity in favor of the carboboration product over the hydroboration side product. For example, we observed that use of MeOH on the *p*-tolyl substituted substrate delivered a mixture of carboboration (**29**) and hydroboration products in 58% and 40% conversion yields, respectively. However, use of ^{i}PrOH significantly improved the conversion to the carboboration product to 78% (22% of hydroboration), thus allowing product **29** to be isolated in 75% yield. Possibly, in this case the coordination ability of the alkene to the metal is weakened due its extended conjugation through the aryl moiety and, consequently, decreasing the rate of the competing protonolysis of the vinyl-copper intermediate is crucial to increase the selectivity towards carboboration.[35]



^{a} From *Z* olefin. ^{b} From *E* olefin. ^{c} From *E/Z* mixture of olefins.

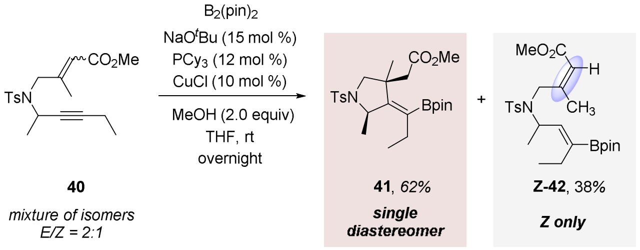
Scheme 12. Reaction scope

The process was found to be amenable to a number of functional groups that provide potentially useful handles for further manipulation. For example, the presence of sites that could undergo reaction with organometallic reagents, such as alkyl chlorides (substrates **33** and **37**), allylic ester **34**, or Weinreb amide **35**, did not result in a significant decrease in reactivity, or formation of byproducts. In addition, the presence of a TBS protected alcohol (**38**) did not interfere with the reactivity. In the case of a free alcohol (**39**), however, we found that the cyclic product was obtained cleanly, although in this case the boronic ester had been lost in the process. The fact that all other features of the reaction (cyclic structure, stereochemistry of the double bond) were observed led us to reason that the corresponding tetrasubstituted vinyl boronate was formed. Subsequent intramolecular nucleophilic attack of the deprotonated alcohol to the boron to form a boron-"ate" intermediate would, in turn, enhance the rate of its transmetalation with Cu[36] followed by proto-demetalation. Additionally, under the standard reaction conditions, and using ^{i}PrOH as source of protons, we were able to run larger scale experiments with decreased catalyst loadings. In particular, as shown in Scheme 13, we found that the reaction of 1 gram of substrate **4** (as 2:1 *E*/*Z* mixture) could be transformed into **7** in 95% yield using 3 mol % of the Cu catalyst.

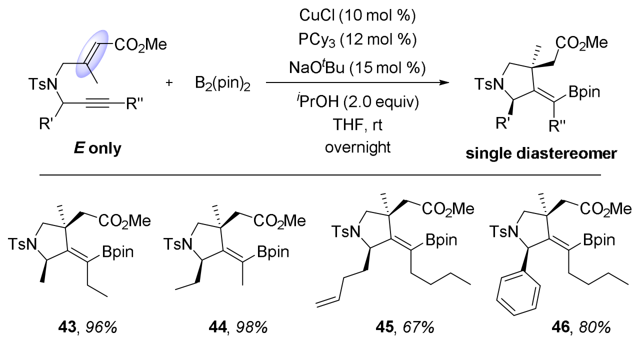


Scheme 13. Gram-scale experiment

We also examined the possibility of introducing an additional substituent at the propargylic position. Since a quaternary stereocenter is formed during the reaction, this propargylic substitution could be problematic in terms of diastereoselection. To analyze this potential issue we prepared substrate **40**, obtained as a 2:1 mixture of *E*/*Z* isomers and bearing a methyl group at the propargylic position (Scheme 14). When **40** was subjected to the reaction conditions, we observed a 2:1 mixture of the corresponding carboborylated product **41** and hydroborylated product **42**. Notably, ^{1}H NMR analysis of the reaction mixture revealed that the former had formed as a single diastereomer;[37] moreover, it showed the olefin stereochemistry of the latter to be only *Z*. This observation suggests that only *E*-**40** reacted to form the cyclic product, whereas the corresponding *Z* olefin does not react after the alkyne borylcupration stage. This assumption was supported by the reactivity observed for (*E*)-configured substrates (Scheme 15), which possessed both alkyl and aryl fragments at the propargylic position. In all four cases, the transformation took place to yield the corresponding carbocycles **43-46** in good to excellent yields (67-98%), and with >98% diastereoselectivity. The relative stereochemistry of these compounds was further established by X-ray crystallographic analysis of **44**.[38]

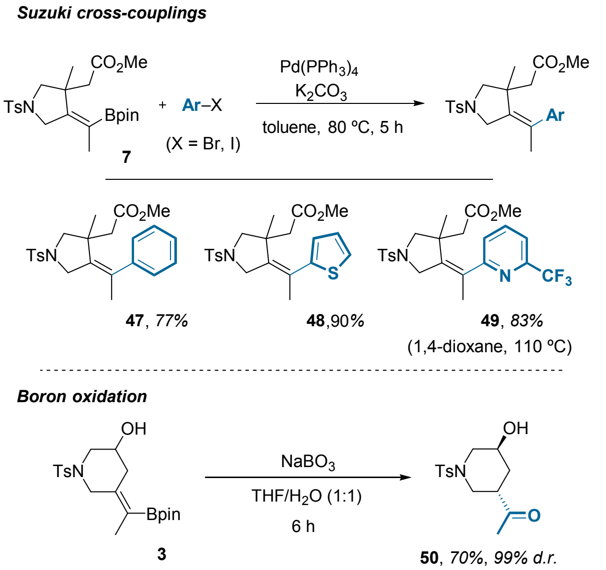


Scheme 14. Influence of the olefin geometry



Scheme 15. Diastereoselectivity of the transformation

Finally, we sought to explore the reactivity of these sterically encumbered tetrasubstituted vinylboronates in potentially interesting transformations, such as Suzuki cross-coupling reactions or oxidations of the vinyl boronate fragment (Scheme 16). Firstly, substrate **7** was successfully coupled with phenyl iodide (product **47**, 77% yield). Heteroaromatic halides were also found to be amenable to this coupling, and we were able to couple 2-thiophenyl bromide (product **48**, 90% yield) and 2-bromo-6-(trifluoromethyl)pyridine (product **49**, 83% yield). On the other hand, treatment of substrate **3** with sodium perborate in THF/H_2O resulted in formation of the corresponding ketone **50** in 70% yield and as a single diastereomer.



Scheme 16. Transformations of tetrasubstituted vinyl boronates

Conclusion

The combination of experimental and computational studies has allowed for the first time gaining a solid understanding on the activation role of the alkoxide additive in Cu-catalyzed $B_2(pin)_2$-carboboration of internal alkynes. Our results suggest that in reactions exploiting an S_N-type mechanism for trapping the boryl-cuprate intermediate with R–X species, the alkoxide preferentially activates the boron atom to form a vinylboron-ate species, rather than the previously suggested copper activation through a heterocuprate complex. Such attack of the alkoxide on the boron atom results in an increased electron density at the β-vinylic carbon that triggers the nucleophilic displacement. This provides an alternative explanation to the need for stoichiometric amounts of alkoxide beyond the suggested role as promoter for catalyst regeneration via CuX→CuOR, as evidenced from the use of epoxides instead of R-X as electrophiles. This knowledge has enabled the rational design of a unique borylative annulation with the ability of (i) operating under a catalytic amount of alkoxide and (ii) generating all-carbon quaternary centers, which are two features that are not compatible with the vast majority of reported methods relying on S_N-type mechanisms. Instead, this strategy benefits from an unprecedented migratory insertion across a β,β-disubstituted activated olefin for the trapping of the boryl-cupration intermediate. Important challenges derived from selectivity control were surmounted by playing on the catalyst system, with the nature of the phosphine and the pK_a of the protonating additive playing a crucial role. As a result, a broad range of synthetically versatile and densely functionalized pyrrolidines containing a stereochemically defined tetrasubstituted vinylboronate and an all-carbon quaternary stereocenter can be prepared in good yields and excellent levels of regio- and diastereoselectivity.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectral data, complete DFT studies, and X-ray data for compound **44**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) Indeed, the Cu^I-catalyzed borylation of allylic epoxides was shown to occur with substoichiometric amount of NaO^tBu (30 mol %), which was ascribed to the formation of a CuOR intermediate upon epoxide ring-opening that regenerates the catalyst by reaction with $B_2(pin)_2$: Tortosa, M. Synthesis of *syn* and *anti* 1,4-Diols by Copper-Catalyzed Boration of Allylic Epoxides. *Angew. Chem., Int. Ed.* **2011**, *50*, 3950–3953.

(17) During the course of our investigation, the Cu-catalyzed $B_2(pin)_2$-borylation of epoxides was disclosed. The reaction appears to require 3 equiv of LiO^tBu, although the reported optimization studies do not include testing the amount of base: Ahmed, E.-A. M.A.; Lu, X.; Gong, T.-J.; Zhang, Z.-Q.; Xiao, B.; Fu, Y. Copper-Catalyzed/Mediated Borylation Reactions of Epoxides with Diboron Reagents: Access to β-Hydroxyl Boronic Esters. *Chem. Commun.* **2017**, 53, 909–912.

(18) (a) Semba, K. Fujihara, T. Terao, J. Tsuji, Y. Copper-Catalyzed Highly Regio- and Stereoselective Directed Hydroboration of Unsymmetrical Internal Alkynes: Controlling Regioselectivity by Choice of Catalytic Species. *Chem. Eur. J.* **2012**, *18*, 4179–4184; (b) Moure, A.L.; Mauleón, P.; Gómez Arrayás, R.; Carretero, J.C. Formal Regiocontrolled Hydroboration of Unbiased Internal Alkynes via Borylation/Allylic Alkylation of Terminal Alkynes. *Org. Lett.* **2013**, *15*, 2054–2057, and reference 11c.

(19) We have explored the use of other metal alcoxides in the reaction of substrate **1**: Li salts such as LiOMe, LiO^iPr, LiOEt, and the Li salt of Menthol, result in lower yields (less than 70% NMR yield in the best case). KO^tBu gave even worse results (21% NMR yield), while KHMDS proved to be slightly more efficient (40%).

(20) Although in principle a stoichiometric base or MeOH is necessary for turnover, it should be noted that Lin and Tian also describe[10] how the reaction performed in the presence of MeOD does not result in deuterium incorporation in the molecule. Also, in their SI the authors describe how the reaction performed in the absence of MeOH still takes place in 61% yield. These two observations, along with our own, indicate the presence of other proton sources in the reaction mixture, and strongly suggest that the Cu catalyst is being regenerated in a different way. It could be speculated that products derived from slow decomposition of B_2pin_2 (such as pinBOH or B_2pin_3, see: Lesley, G.; Nguyen, P.; Taylor, N.J.; Marder, T.B.; Scott, A.J.; Clegg, W., Norman, N.C. O*rganometallics* **1996**, *15*, 5137-5154) are behind these unexpected observations.

(21) Borner, C.; Anders, L.; Brandhorst, K.; Kleeberg, C. Elusive Phosphine Copper(I) Boryl Complexes: Synthesis, Structures, and Reactivity. *Organometallics* **2017**, *36*, 4687–4690.

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(23) (a) Yoshida, H.; Kimura, M.; Osaka, I.; Takaki, K. Copper-Catalyzed Borylstannylation of Alkynes with Tin Fluorides. *Organometallics* **2017**, *36*, 1345–1351. ^{19}F NMR showed no σ-bond metathesis to form FBPin when the reaction was run with CsF in THF, which was attributed to the low solubility of CsF in ethereal solvents. See: (b) Wynn, D.A.; Roth, M.M.; Pollard, B.D. The Solubility of Alkali-Metal Fluorides in Non-Aqueous Solvents with and without Crown Ethers, as Determined by Flame Emission Spectrometry. *Talanta* **1984**, *31*, 1036–1040. This observation led us to switch to DMF as reaction solvent. For the carboboration of alkynes in this solvent, see reference 3b.

(24) See Supporting Information for details.

(25) Pyrrolidine **7** was obtained with 50% ee when ligand (*R*)-Monophos was used. Unfortunately, further attempts to improve this result using other chiral ligands led to discouraging results, mainly plagued by side reactions such as the competing conjugate borylation of the acrylate moiety and hydroboration of the alkyne due to the strong influence of the ligand on reactivity. See Supporting Information for details.

(26) For a report on the impact of different alcohols in borylation reactions, see: (a) Sasaki, Y.; Zhong, C.; Sawamura, M.; Ito, H. Copper(I)-Catalyzed Asymmetric Monoborylation of 1,3-Dienes: Synthesis of Enantioenriched Cyclic Homoallyl- and Allylboronates. *J. Am. Chem. Soc.* **2010**, *132*, 1226–1227. See also: (b) Ascic E.; Buchwald, S.L. Highly Diastereo- and Enantioselective CuH-Catalyzed Synthesis of 2,3-Disubstituted Indolines. *J. Am. Chem. Soc.* **2015**, *137*, 4666–4669.

(27) Isolation of PPh_3CuF was not possible. See: Woidy, P.; Karttunen, A.J.; Widenmeyer, M.; Niewa, R.; Kraus, F. On Copper(I) Fluorides, the Cuprophilic Interaction, the Preparation of Copper Nitride at Room Temperature, and the Formation Mechanism at Elevated Temperatures. *Chem. Eur. J.* **2015**, *21*, 3290–3303. However, and in agreement with our hypothesis, when we presumably formed PPh_3CuF by mixing CuCl (20 mol %), PPh_3 (24 mol %), and TBAF (1 M THF, 40 mol %, aprox. 5% water), then added this mixture to a solution of SM + B_2pin_2 + MeOH, we observed preferential formation of product **7** (**4**:**6**:**7** = 4:26:70). We thank a reviewer for suggesting this experiment.

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Wren, D.; Prince, A. *J.* Prostaglandins. IX. Synthesis of (±)-Prostaglandin E1, (±)-11-Deoxyprostaglandins E1,F1α, and F1β, and (±)-9-Oxo-13-*cis*-Prostenoic Acid by Conjugate Addition of Vinylcopper Reagents. *J. Am. Chem. Soc.* **1972**, 94, 7823–7827.

(31) The group of Yun has demonstrated that the Cu-catalyzed $B_2(pin)_2$-borylation of internal aryl alkynes of type Ar–C≡C–alkyl takes place at the alkyne carbon atom distal to the aryl motif when the alkyl substituent is less bulky than the aryl group: (a) Lee, J.-E.; Kwon, J.; Yun, J. Copper-Catalyzed Addition of Diboron Reagents to α,β-Acetylenic Esters: Efficient Synthesis of β-Boryl-α,β-Ethylenic Esters. *Chem. Commun.* **2008**, 733–734. (b) Kim, H.R.; Jung, I.G.; Yoo, K.; Jang, K.; Lee, E.S.; Yun, J.; Son, S.U. Bis(imidazoline-2-thione)–Copper(I) Catalyzed Regioselective Boron Addition to Internal Alkynes. *Chem. Commun.* **2010**, *46*, 758–760. (c) Moon, J.H.; Jung, H.-Y.; Lee, Y. J.; Lee, S.W.; Yun, J.; Lee, J.Y. Origin of Regioselectivity in the Copper-Catalyzed Borylation Reactions of Internal Aryl Alkynes with Bis(pinacolato)diboron. *Organometallics* **2015**, *34*, 2151–2159; and references cited therein. With this knowledge in hand, simply replacing the methyl substituent on the alkyne by a phenyl group enabled complete regioselective switch in the alkyne borylation to afford the desired vinyl boronates **17-19**. See supporting information for details.

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(33) We have studied the possibility of a Cu(I) to Cu(III) oxidative addition by DFT. In particular, we have tested a number of structures that result in the conformation prior to oxidative addition (as described by Nakamura,[14], Scheme 24 in p. 2357, in which oxidative additions to epoxides are discussed). However, all the calculations performed in this regard bypass the oxidative addition mechanism, and converge to the six-membered transition state prior to the proposed S_N2 mechanism we postulate.

(34) In our hands, treatment of **XI** with MeOD after 3 hours showed high levels of deuteration at the olefinic carbon, demonstrating its stability.

(35) See Supporting Information for a more detailed study.

(36) (a) Brown, H.C.; Molander, G. Stereospecific Synthesis of Conjugated Enynes from Alkenyldialkylboranes via Alkenylcopper Intermediates. *J. Org. Chem.* **1981**, *46*, 645–647. (b) Miyaura, N.; Sasaki, N.; Itoh, M.; Suzuki, A. The Coupling Reaction of Copper(I) Methyltrialkylborates with Benzyl Bromides. A Convenient Synthesis of Alkylbenzenes from Organoboranes. *Synthesis* **1976**, 618–619.

(37) See Supporting Information for NMR studies.

(38) CCDC repository number 1839050. See Supporting Information for details.

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