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Catalytic Anti-Markovnikov Hydrobromination of Alkynes

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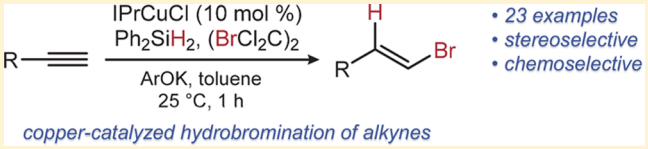
Supporting Information

ABSTRACT: We have developed the first *catalytic* method for anti-Markovnikov hydrobromination of alkynes. The reaction affords terminal *E*-alkenyl bromides in high yield and with excellent regio- and diastereoselectivity. Both aryl- and alkyl-substituted terminal alkynes can be used as substrates. Furthermore, the reaction conditions are compatible with a wide range of functional groups, including esters, nitriles, epoxides, aryl boronic esters, terminal alkenes, silyl ethers, aryl halides, and alkyl halides. A preliminary study of the reaction mechanism suggests that the hydrobromination reaction involves hydrocupration of an alkyne, followed by the bromination of the alkenyl copper intermediate. This study also suggests that 2-*tert*-butyl potassium phenoxide functions as a mild catalyst turnover reagent and provides a better understanding of the unique effectiveness of $(BrCl_2C)_2$ among brominating reagents.



INTRODUCTION

Alkenyl halides are important intermediates in organic synthesis. They are used as coupling partners in transition metal catalyzed cross-coupling reactions[1] and as precursors to a wide range of organometallic reagents, including organozinc, organolithium, and Grignard reagents.[2] Despite the prominent role of alkenyl halides in organic chemistry, the methods for their synthesis have remained mostly unchanged over the last 40 years. Although various synthetic precursors have been used in synthesis of alkenyl halides,[3,4] one of the most common methods is still the anti-Markovnikov hydrohalogenation of alkynes. This transformation involves hydrometalation of an alkyne using zirconium,[5] tin,[6] boron,[7] or aluminum hydrides,[8,9] followed by electrophilic halogenation of the stoichiometric alkenyl metal intermediate (see Figure 1). In general, the hydrometalations are highly *syn* selective,[10] ensuring the formation of the (*E*)-alkenyl metal intermediate. In addition, anti-Markovnikov selectivity is commonly observed, although high Markovnikov selectivity[11,9] has been observed in transition metal catalyzed hydrometalation reactions. Overall, the hydrometalation−halogenation sequence is effective in providing terminal *E*-alkenyl halides with high regio- and diastereoselectivity.

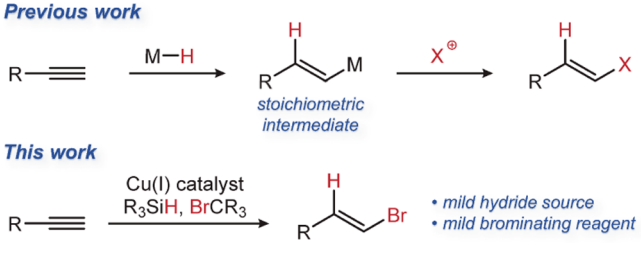


Figure 1. Anti-Markovnikov Hydrohalogenation of Alkynes.

Unfortunately, the high reactivity of aluminum and zirconium reagents limits the functional group compatibility and the scope of these methods.[12] In addition, zirconocene hydrochloride is expensive and sensitive to light and moisture,[12,13] which has prompted the development of numerous methods for its in situ preparation.[14] Hydrostannylation offers excellent functional group compatibility and is often used in the hydrobromination of complex substrates;[15] however, toxic byproducts are also formed. The method based on hydroboration[7] is rarely used, as it requires multiple steps and is often low yielding.[16] Finally, all of these methods require *stoichiometric* hydrometalation of the substrate prior to the halogenation step.

In this article we report the first catalytic anti-Markovnikov hydrohalogenation of alkynes (Figure 1). We describe the development of the reaction, the exploration of the reaction scope, and the study of the reaction mechanism.

RESULTS AND DISCUSSION

Approach and Reaction Development. One of the major difficulties in developing a catalytic version of the hydrohalogenation reaction is the efficient formation of an appropriate metal hydride reagent under catalytic conditions, where hydrometalation is just one of the steps in the catalytic cycle. Recently, we demonstrated an effective hydrometalation under catalytic conditions in the context of the catalytic semireduction of alkynes (eq 1).[17] We showed that the semireduction can be accomplished by hydrocupration, followed by protonation of the alkenyl copper intermediate. In this transformation, the key catalytic intermediate responsible for the hydrometalation of alkyne is a copper hydride complex formed by transmetalation of a copper alkoxide with a silane.

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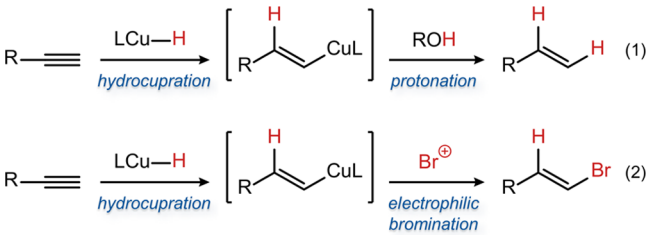
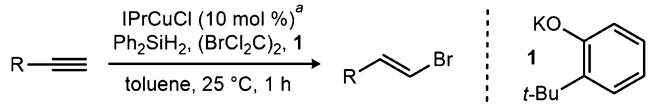


Our strategy for the development of the catalytic hydrobromination (eq 2) is based on the approach we used in the semireduction of alkynes. However, the development of the hydrobromination reaction presents two new challenges. In the semireduction, the protonation of the alkenyl copper intermediate by an alcohol (see eq 1) leads directly to the catalyst turnover, as the resulting copper alkoxide can subsequently form the copper hydride intermediate by transmetalation with a silane. In the hydrobromination reaction, a new approach to catalyst turnover is needed. The second challenge is to identify the brominating reagent compatible with our approach.

Despite these challenges, we have developed an efficient method for catalytic hydrobromination of alkynes shown in Table 1. The best results are obtained using $(BrCl_2C)_2$ as a brominating reagent, with IPrCuCl as a catalyst and Ph_2SiH_2 as a hydride source. Phenoxide **1** is a necessary additive responsible for the catalyst turnover.[18] The reaction is performed at room temperature and is completed within an hour. Furthermore, $(BrCl_2C)_2$, while not often used as a brominating reagent, is a cheap, readily available, and stable crystalline solid.

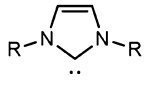
Table 1. Development of Catalytic Hydrobromination of Alkynes

Best conditions:



Entry	Change relative to best conditions	Yield (%)
1	none	95
2	no catalyst	0
3	ICyCuCl *instead of* IPrCuCl	0
4	IMesCuCl *instead of* IPrCuCl	0
5	PMHS *instead of* Ph_2SiH_2	24
6	$(EtO)_3SiH$ *instead of* Ph_2SiH_2	17
7	DCM *instead of* toluene	66
8	chlorobenzene *instead of* toluene	86
9	THF *instead of* toluene	4
10	PhOK *instead of* **1**	79
11	*t*-BuOK *instead of* **1**	0
12	$BrCH_2CH_2Br$ *instead of* $(BrCl_2C)_2$	0

[a] 4-$MeOC_6H_4(CH_2)_6CCH$ (1.0 equiv), Ph_2SiH_2 (1.5 equiv), $(BrCl_2C)_2$ (1.3 equiv), and **1** (1.6 equiv). $(BrCl_2C)_2$ added over 1 h.



IPr R = 2,6-diisopropylphenyl
IMes R = 2,4,6-trimethylphenyl
ICy R = cyclohexyl

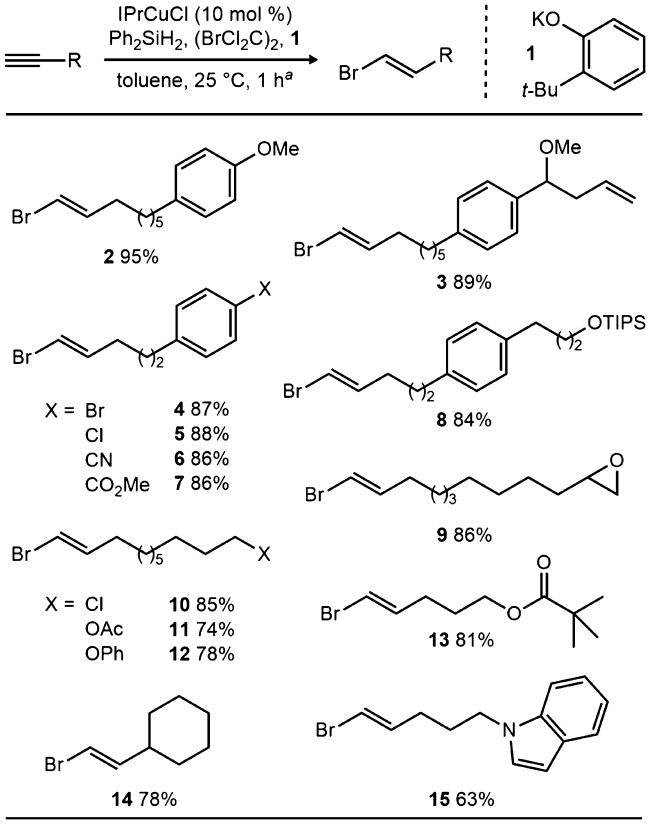
We made several observations, summarized in Table 1, during the process of reaction optimization. We found that IPrCuCl catalyst was necessary and uniquely effective in promoting the reaction. Even closely related NHC (*N*-heterocyclic carbene) copper complexes were completely ineffective as catalysts. Other silanes provided significantly lower yields of the desired product.

Reactions performed in dichloromethane and chlorobenzene provided significant amounts of the desired products, while the results obtained in THF are representative of the results obtained in a number of other organic solvents.

Phenoxide **1** provided significantly better results than several other closely related phenoxides, or potassium *tert*-butoxide, which is commonly used as a turnover reagent in reactions mediated by copper hydride complexes. Other common brominating reagents, such as 1,2-dibromoethane or NBS, were completely ineffective in the reaction. The underlying causes for some of the findings shown in Table 1 will be discussed in the context of the reaction mechanism at the end of this section.

Hydrobromination of Alkyl-Substituted Alkynes. The reaction conditions described in Table 1 proved to be effective in the hydrobromination of a number of alkyl-substituted alkynes (see Table 2). The reaction was compatible with several functional groups that are often reduced using other methods for alkyne hydrobromination, such as esters, nitriles, epoxides, and alkyl halides. The hydrobromination can also be accomplished in the presence of alkenes, aryl halides, aryl ethers, and silyl ethers. Heterocycles, such as indole, are also compatible with the reaction. Finally, alkynes with branched alkyl substituents are also tolerated (**14**). In all cases, we

Table 2. Catalytic Hydrobromination of Alkyl-Substituted Alkynes



[a] Alkyne (1.0 equiv, 0.5 mmol), Ph_2SiH_2 (1.5 equiv), $(BrCl_2C)_2$ (1.3 equiv), and **1** (1.6 equiv). $(BrCl_2C)_2$ added over 1 h.

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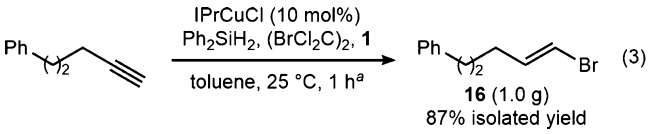
observed only the formation of a single regio- and diastereoisomer of the alkenyl bromide.

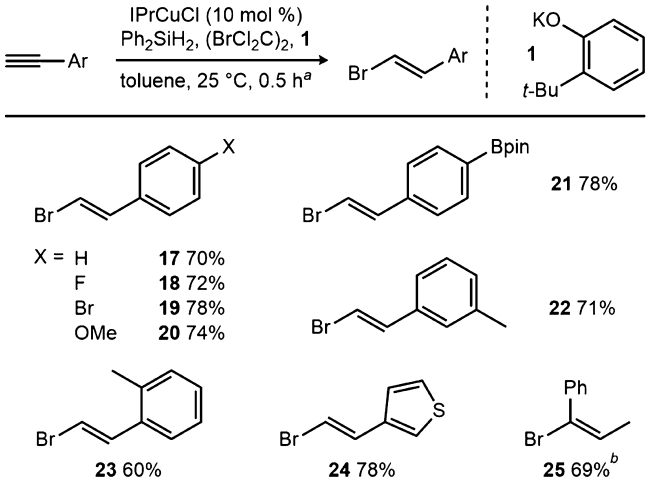
To demonstrate the utility of the new procedure, we performed the hydrobromination reaction on a preparative scale. Under the standard reaction conditions described in Table 2, we were able to prepare 1 g of alkenyl bromide **16** in excellent yield (eq 3).



(3)

Hydrobromination of Aryl-Substituted Alkynes. We also explored the reactivity of aryl-substituted alkynes, and we found that styrenyl bromides with both electron-donating and electron-withdrawing substituents could be successfully prepared (see Table 3). Additionally, we were surprised to find

Table 3. Catalytic Hydrobromination of Aryl-Substituted Alkynes

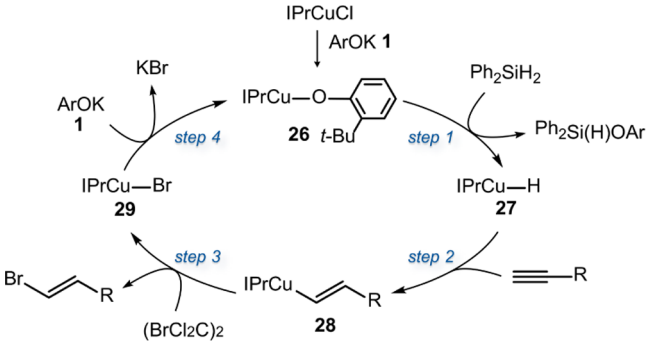


[a]Alkyne (1.0 equiv, 0.5 mmol), Ph_2SiH_2 (1.5 equiv), $(BrCl_2C)_2$ (1.3 equiv), and **1** (1.6 equiv). $(BrCl_2C)_2$ added over 0.5 h. [b]1-Phenyl-1-propyne used as starting material. Reaction performed at 45 °C over 1 h.

that aryl boronic esters are compatible with the hydrobromination reaction, as these compounds are known to participate in several copper-catalyzed transformations under closely related conditions.[19] As demonstrated by the synthesis of **22** and **23**, *meta* substitution is well tolerated, while the *ortho* substitution leads to a lower yield of the desired product. The synthesis of **24** suggests that some heteroaryl acetylenes can also be used as substrates.[20] Finally, the synthesis of **25** demonstrates that regioselective hydrobromination of disubstituted aryl acetylenes can also be accomplished. In all reactions presented in Table 3, the formation of only one regio- and diastereoisomer of the product was observed.

Mechanism. We propose that the reaction proceeds according to the mechanism shown in Scheme 1. The proposed catalytic cycle involves transmetalation of copper phenoxide **26** with the silane to form copper hydride **27** (step 1), which, after hydrocupration of the alkyne (step 2), provides alkenyl copper intermediate **28**. Subsequent electrophilic bromination of the alkenyl copper intermediate (step 3) provides the desired

Scheme 1. Proposed Catalytic Cycle

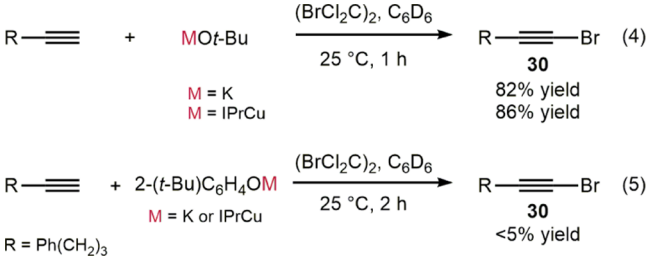


product and copper bromide **29**. Catalyst turnover (step 4) is accomplished by ligand substitution in the presence of phenoxide **1**. Considering that the hydrocupration of alkynes (step 3) has been well-documented in the literature,[21] our focus in the process of the reaction development was on the other three steps of the proposed catalytic cycle.

One of the challenges in developing the catalytic hydrobromination reaction is achieving the turnover of the catalyst (Scheme 1, step 4). We were intrigued by our initial finding that alkoxide-based turnover reagents commonly used in catalytic reactions of copper hydrides, such as potassium *tert*-butoxide, performed poorly in the catalytic hydrobromination (Table 1, entry 11). To provide an explanation for this observation, we did a more detailed analysis of the hydrobromination reaction performed with potassium *tert*-butoxide as an additive. We found that alkynyl bromide was the major byproduct formed in this reaction.

Stoichiometric experiments shown in eq 4 (Scheme 2) demonstrate that alkynyl bromide **30** can be formed from the

Scheme 2



alkyne in the presence of either copper or potassium *tert*-butoxide. In contrast, we found that neither copper phenoxide nor potassium phenoxide promotes the formation of the alkynyl bromide (eq 5). These results suggest that the low basicity of the turnover reagent is essential for the success of the catalytic hydrobromination, and they explain the effectiveness of the phenoxide additives.

While the transmetalation of copper alkoxides with silanes is well-precedented in the literature,[21] the transmetalation involving copper phenoxide and a silane has not been previously described (step 1). To explore the feasibility of this transmetalation, we prepared **26** from IPrCuCl and potassium phenoxide **1** (eq 6; Scheme 3). In a reaction with Ph_2SiH_2, IPrCuH was formed within minutes at room temperature (eq 7). Significantly slower transmetalation was observed with other silanes, such as PMHS and $(EtO)_3SiH$, while no transmetalation was observed with less reactive

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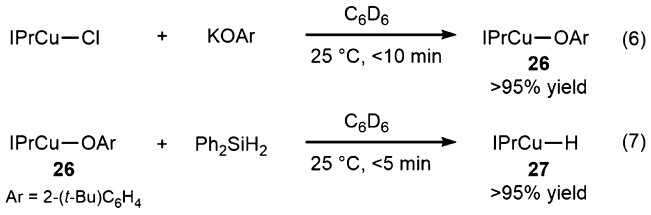
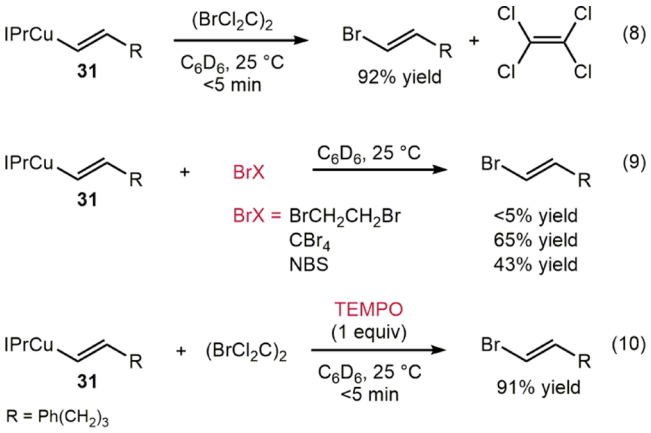
Scheme 3. Catalyst Turnover and Transmetalation



Et_3SiH. The results of experiments shown in eqs 6 and 7 clearly demonstrated the feasibility of the proposed transmetalation (step 1) and the proposed catalyst turnover (step 4) steps.

In an effort to identify a brominating reagent suitable for the hydrobromination reaction, and at the same time learn more about the electrophilic bromination of the alkenyl copper intermediate (step 3), we prepared complex **31** and explored its reactivity with a range of brominating reagents (Scheme 4). In a

Scheme 4. Electrophilic Bromination



stoichiometric reaction with $(BrCl_2C)_2$ we observed near quantitative formation of the alkenyl bromide, in less than 5 min at room temperature (eq 8). Importantly, tetrachloroethylene and IPrCuBr (**29**) were both identified as byproducts of this reaction. In a reaction with a less reactive 1,2-dibromoethane, alkenyl bromide was not formed, even at elevated temperature (eq 9). More reactive brominating reagents, such as NBS and CBr_4, gave lower yields of the desired bromoalkene (eq 9) and resulted in partial decomposition of the alkenyl copper complex. To further probe the mechanism of the reaction between **31** and $(BrCl_2C)_2$, we performed the reaction in the presence of an equivalent of TEMPO. Interestingly, the presence of TEMPO had no significant effect on the outcome. This result suggests that bromination of **31** does not involve free radical intermediates.

Overall, the results presented in Scheme 4 demonstrate the feasibility of the proposed electrophilic bromination of the alkenyl copper intermediate and explain the superior performance of $(BrCl_2C)_2$ in the catalytic reaction.

CONCLUSION

We have developed the first catalytic hydrobromination of alkynes. The reaction is compatible with both alkyl- and aryl-substituted alkynes, and with a wide range of functional groups, including esters, nitriles, epoxides, aryl boronic esters, alkyl halides, and aryl halides. The key step in the reaction is a catalytic hydrometalation which is highly anti-Markovnikov and *syn* selective. As a result, terminal *E*-alkenyl bromides are obtained with excellent regio- and diastereoselectivity. A preliminary study of the reaction mechanism provides support for the proposed mechanism involving hydrocupration of an alkyne followed by the electrophilic bromination of the alkenyl copper intermediate. This study also provides insight into the key properties of the brominating and turnover reagents used in the hydrobromination reaction. Finally, the discovery of phenoxides as mild turnover reagents is likely to enable the development of new catalytic reactions with copper hydrides as key catalytic intermediates.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. 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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