

Copper-Catalyzed Hydroalkylation of Terminal Alkynes

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S Supporting Information

ABSTRACT: We have developed a copper-catalyzed hydroalkylation of terminal alkynes using alkyl triflates as coupling partners and $(\text{Me}_2\text{HSi})_2\text{O}$ as a hydride donor. The hydroalkylation proceeds with excellent anti-Markovnikov regioselectivity and provides exclusively (*E*)-alkenes. We have demonstrated that both alkyl- and aryl-substituted alkynes can be used as substrates, together with 1° alkyl and benzylic triflates. Finally, the transformation can be accomplished in the presence of a wide range of functional groups. Overall, the new hydroalkylation reaction allows highly efficient and diastereoselective synthesis of (*E*)-alkenes from readily available terminal alkynes and alkyl triflates. On the basis of a preliminary mechanistic study, we propose that the hydroalkylation reaction involves copper hydride formation, hydrocupration of an alkyne, and alkylation of an alkenyl copper intermediate.

(*E*)-Alkenes are ubiquitous in organic chemistry and numerous methods for their synthesis have been developed over the years. Traditional methods, such as dissolving metal reduction of alkynes,¹ Schlosser modification of the Wittig reaction,² or the Julia-Kocienski reaction,³ are still commonly used. Several catalytic methods are also available. In addition to the Heck reaction,⁴ the most commonly used are numerous transformations based on cross-coupling of functionalized (*E*)-alkenes, such as alkenyl halides or alkenyl metal reagents,⁵ and those based on the *E*-selective reduction of internal alkynes.⁶

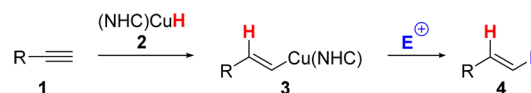
A particularly efficient approach to the synthesis of alkenes is intermolecular hydroalkylation of alkynes. This transformation leads to an increase in both structural (new C–C bond is formed) and stereochemical (double bond geometry) complexity and offers potential for complete control of both regio- and diastereoselectivity. Furthermore, terminal alkynes and alkyl electrophiles are readily available starting materials. Despite the great potential of hydroalkylation as a method for synthesis of (*E*)-alkenes, there are still no catalytic methods for simple hydroalkylation of terminal alkynes. While there are several excellent methods for reductive cross-coupling of internal⁷ alkynes with π electrophiles, such as aldehydes,^{8,9} formamides,¹⁰ ketones,¹¹ enones,¹² and imines,¹³ reductive cross-coupling reactions with alkyl (σ) electrophiles are exceedingly rare. The most general example of such a reaction is a reductive coupling of internal alkynes with epoxides, reported in 2003.^{14,15} To the best of our knowledge, catalytic hydroalkylation of alkynes using alkyl halides or sulfonate esters as electrophiles has not been reported.

In this communication, we describe the development of an *E*-selective catalytic hydroalkylation of terminal alkynes using alkyl

triflates as electrophiles. We describe the reaction development, our exploration of the reaction scope, and the results of a preliminary study of the reaction mechanism.

We and others have recently disclosed methods for catalytic semireduction,¹⁶ hydrocarboxylation,¹⁷ and hydrobromination¹⁸ of alkynes using a general approach outlined in Scheme 1. All of

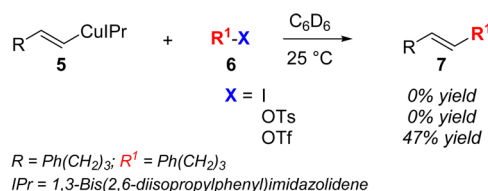
Scheme 1. General Approach to Catalytic Hydrofunctionalization of Alkynes



these reactions involve hydrocupration of an alkyne,¹⁹ followed by electrophilic functionalization of the alkenyl copper intermediate (3). We were intrigued by the idea that, at least in principle, we could accomplish hydroalkylation of alkynes using the same general approach.

To identify an appropriate electrophile for such a hydroalkylation reaction, we explored the reactivity of the presumed alkenyl copper intermediate 5 with a range of alkyl electrophiles (Scheme 2). We observed no reaction with alkyl iodide or alkyl

Scheme 2. Reaction of Alkenyl Copper Complex with Alkyl Electrophiles



tosylate, over a wide range of temperatures. However, the alkyl triflate provided the desired alkylation product at room temperature in ~50% yield and led us to focus our efforts on this class of electrophiles.

The choice of alkyl triflates as electrophiles introduced additional challenges. The turnover reagents previously used in copper-catalyzed hydrofunctionalization reactions (alkoxides,¹⁶ phenoxides,¹⁸ and carboxylates¹⁷) are not compatible with alkyl triflates. Therefore, we needed a turnover reagent that is compatible with alkyl triflates but is still able to promote the formation of copper hydride. An even bigger concern was the reduction of alkyl triflates in the presence of a silane and an NHC copper catalyst, recently reported by our group.²⁰ The efficiency

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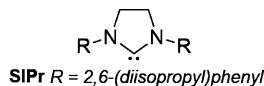
of the reduction suggested that, in the proposed hydroalkylation reaction, it may be difficult to avoid the unwanted reduction of the alkyl triflate electrophile.

Despite these challenges, we were able to develop hydroalkylation of terminal alkynes shown in Table 1. Essential for the

Table 1. Development of Hydroalkylation Reaction^a

entry	change from optimal conditions	% yield
1	no change	95%
2	IPrCuOTf instead of SIPrCuOTf	85%
3 ^a	ICyCuOTf instead of SIPrCuOTf	3%
4 ^a	1.0 equiv alkyl triflate instead of 1.5	44%
5 ^a	0.6 equiv TMDSO instead of 2.0	50%
6	triethoxy silane instead of TMDSO	27%
7	diethoxy methyl silane instead of TMDSO	66%
8	PMHS instead of TMDSO	32%
9	1.0 equiv of CsF instead of 2.0	91%
10 ^b	ether instead of 1,4-dioxane	82%
11 ^b	toluene instead of 1,4-dioxane	70%
12 ^b	DCM instead of 1,4-dioxane	82%

^aR = Ph(CH₂)₃; R¹ = CH₃(CH₂)₉. ^bUsed 1.0 equiv of CsF. ^cThirty-six hours.



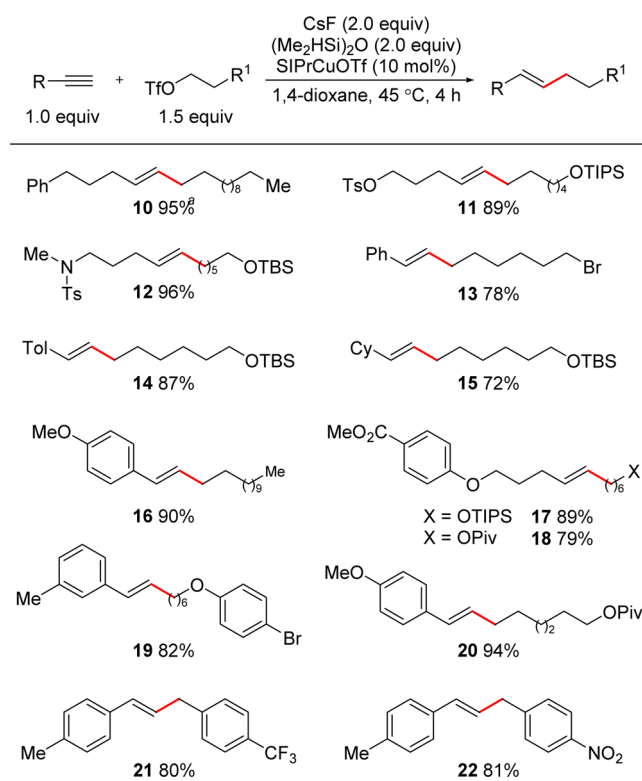
success of the reaction is the use of CsF, which is compatible with alkyl triflates and can also function as an effective turnover reagent. As shown in Table 1, the best results are obtained using SIPrCuOTf as a catalyst, (Me₂HSi)₂O as a hydride source, and 1,4-dioxane as a solvent. Surprisingly, these reaction conditions are remarkably similar to the reaction conditions we previously developed for the reduction of alkyl triflates. Nevertheless, the product of alkyl triflate reduction was formed in less than 5% yield, demonstrating the excellent selectivity of the catalytic system.

During the development of the hydroalkylation reaction we made several observations. The choice of catalyst is crucial for the success of the reaction. SIPr- and IPrCuOTf catalyze the desired reaction efficiently (Table 1, entries 1 and 2), while other NHC ligands that are similar to SIPr electronically,²¹ but differ sterically, afford little or no hydroalkylation product (entry 3).

We found that excess alkyl triflate is necessary for efficient cross coupling (entry 4). Similarly, lower yield of the cross-coupling product was obtained when 0.6 equiv of the silane was used (entry 5). In that case, in addition to the cross-coupling product, the dodecyl fluoride was formed in 20% yield.^{22,23} The copper-catalyzed formation of alkyl fluoride was effectively eliminated when 2 equiv of the silane was used. Other common silanes did not perform nearly as well as (Me₂HSi)₂O under the optimized conditions (entries 6–8). With one equivalent of CsF the observed decrease in yield is not significant (entry 9), but there is a substantial decrease in the rate of the reaction.²⁴ Finally, the reaction proceeds in other common organic solvents (entries 10–12), but at a substantially lower rate.

The standard reaction conditions shown in Table 1 proved effective in the hydroalkylation of various types of alkynes including alkyl-substituted alkynes, α -branched alkyl alkynes, and aryl acetylenes (see Table 2). The hydroalkylation can be

Table 2. Catalytic Hydroalkylation of Alkynes^a



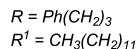
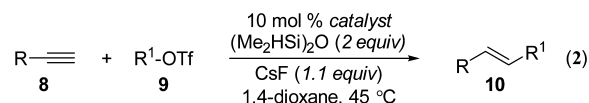
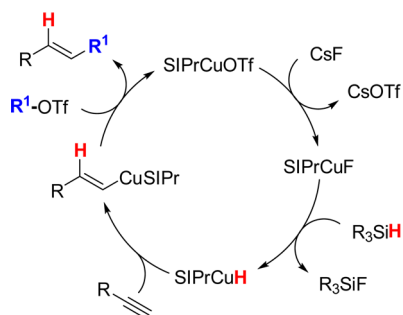
^aAll reactions were performed on 0.5 mmol scale. Yields of isolated products after column chromatography are reported.

accomplished with a variety of primary alkyl triflates, including benzylic triflates (compounds **21** and **22**, Table 2). It is important to note that all triflates used in Table 2 are prepared in high purity and in good yield from the corresponding alcohols.²⁵ The mild reaction conditions allow successful hydroalkylation of alkynes in the presence of a wide range of functional groups. Silyl ethers, alkyl bromides, alkyl tosylates, esters, ethers, aryl bromides, sulfonamides, and nitro arenes are all compatible with the standard reaction conditions. In all examples described in Table 2, a single regio- and diastereoisomer of the product is formed.

During the explorations of the substrate scope, we have also identified some limitations of the new method. We found that when α -branched alkyl triflates or electron-deficient aryl acetylenes are used as substrates, the hydroalkylation products are obtained in significantly lower yields.²⁶ In addition, when internal alkynes are used as substrates in reactions performed under standard reaction conditions, the formation of the hydroalkylation products was not observed.

On the basis of the result of the stoichiometric reaction shown in Scheme 2 and previous work on the mechanism of related hydrofunctionalization reactions,^{16–18} we propose that the hydroalkylation proceeds according to the mechanism shown in Scheme 3. The SIPrCuOTf catalyst reacts with CsF to form SIPrCuF, which after transmetalation with silane forms SIPrCuH. Subsequent hydrocupration of an alkyne, followed

Scheme 3. Proposed Catalytic Cycle



Conditions	Catalyst	Stir Rate
A	SIPrCuOTf	300 rpm
B	SIPrCuOTf	1500 rpm
C	SIPrCuF	1500 rpm

by alkylation of the alkenyl copper intermediate with alkyl triflate forms the product and regenerates SIPrCuOTf.

The feasibility of all the elementary steps in the proposed catalytic cycle is supported by experimental evidence. Recently, we demonstrated the formation of the NHCCuF from corresponding triflate complexes in the presence of alkali metal fluorides.²³ The hydrocupration of alkynes by NHC-copper hydride complexes is well established.¹⁹ The stoichiometric experiment described in Scheme 2 demonstrates the feasibility of the key step responsible for the formation of the carbon–carbon bond. Finally, the proposed transmetalation from silane to copper is supported by the stoichiometric experiment shown in eq 1. We found that SIPrCuF reacts with (Me₂HSi)₂O almost instantly at room temperature to generate SIPrCuH in quantitative yield.²⁷ SIPrCuH was stable under N₂ in C₆D₆ for over 30 min.



In an effort to provide further insight into the reaction mechanism and explore the relative rates of elementary steps involved in the catalytic cycle, we examined the kinetics of the hydroalkylation reaction. Initial experiments revealed a surprising induction period (see Figure 1, conditions A and B).

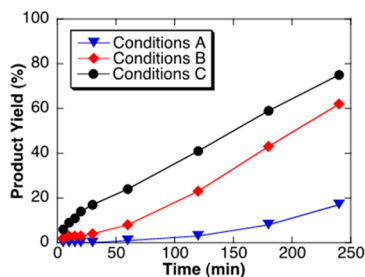


Figure 1. Reaction profiles demonstrating catalyst and stir rate dependence for conditions A (SIPrCuOTf, 300 rpm), B (SIPrCuOTf, 1500 rpm), and C (SIPrCuF, 1500 rpm) as described in eq 2 (data was not fitted).

Furthermore, we found that both the induction period and the rate of the reaction strongly depend on the rate at which the reaction mixture is stirred (Figure 1, conditions A and B). We speculated that phase transfer of fluoride may limit the rate at which copper fluoride is initially formed and, in that way, cause the induction period. Indeed, when SIPrCuF was used as a catalyst there was no induction period (Figure 1, condition C). The induction period could also be reduced by vigorously stirring CsF in the heated reaction solvent for 25 min before addition of the other reagents.

In further kinetics experiments we established that the rate of the reaction does not depend on the concentration of the alkyne, silane, or the alkyl triflate.²⁵ These results, together with the stir-rate dependence of the reaction rate, strongly suggest that the phase transfer of fluoride ultimately determines the rate of the hydroalkylation reaction. In the context of the proposed mechanism, that would make the formation of SIPrCuF the turnover-limiting step of the catalytic cycle.

As previously pointed out alkyl triflates can be transformed into alkyl fluorides²³ or alkanes²⁰ under reaction conditions that are remarkably similar to the conditions used in the hydroalkylation reaction. In that light, the selectivity of the hydroalkylation reaction is surprising, and a more detailed study aimed at understanding this selectivity is under way.

We have developed copper-catalyzed hydroalkylation of terminal alkynes using alkyl triflates as electrophiles and (Me₂HSi)₂O as a hydride donor. The hydroalkylation proceeds with complete control of both regio- and diastereoselectivity and allows an efficient synthesis of (*E*)-alkenes from readily available starting materials. We have demonstrated that both alkyl- and aryl-substituted alkynes can be used as substrates, together with a range of primary alkyl triflates. We propose that the hydroalkylation reaction involves hydrocupration of the alkyne followed by electrophilic functionalization of the alkenyl copper intermediate. A preliminary study of the reaction mechanism suggests that the formation of the SIPrCuF intermediate is the turnover-limiting step of the catalytic cycle.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, kinetic plots, 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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- (24) See Figure S1 in Supporting Information.
- (25) See Supporting Information for details.
- (26) Data not shown. We speculate that in reactions with electron-deficient aryl acetylenes, the catalyst is inactivated by the formation of a catalytically inactive copper acetylide. We have observed a similar limitation of the substrate scope in the recently reported hydrobromination reaction (see ref 18).