Stereospecific and Regioselective Synthesis of *E*-Allylic Alcohols Through Reductive Cross Coupling of Terminal Alkynes

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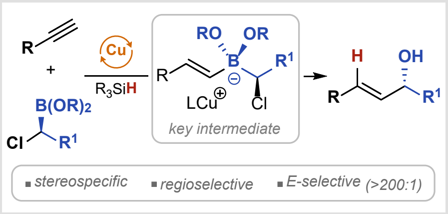
ABSTRACT: We have developed a convergent method for the synthesis of allylic alcohols that involves a reductive coupling of terminal alkynes with α-chloro boronic esters. The new method affords allylic alcohols with excellent regioselectivity (anti-Markovnikov) and an E/Z ratio greater than 200:1. The reaction can be performed in the presence of a wide range of functional groups and has a substrate scope that complements the stoichiometric alkenylation of α-chloro boronic esters performed using alkenyl lithium and Grignard reagents. The transformation is stereospecific and allows the robust and highly selective synthesis of chiral allylic alcohols. Our studies support a mechanism that involves hydrocupration of the alkyne and cross-coupling of the alkenyl copper intermediate with α-chloro boronic esters. Experimental evidence excludes a radical mechanism of the cross-coupling step and is consistent with the formation of a boron-ate intermediate and 1,2-metallate shift.

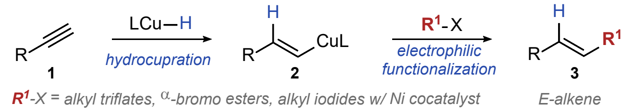


INTRODUCTION

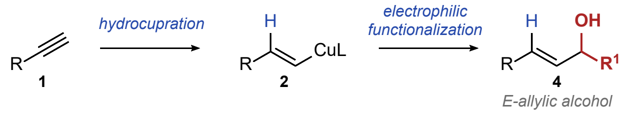
Hydroalkylation of terminal alkynes is a powerful method for making disubstituted alkenes with different substitution patterns and high selectivity.[1-9] Our group has developed several catalytic hydroalkylation reactions that produce *E*-alkenes using an approach with two key steps (Scheme 1a): first, hydrocupration of an alkyne[10,11] (**1**) forms an alkenyl copper intermediate (**2**) with precise control over the regio- and diastereoselectivity;[12-18] second, the alkenyl copper intermediate stereospecifically reacts with various alkyl electrophiles, such as alkyl triflates,[6] α-halo carbonyls,[8] or alkyl halides in the presence of a metal cocatalyst to yield *E*-alkene products (**3**).[7] The successful implementation of this strategy requires identifying alkyl electrophiles that are sufficiently reactive to overcome the relatively low reactivity of alkenyl copper complexes, but do not react with copper hydride complexes.

Scheme 1. Hydrocupration in Transformations of Terminal Alkynes

a) Hydrocupration of Terminal Alkynes in Synthesis of *E*-Alkenes



b) Hydrocupration of Terminal Alkynes in Synthesis of *E*-Allylic Alcohols

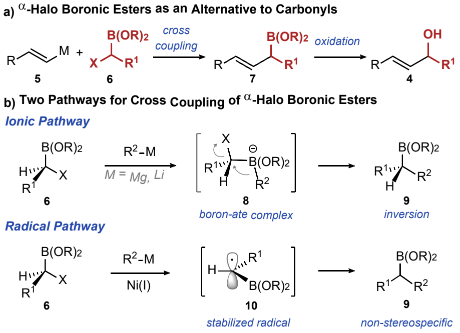


We have been interested in expanding the hydroalkylation approach to enable synthesis of *E*-alkenes with simultaneous introduction of a functional group in the allylic position. Allylic alcohols are particularly attractive targets for such a transformation as they are often featured in bioactive molecules and synthetic intermediates.[19] We reasoned that terminal alkynes can be transformed into allylic alcohols with anti-Markovnikov selectivity through hydrocupration and reaction of the alkenyl copper intermediate (**2**) with an appropriate electrophile (Scheme 1b).

The most intuitive way to access allylic alcohols from the alkenyl copper intermediate is reaction with aldehydes or ketones. Unfortunately, integrating carbonyls into the hydroalkylation approach outlined in Scheme 1a presents several challenges. NHC supported copper hydride complexes involved in formation of the alkenyl copper intermediate efficiently add to carbonyls and promote their reduction.[20-23] Another challenge stems from relatively low reactivity of alkenyl copper intermediates. Despite numerous examples of reactions of allylic[24-31] and propargylic[32,33] copper complexes with carbonyls, we found that under a variety of reaction conditions, stoichiometric reactions between NHC-supported alkenyl copper complexes and aldehydes do not occur (see SI).

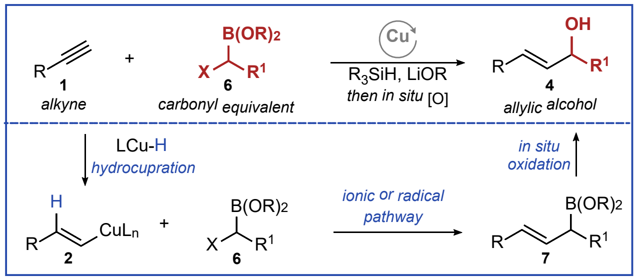
α-Halo boronic esters (**6**) can act as a functional equivalent of carbonyl electrophiles. They can be made directly from aldehydes and ketones[34] and provide allylic alcohols (**4**) after cross-coupling with alkenyl organometallic reagents (**5**) and in situ oxidation (Scheme 2a).[35] Furthermore, the key cross-coupling with organometallic compounds can proceed via two distinct mechanisms (Scheme 2b). As Matteson's pioneering work has shown, with nucleophilic organolithium and Grignard reagents, the cross-coupling involves the formation of boron-ate complexes (**8**) and a subsequent 1,2-metallate shift.[36-39] Alternatively, transition metal catalyzed cross-coupling reactions involve stabilized α-boryl radical intermediates[40-43] (**10**) formed through single electron transfer (SET) reduction of α-halo boronic esters.[44-48] Even though the same cross coupling product (**9**) is formed in both pathways, mechanistic differences produce two different stereochemical outcomes: the ionic pathway is stereospecific (inversion at the α stereocenter), while the radical pathway leads to the loss of stereochemical information.

Scheme 2. α-Halo Boronic Esters as Electrophiles



Alkenyl copper complexes are both nucleophilic and capable of SET reduction of activated organohalides.[8] As a result, both ionic and radical mechanisms offer plausible pathways for coupling with α-halo boronic esters. This creates an opportunity to combine the unique reactivity of α-halo boronic esters with established hydrocupration of alkynes and develop a new method for the synthesis of allylic alcohols. As shown in Scheme 3, allylic alcohols (**4**) would be generated through a convergent reductive cross coupling of terminal alkynes (**1**) and α-halo boronic esters (**6**), followed by in situ oxidation.

Scheme 3. Proposed Synthesis of Allylic Alcohols



The importance of allylic alcohols in organic synthesis has prompted the development of numerous approaches for their synthesis.[19] For example, asymmetric synthesis of allylic alcohols can be accomplished through kinetic resolution,[49] dynamic kinetic resolution,[50,51] reduction of enones,[52,53] allylic substitution,[54,55] or through organocatalytic reactions.[56] Among methods that result in the formation of a new C-C bond, the most general is the addition of organozinc reagents derived from alkynes through hydrometallation and transmetalation. This approach was pioneered by Oppolzer[57] and further developed by Walsh,[58-60] Seto,[61,62] Wipf,[63] and others.[64-66] Other organometallic reagents have also been used, but with less success.[67-70]

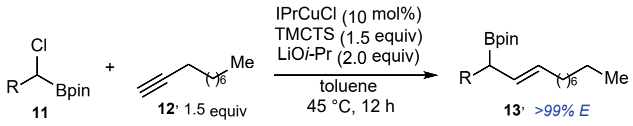
The key feature of the transformation shown in Scheme 3 is that it avoids stoichiometric formation of alkenyl metal reagents from alkynes. The benefits of using alkynes directly have been amply demonstrated[71,72] through the pioneering work of Jamison,[73,74] Montgomery,[75-81] Krische,[82,83] and others[84-86] on reductive cross coupling of alkynes with carbonyls. Their approach has provided excellent results in asymmetric synthesis of allylic alcohols starting with internal alkynes.[73,81,83,86] Although terminal alkynes have also been used in these reactions,[77-80] unlike internal alkynes, they have not been amenable to applications in asymmetric synthesis of allylic alcohols.[76,81] We set out to address this challenge by pursuing the development of the asymmetric anti-Markovnikov reductive cross coupling of terminal alkynes and α-halo boronic esters.[87] In the process, we aimed to resolve the underlying mechanistic ambiguity (ionic vs radical) of the reaction and exploit the stereochemical consequences of the actual mechanism.

Table 2. Substrate Scope

RESULTS AND DISCUSSION

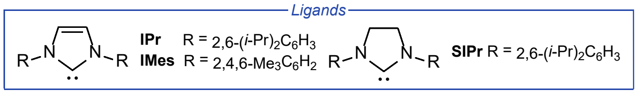
Reaction Development. Following the approach outlined in Scheme 3, we developed a copper-catalyzed reductive coupling of alkynes and α-halo boronic esters (Table 1). The best results were obtained using IPrCuCl as the precatalyst, tetramethylcyclotetrasiloxane (TMCTS) as the hydride source, and LiO*i*-Pr as the turnover reagent (entry 1). A modest excess of alkyne (1.5 equiv) relative to the α-chloro Bpin (pin = pinacolato) was used in the reaction.

Table 1. Reaction Development

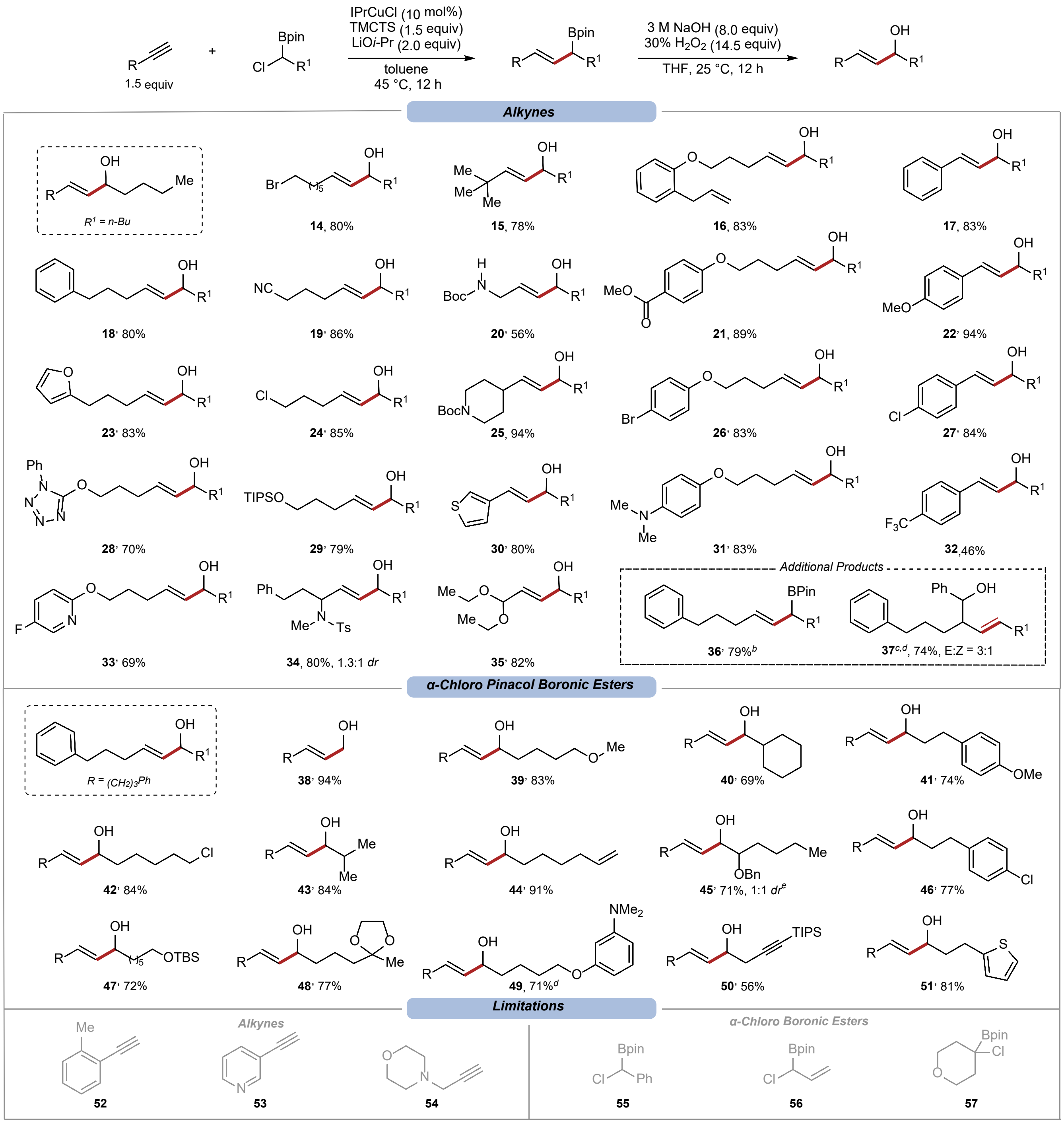


entry	change from standard conditions	yield
1	none	88%
2	SIPrCuCl *instead of* IPrCuCl	78%
3	IMesCuCl *instead of* IPrCuCl	19%
4	PMHS *instead of* TMCTS	79%
5	DMMS *instead of* TMCTS	24%
6	NaO*i*-Pr *instead of* LiO*i*-Pr	43%
7	LiO*t*-Bu *instead of* LiO*i*-Pr	76%
8	LiOMe *instead of* LiO*i*-Pr	0%
9	THF *instead of* toluene	31%
10	benzene *instead of* toluene	87%
11	isooctane *instead of* toluene	77%
12	25 °C *instead of* 45 °C	47%
14^b	$Cl(CH_2)Bpin$ *instead of* **11**	94%
15^b	$Br(CH_2)Bpin$ *instead of* **11**	58%
16^b	$I(CH_2)Bpin$ *instead of* **11**	0%

^{a}Yield determined by GC using internal standard. R = n-Butyl, ^{b}Product was **13-H** with R=H.



The results in Table 1 show how different reaction parameters affect the yield of the desired product. The highest yields were obtained with copper catalysts supported by IPr and SIPr ligands. IMes, which is closely related to IPr and SIPr, only afforded 19% of **13** (entries 2 and 3). The identity of the silane was critical to the success of the reaction.



[a] Yields of isolated products are reported. Reactions performed on 0.5 mmol scale. [b] Allylic boronic ester isolated without oxidation (see SI). [c] Reaction of **36** with benzaldehyde. [d] Reactions performed on 0.25 mmol scale. [e] Starting α-chloro boronic ester was a 1:1 mixture of diastereoisomers.

While cyclic tetramer TMCTS and closely related PMHS (PMHS = polymethylhydrosiloxane) showed good reactivity, structurally similar monomeric silanes like DMMS (DMMS = dimethoxy(methyl)silane) gave diminished yields (entries 4 and 5). Other silanes gave little or no desired product (see SI, Table S3). Lithium isopropoxide and lithium *tert*-butoxide both worked well as turnover reagents (entries 1 and 7) but changing the counter ion to sodium produced inferior results (entry 6). Lithium methoxide also performed poorly, possibly due to low solubility (entry 8). At lower temperature (25 °C), only 47% yield of the product was formed after 12 h (entry 12), and the reaction required 3 days to complete (see SI). Less sterically demanding $Cl(CH_2)Bpin$ performed better than **11** (entry 14). Interestingly, more reactive α-bromo and α-iodo boronic esters performed worse as substrates in the reaction (entries 15 and 16).

Substrate Scope. Using our optimized conditions, we explored the scope of the reaction. After in situ oxidation of the allylic boronic esters, various allylic alcohols were obtained in good yields (Table 2). In general, we observed only the *E* isomer of the allylic alcohols in ^1H NMR of the crude reaction mixtures. Careful GC analysis of the crude reaction mixture containing product **18** using authentic samples of *E* and *Z* isomers confirmed an E/Z ratio greater than 200:1

(see SI for details). Alkynes containing alkyl bromides (**14**), alkyl chlorides (**24**), nitriles (**19**), esters (**21**), protected amines (**25**), protected alcohols (**29**), aryl chlorides (**27**), aryl bromides (**26**), sulfonamides (**34**), and acetals (**35**) were well tolerated. The presence of mildly acidic Boc-protected primary amine (**20**) was not detrimental for the reaction, although the yield of the desired product was diminished. Aryl acetylenes with electron-donating (**22**) and mildly electron-withdrawing (**27**) functional groups performed well, while the presence of a strongly electron-withdrawing group (**32**) resulted in a diminished yield. The reaction also tolerated alkynes with sterically demanding alkyl substituents (**15**). Several heterocycles could successfully be incorporated into the alkyne substrates, including furans (**23**), tetrazoles (**28**), thiophenes (**30**), and fluoro pyridines (**33**).

Allylic boronic ester **36** can be isolated after careful column chromatography in 79% yield. This allows a range of other products to be accessed using established transformations of allylic boronic esters.[88-90] In some instances, crude allylic boronic ester can be used directly in subsequent transformations. For example, when benzaldehyde is added to the crude reaction mixture containing **36**, transposed homoallylic alcohol **37** is obtained in 74% overall yield.

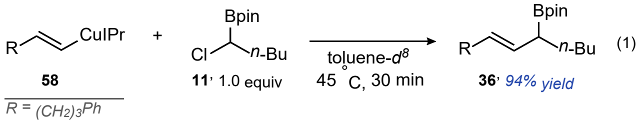
We also investigated the reactivity of various α-chloro Bpins and found that their functional group compatibility is similar to the selectivity observed in reactions of functionalized alkynes. The unsubstituted α-chloro boronic ester (**38**) gave an excellent yield, while additional substitution at the β position of boronic esters (**43** and **45**) resulted in lower yields.

We noted several limitations of the new reaction. Ortho-substituted aryl alkynes (**52**) and alkynes containing strongly coordinating groups (**53**, **54**) gave low yields of allylic alcohol products. α-Chloro boronic esters containing aryl (**55**) or alkenyl (**56**) substituents at the α-carbon provided no allylic alcohol product. Similarly, α, α-dialkyl-α-halo boronic esters (**57**) did not afford the expected tertiary allylic alcohols, indicating the negative effect of steric hindrance on the reaction.

Comparison with stoichiometric alkenylation of α-chloro boronic esters. The catalytic alkenylation reaction of α-chloro boronic esters is a complement and not a replacement for the stoichiometric reactions performed using alkenyl lithium or Grignard reagents. An excellent recent study by Kazmaier et al.[91] has shown that consistently high yields in stoichiometric alkenylation reactions are observed when at least one of the reactants is sterically hindered. Trisubstituted, *Z*-disubstituted, and 2-alkenyl organometallic reagents generally perform well. With less hindered organometallic reagents, only sterically hindered α-chloro boronic esters perform well. The trends we observed in the catalytic reaction are complementary: less hindered α-chloro boronic esters perform the best and *E*-alkenyl fragments are delivered.

Reaction Mechanism. We had two main goals in mind when exploring the reaction mechanism. First, we wanted to establish if the alkenyl copper complex is a catalytic intermediate in the reaction. Second, we wanted to determine if the cross coupling of the alkenyl copper and α-chloro boronic esters proceeds through a radical or ionic mechanism. Establishing the exact mechanism was important because of the differences in the stereochemical outcomes of the two pathways and implications that would have on the synthesis of chiral allylic alcohols.

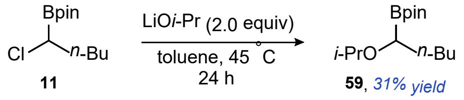
Initial mechanistic experiments focused on presumed intermediates in the catalytic reaction. In a stoichiometric experiment, we found that reacting alkenyl copper complex **58** with α-chloro boronic ester **11** quickly produces allylic boronic ester **36** (eq 1). This result supports the proposed involvement of an alkenyl copper intermediate and its reaction with α-chloro boronic esters.



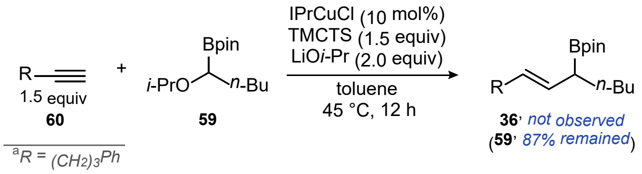
We also examined α-alkoxy boronic esters as possible intermediates in the reaction. As expected, LiO*i*-Pr reacts with α-chloro boronic ester **11** at 45 °C to produce α-alkoxy boronic ester **59** (Scheme 4a).[92] However, the reaction is slower than the catalytic hydroalkylation reaction performed at the same temperature and affords only 17% of **59** after 12 h, and 31% after 24 h. Furthermore, when used as a substrate in a catalytic reaction, α-isopropoxy boronic ester **59** did not afford the desired product (Scheme 4b) with 87% of **59** remaining after 12 h. Together, these results make α-isopropoxy boronic esters unlikely intermediates in the reaction.

Scheme 4. α-Alkoxy Boronic Esters as Intermediates

a) α-Alkoxy Boronic Ester Formation



b) α-Alkoxy Boronic Esters in Hydroalkylation Reaction[a]

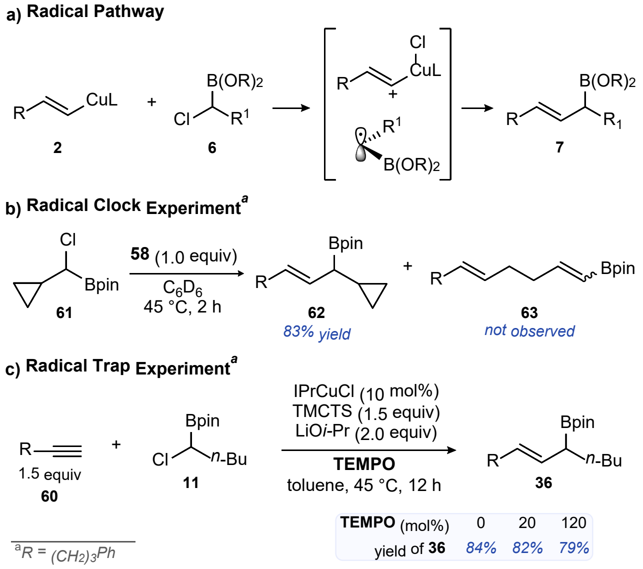


[a] R = (CH$_2$)$_3$Ph

Next, we focused on exploring the mechanism of the key reaction between the alkenyl copper intermediate and the electrophile. A plausible radical mechanism involving SET reduction of α-chloro boronic esters by the alkenyl copper intermediate is presented in Scheme 5a. α-Chloro boronic esters have been shown to undergo SET reduction[44-48] to form the stabilized alkyl radical. At the same time, alkenyl copper complex (**2**) is known to reduce α-bromo carboxylic esters through SET.[8]

To evaluate the relevance of the proposed radical mechanism, we performed radical clock and radical trap experiments. Alkenyl copper **58** reacts with cyclopropyl α-chloro Bpin (**61**) to produce only the unrearranged product **62** in 83% yield (Scheme 5b). We also found that up to 120 mol% of TEMPO can be added to the catalytic reaction without a significant decrease in the yield of the allylic boronic ester (Scheme 5c). The results of the two experiments are inconsistent with the SET mechanism and the formation of free radical intermediates.[93,94]

Scheme 5. Radical Mechanism



[a] R = $(CH_2)_3Ph$

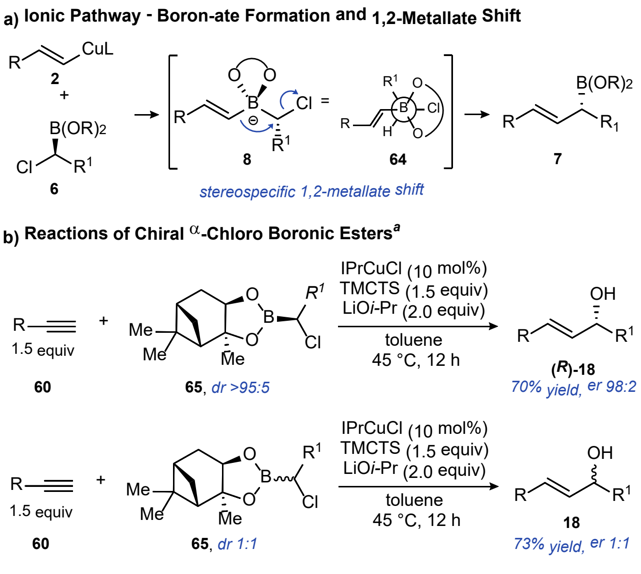
An alternative mechanistic hypothesis for the cross coupling is presented in Scheme 6a. The addition of alkenyl copper (**2**) to the α-chloro boronic ester (**6**) forms a boron-ate complex (**8**). This complex undergoes a 1,2-metallate shift exclusively through a conformation with antiperiplanar arrangement of the migrating alkenyl group and the leaving group at the α carbon (see **64**).[38] As a result, the cross coupling is stereospecific and proceeds with the inversion of configuration at the α-carbon.

To probe this alternative mechanistic hypothesis, we investigated the reaction with a single enantiomer of α-chloro boronic ester **65** (>99% ee, >95:5 dr), prepared using α-pinane diol as a chiral auxiliary (Scheme 6). The *R* configuration of the obtained allylic alcohol **(*R*)-18** indicates inversion of configuration at the α-carbon of the boronic ester (see SI). There is also strong support for the stereospecificity of the reaction. The enantiomeric ratio of the allylic alcohol **(*R*)-18** (98:2) reflected the diastereomeric ratio of the starting α-chloro boronic ester (>95:5). Furthermore, the chiral auxiliary alone had no effect on reaction selectivity: a 1:1 mixture of diastereoisomeric α-chloro boronic esters produced racemic allylic alcohol **18** (Scheme 6b). Overall, the stereochemical outcomes of these experiments are fully consistent with an ionic mechanism involving boron-ate formation and stereospecific 1,2-metallate shift.[95]

With evidence pointing to the ionic mechanism, we searched for evidence supporting the formation of the boron-ate complex in stoichiometric reactions of alkenyl copper intermediate with various boronic esters. Monitoring stoichiometric reactions of alkenyl copper intermediate (**58**) with α-isopropoxy boronic ester **59** or allylic boronic ester **36** by in situ ^{1}H and ^{11}B NMR showed no change of the starting materials even at 90 °C (Scheme 7a). Similarly, monitoring a stoichiometric reaction of **58** and α-chloro boronic ester **11** in toluene-d^8 at temperatures between -50 °C and 25 °C (Scheme 7b) did not provide definitive evidence for the formation of the boron-ate intermediate (see SI).

Scheme 6. Ionic Mechanism

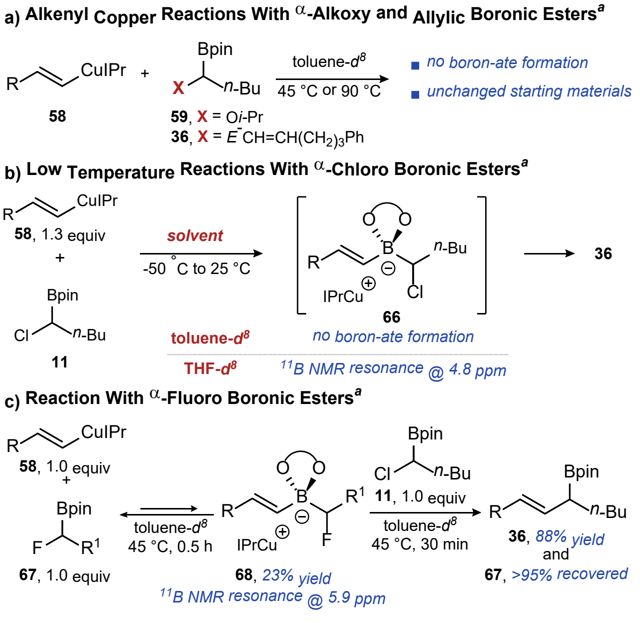
Table 3. Synthesis of Enantioenriched Allylic Alcohols



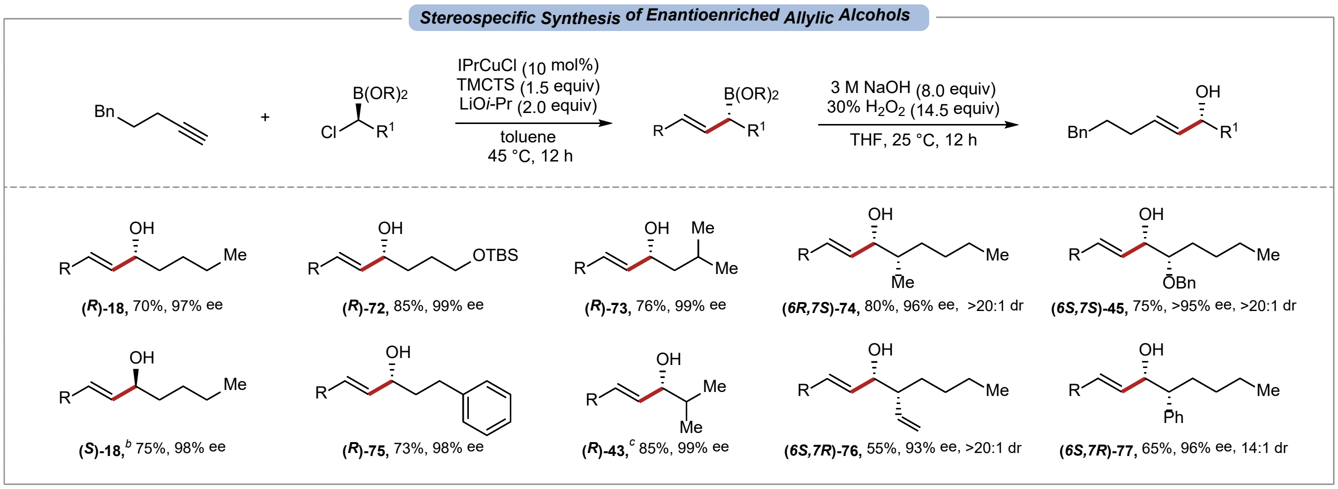
[a] R = $(CH_2)_3Ph$, R^1 = n-Bu

However, the same experiment performed in THF-d^8 provided evidence consistent with the presence of a low concentration of boron-ate intermediate **66** within the temperature range (broad resonance in ^{11}B NMR at 4.8 ppm). These results support reversible, though unfavorable, boron-ate formation in a reaction of α-chloro boronic esters. Presumably, the higher dielectric constant of THF (ε=7.6 for THF vs ε=2.4 for toluene) increases the concentration of **66**. Furthermore, in a reaction with α-fluoro boronic ester **67**, we saw evidence of the boron-ate formation in 23% yield within 30 min (Scheme 7c). The balance of the starting materials remained unchanged after an additional 2 h.

Scheme 7. Boron-ate Complex Formation



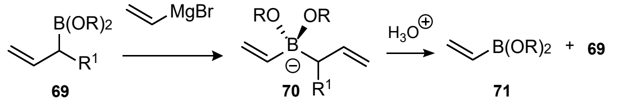
[a] R = $(CH_2)_3Ph$, R^1 = $(CH_2)_2C_6H_4$(4-OMe)



[a]Yields of isolated products are reported. Reactions performed on 0.5 mmol scale. Enantiomeric excess of allylic alcohols determined by chiral HPLC. Boronic ester of (+)-pinanediol was used. R = $(CH_2)_3Ph$. [b]Boronic ester of (-)-pinanediol was used with the opposite absolute configuration at the α carbon. [c]Bpin ester was used.

Upon addition of α-chloro boronic ester **11** to the reaction mixture containing boron-ate complex **68**, we observed full recovery of the α-fluoro boronic ester (**67**) and the formation of cross-coupling product **36**. These results argue for a reversible and thermodynamically unfavorable formation of the boron-ate complex **68**.

The reactions of the alkenyl copper intermediate with various boronic esters provide a mechanistic basis for understanding the differences in the scopes of this catalytic reaction and the stoichiometric alkenylation with organolithium and Grignard reagents (see above). Kazmaier has recently shown that the main side reaction in stoichiometric alkenylation is the addition of the organometallic reagent to the allylic boronic ester product (eq 2).[91] Protonolysis of the resulting boron-ate complex (**70**) at the end of the reaction provides a mixture of the desired allylic boronic ester (**69**) and the undesired vinyl boronic ester (**71**). As a result, good yields in stoichiometric reactions are realized only with substrates that can sterically impede the formation of boron-ate complex **70**.

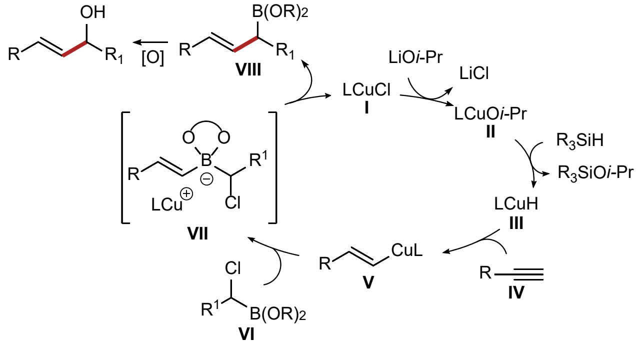


(2)

We found that the alkenyl copper intermediate does not react with allylic boronic esters, or if it does, the reaction is reversible and thermodynamically unfavorable (see Scheme 7a). As a result, the main side reaction described by Kazmaier does not occur in the copper-catalyzed transformation,[96] extending the scope to less sterically demanding substrates.

Based on our mechanistic investigation and the established chemistry of copper hydride complexes, we suggest the formation of allylic alcohols proceeds through the mechanism shown in Scheme 8. The process starts with the formation of copper hydride (**III**) through transmetalation of copper alkoxide with a silane,[10] followed by the formation of alkenyl copper complex (**V**) through hydrocupration of the terminal alkyne.[10] Addition to α-chloro boronic ester forms boron-ate complex (**VII**). Finally, 1,2-metallate shift, and subsequent oxidation, produce the desired allylic alcohol.

Scheme 8. Proposed Mechanism



Application to Stereospecific Synthesis of Allylic Alcohols. Our mechanistic studies suggest that the new reaction can be applied in the robust and highly selective synthesis of chiral allylic alcohols from terminal alkynes. We demonstrated that the stereochemistry of the starting materials fully controls the absolute configuration and enantiomeric excess of the allylic alcohols. The required enantioenriched α-chloro boronic ester can be accessed in several ways using different starting materials.[97] A highly selective asymmetric synthesis from alkyl boronic esters was originally discovered by Matteson[98] and developed by others[99] and relies on chiral auxiliaries. Jacobsen[100] recently reported an approach based on enantioselective catalytic 1,2-metallate shift, while the method reported by XU[34] uses carbonyls as starting materials. Finally, enantioselective hydrogenation also provides access to highly enantioenriched α-chloro boronic esters.[101]

In practice, we found Matteson's synthesis of chiral α-chloro boronic esters using readily available and affordable α-pinanediol to be highly selective and easy to execute. A range of chiral α-chloro Bpinane esters (pinane = pinane diol) were prepared by this method and used in the hydroalkylation reaction to provide chiral allylic alcohols (Table 3). Boronic esters with branching in the β and γ positions gave excellent selectivity (**43** and **73**). Even boronic esters with linear alkyl substituents reacted with excellent selectivity. This is particularly attractive given that enantioenriched dialkyl allylic alcohols are difficult to access by direct alkenylation of linear unbranched aldehydes.[102] Products **18**, **72**, and **75** were all obtained in high stereoselectivity and yield, showcasing the utility of our method. Furthermore, access to both (+)-and (-) isomers of pinane diol auxiliary allowed us to prepare *R* and *S* enantiomers of alcohol **18**. Enantioenriched α-chloro Bpin esters performed as well as Bpinane esters, providing **43** in excellent enantiopurity. Finally, Matteson's homologation method allowed the synthesis of highly enantioenriched allylic alcohols containing two stereocenters with high diastereoselectivity (**45**, **74**, **76**, and **77**).

CONCLUSIONS

In conclusion, we have developed a method for the convergent synthesis of allylic alcohols directly from terminal alkynes. This transformation involves reductive cross coupling of an alkyne with an α-chloro boronic ester followed by in situ oxidation of the boronic ester to an alcohol. The process is highly selective for the *E*-alkene and tolerates a broad range of functional groups. Experimental studies support a mechanism that involves hydrocupration of the alkyne and formation of the alkenyl copper intermediate. Cross coupling of the intermediate with an α-chloro boronic ester involves boronic formation and 1,2-metallate shift. The overall process is stereospecific and proceeds with inversion at the stereocenter of the α-chloro boronic ester, allowing for the convenient synthesis of enantioenriched allylic boronic ester products. This reaction integrates hydrometallation and boron-ate chemistry eschewing the need for stoichiometric organometallic reagents to form the boron-ate complex.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website
Experimental procedures, results of mechanistic experiments, and product characterization (pdf).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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(96) It is interesting to note that we do not see further reaction of the allylic boronic ester in the presence of the copper catalyst and an alkoxide promoter. We suspect that fast transmetalation of copper alkoxide with a silane outcompetes the transmetalation with allyl boronic esters.

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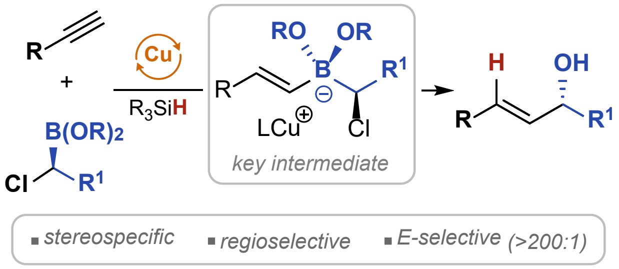
(102) Methods described in references 57-70 rarely feature examples of simple unbranched *E*-allylic alcohols being formed. In a few instances where formation of such products is described, they are obtained with substandard selectivity (<90% ee) and in lower yields (for example, see references 59, 62, and 70).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