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Asymmetric Synthesis of Trisubstituted Allenes: Copper-Catalyzed Alkylation and Arylation of Propargylic Phosphates

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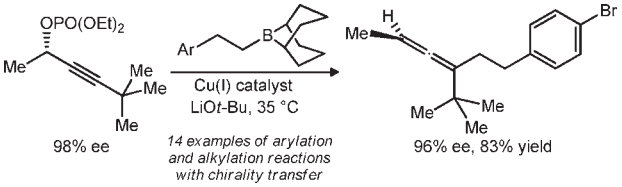
ABSTRACT



Asymmetric synthesis of trisubstituted allenes is accomplished by copper-catalyzed alkylation and arylation of propargylic phosphates using organoboron nucleophiles. Excellent chirality transfer and regioselectivity, together with good functional group compatibility, were observed in reactions with both alkyl boranes and arylboronic esters.

Allenes play an important role in organic chemistry as synthetic targets[1] and intermediates.[2] While numerous methods for their synthesis exist,[3] asymmetric synthesis of chiral allenes is still a considerable challenge. Most methods mandate the presence of a specific functional group in the allene product,[4] and have a limited substrate scope. Reactions developed by Myers[5] and Ready[6] have no such requirements and can be applied to the synthesis of a wide variety of chiral allenes. Unfortunately, neither method can be used to prepare trisubstituted allenes. In view of the limitations of existing methodology and the utility of chiral trisubstituted allenes as synthetic intermediates,[7] we pursued the development of a practical method for their synthesis.

We used copper-catalyzed substitution of propargylic electrophiles as a starting point for the development of such a method.[8,3a] This transformation has a broad scope and relies on readily available substrates. However, its applications in asymmetric synthesis have been limited

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mainly to reactions of substrates featuring terminal alkynes[9] or benefiting from the "alkoxy effect"[7a,10] discovered by Marshall.[11]

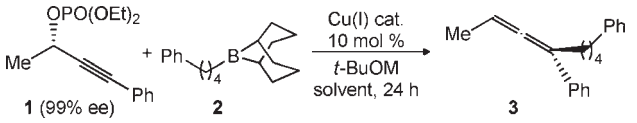
Several problems prevent a more general application of Cu-catalyzed propargylic substitution in asymmetric synthesis. For example, racemization of allene products caused by organocuprates,[12] Grignard reagents,[12] or Cu metal[13] is often encountered in these reactions. In addition, regio- and stereoselectivity of the reaction can vary significantly with subtle changes of the electrophile, nucleophile, and leaving group.[9b,14] These problems can be attributed to the presence of organocuprate intermediates,[12,15] which form in the presence of hard organometallic nucleophiles commonly used in these reactions. We speculated that cuprate formation could be avoided with less reactive nucleophiles and decided to explore the use of organoboron compounds in Cu-catalyzed propargylic substitutions. During the preparation of this manuscript, a similar *alkylation* of propargylic phosphates was published by Sawamura et al. focusing on the regioselectivity of the alkylation reaction.[15] Sawamura reported three reactions with high chirality transfer, two of which rely on the "alkoxy effect" previously used in reactions of Grignard reagents.[7a,10]

In initial experiments, we explored the reaction of alkyl borane **2** with enantioenriched phosphate **1** using conditions originally developed for arylation of allylic electrophiles.[16] The desired allene product **3** was formed in modest yield and with low chirality transfer (Table 1, entry 1). Encouragingly, only the product of the S_N2' substitution was detected in the crude reaction mixture. Catalyst optimization (Table 1, entries 2−5) resulted in a significant improvement of the yield, but not the enantiomeric excess of the allene. The low chirality transfer is a result of the inherent selectivity of the substitution step, as we found that neither the phosphate nor the allene product racemize under the reaction conditions.

Significantly higher chirality transfer was observed when 1,4-dioxane was replaced by pentane (Table 1, entry 6). Unfortunately, the allene product was obtained in lower yield and was accompanied by a significant amount of allenyl phosphate **4**.

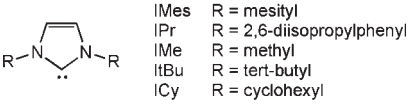
We suspected that this byproduct was formed by deprotonation of the propargylic phosphate[17] and decided to explore other base additives. The use of lithium *tert*-butoxide allowed the reaction to be performed at lower temperature, resulting in a complete suppression of the byproduct formation (Table 1, entry 7). The allene product was obtained in excellent yield and with high chirality transfer (98%).

Table 1. Reaction Optimization



entry[a,b]	cat.	M	t (°C)	solvent	yield[c]	ee[d]
1	IMesCuO*t*-Bu	Na	60	1,4-dioxane	45%	30%
2	IPrCuCl	Na	60	1,4-dioxane	35%	26%
3	IMeCuCl	Na	60	1,4-dioxane	33%	29%
4	I*t*-BuCuCl	Na	60	1,4-dioxane	16%	37%
5	ICyCuCl	Na	60	1,4-dioxane	79%	30%
6[e]	ICyCuCl	Na	60	pentane	47%	81%
7	ICyCuCl	Li	35	pentane	95%	96%

[a] **2** was prepared in situ from 4-phenyl-1-butene (1.5 equiv) and 9-BBN (1.5 equiv). [b] **1** (1.0 equiv), *t*-BuOM (1.0 equiv). [c] Determined by GC. [d] Determined by chiral HPLC. [e] Reaction performed in a sealed vessel.



In Table 2, we show that under optimized reaction conditions the transformation can be accomplished in the presence of silyl ethers, phenyl ethers, alkyl chlorides, thioacetals, aryl bromides, and esters. In addition, 1,1-disubstituted alkenes are viable substrates and provide the desired allene in good yield (Table 2, entry 5). It is worth noting that excellent chirality transfer and regioselectivity were observed in all reactions.[18]

Even with substrates biased against S_N2' substitution, such as *tert*-butyl substituted phosphate **6**, the reaction proceeded with excellent regioselectivity (Table 2, entry 8). Similarly, excellent regio- and stereoselectivity were obtained with trimethylsilyl-substituted phosphate **7** (Table 2, entries 9 and 10). These results stand in contrast to previous reports in which the presence of a bulky substituent at the γ-position of the propargylic electrophile diminishes the regioselectivity or completely prevents the reaction.[15]

Encouraged by the broad scope and consistently high regio- and stereoselectivity in the alkylation reaction, we also explored the reactivity of arylboronic esters. Using conditions similar to those developed for the alkylation reaction, we accomplished highly regio- and stereoselective arylation of propargylic phosphates (Table 3). Good yields

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(15) For example, better regioselectivities are usually observed in stoichiometric vs catalytic reactions. For an example of a direct comparison of a catalytic and a stoichiometric reaction with a Grignard reagent, see: Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *Org. Lett.* **2011**, *13*, 6312.
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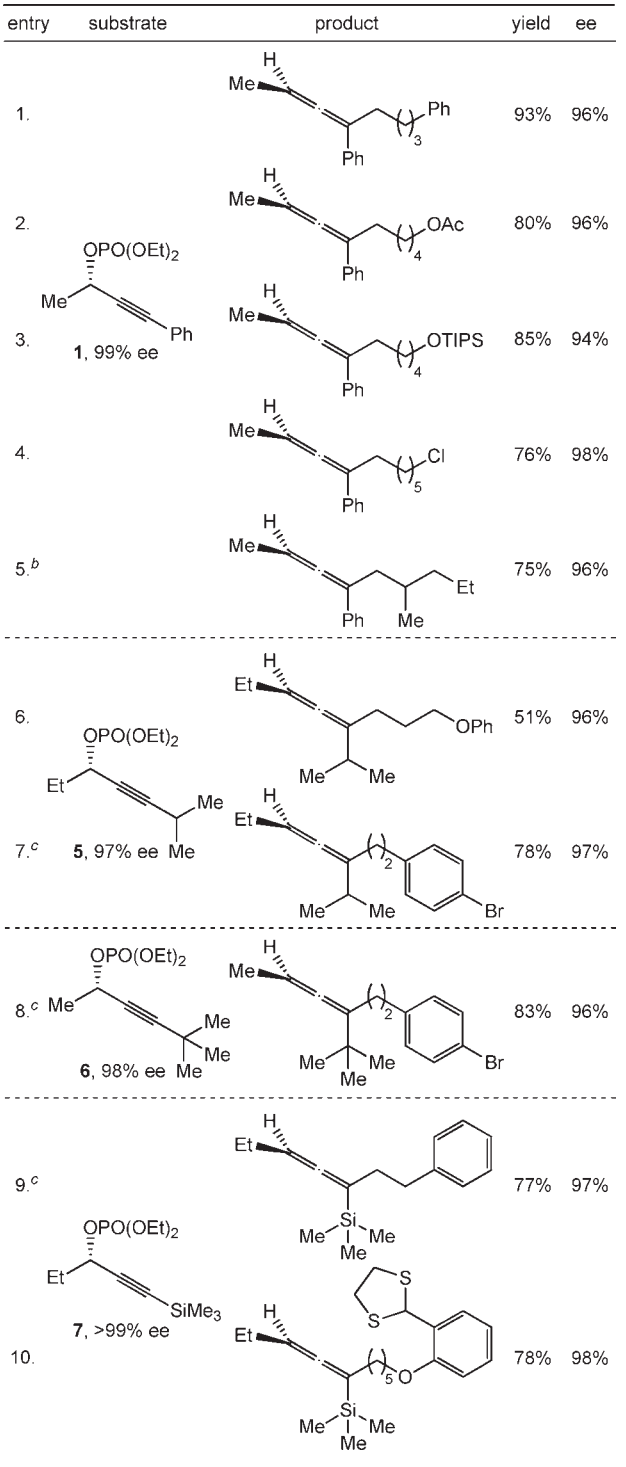
(18) Only one regioisomer of the product could be identified by GC/MS analysis of crude products obtained from alkylation reactions.

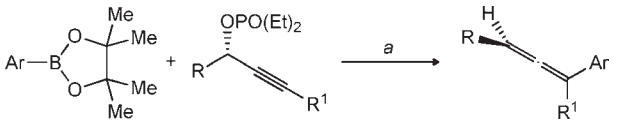
Table 2. Alkylation of Propargylic Phosphates[a]

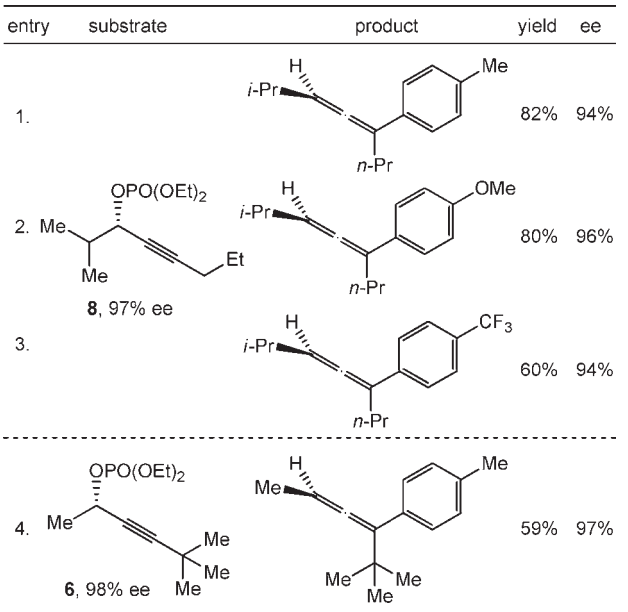


[a] Alkyl borane (1.5 equiv), phosphate (1.0 equiv), *t*-BuOLi (1.0 equiv), ICyCuCl (0.1 equiv), pentane, 35 °C, 6 h. All reactions performed on 0.5 mmol scale. Isolated yields of pure products are reported. [b] Product isolated as a 1:1 mixture of diastereoisomers. [c] Complete conversion of the phosphate required 18 h.

and antiselectivity[19] were obtained in the presence of both electron-donating and -withdrawing substituents (Table 3, entries 2 and 3). Finally, excellent regioselectivity was observed even with **6**, a substrate sterically biased against the S_N2' substitution (Table 3, entry 4).

Table 3. Arylation of Propargylic Phosphates





[a] $ArB(OR)_2$ (1.25 equiv), propargylic phosphate (1.00 equiv), NaO*t*-Pent (1.00 equiv), ICyCuCl (0.10 equiv), isooctane, 60 °C, 24 h. All reactions performed on 0.5 mmol scale. Isolated yields of pure products are reported.

To the best of our knowledge, this is the first example of an S_N2'-selective Cu-catalyzed arylation of propargylic electrophiles. More importantly, aside from a single example reported by Ihara in a Pd-catalyzed reaction,[20] this is the only instance of high chirality transfer (>95%) in arylations of propargylic electrophiles.[21]

Based on previous explorations of copper-catalyzed reactions of organoboron compounds,[16,22] we propose that the allene formation proceeds according to the mechanism outlined in Scheme 1. The first step of the proposed catalytic cycle involves transmetalation from boron to copper, followed by the antiselective substitution involving the putative alkyl copper intermediate and the propargylic electrophile. Finally, the alkoxide form of the

(19) See Supporting Information for the assignment of the absolute stereochemistry of the allene products.

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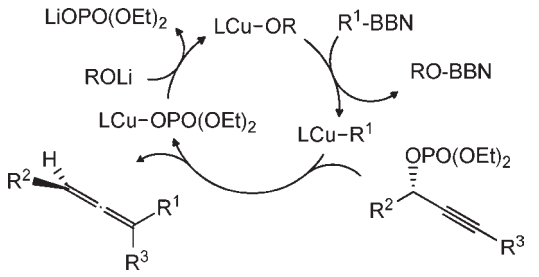
catalyst is regenerated by the reaction with lithium *tert*-butoxide.

Scheme 1. Proposed Catalytic Cycle

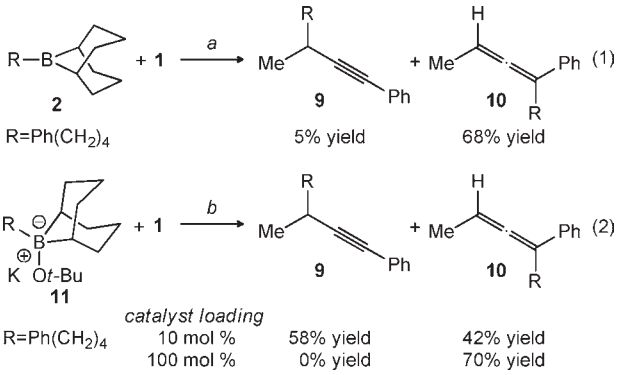


In the context of the catalytic cycle outlined in Scheme 1, we were interested in exploring the mechanism of the transmetalation reaction, which has been previously invoked as a key step in several Cu-catalyzed transformations of organoboron compounds. Most reports propose that the reaction proceeds through a borate intermediate,[15,23] while a sole theoretical study of the transmetalation reaction favors the mechanism involving borane and copper alkoxide.[24] We sought to provide data that would help us distinguish between the two mechanisms.

In a preliminary experiment, we examined the reaction between alkyl borane **2** and lithium *tert*-butoxide in both toluene and 1,4-dioxane using ^{11}B NMR. The borate formation was not observed in either solvent, even at 60 °C. While this result suggests that under the standard reaction conditions transmetalation proceeds through the alkyl borane, it is still possible that a small amount of borate present in equilibrium with borane is responsible for the reaction.

To rule out this possibility, we compared the reactivities of preformed potassium borate **11**[25] and the corresponding alkyl borane **2**. While the alkyl borane yielded the allene product together with a small amount of substituted alkyne **9** (Scheme 2, eq 1), borate **11** yielded **9** as the major product (Scheme 2, eq 2). Interestingly, only the allene product was formed in the presence of a stoichiometric amount of the copper catalyst, suggesting a possible involvement of an organocuprate intermediate in a catalytic reaction with borate **11**. These experiments suggest not only that the transmetalation occurs with both boranes and borates but also that the outcome of the reaction can be different depending on the form of the organoboron compound participating in the reaction.[26]

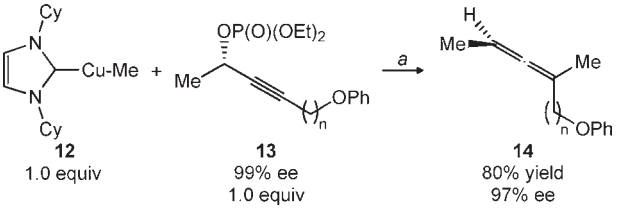
Scheme 2. Reactivity of Potassium Borate[a]



[a] **2** (1.5 equiv), **1** (1.0 equiv), ICyCuCl (0.1 equiv), *t*-BuOK (1.0 equiv), pentane, 35 °C, 24 h. [b] **11** (1.0 equiv), **1** (1.0 equiv), ICyCuCl (0.1 or 1.0 equiv), pentane, 35 °C, 24 h.

In an effort to provide evidence for the role of copper(I) alkyl complexes in the proposed catalytic cycle (Scheme 1), we explored the reactivity of ICyCuMe[27] (**12**) with phosphate **13**. In a stoichiometric reaction shown in Scheme 3, the expected allene product **14** was obtained in 80% yield and 97% ee. Furthermore, when **12** was used as a catalyst in a reaction between **1** and **2**, the desired allene was obtained in 85% yield and 98% ee.[28] The results of both experiments support the proposed role of copper(I) alkyl complexes as intermediates in the catalytic alkylation of propargylic phosphates.

Scheme 3. Stoichiometric Reactivity of Copper(I) Alkyl Complex[a]



[a] 10:1 mixture of pentane and 1,4-dioxane, 35 °C.

In conclusion, we developed a new method for asymmetric synthesis of chiral allenes based on copper-catalyzed alkylation *and* arylation of propargylic phosphates. In addition to good functional group compatibility, the new method offers consistently high chirality transfer and regioselectivity. Overall, the unique effectiveness and the scope of this reaction will make it a valuable addition to the existing methods for the synthesis of chiral allenes.

Acknowledgment. This work was supported by the University of Washington.

Supporting Information Available. Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) Dang, L.; Lin, Z.; Marder, T. B. *Organometallics* **2010**, *29*, 917.

(25) ^{11}B NMR indicated no presence of free alkyl borane in a solution of **11** in toluene-d^8. See Supporting Information for details.

(26) It is important to note that neither **2** nor **11** reacts with the phosphate in the absence of the copper catalyst.

(27) For synthesis of **12**, see Supporting Information.

(28) See Supporting Information for details.