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Copper-Catalyzed Propargylic Reduction with Diisobutylaluminum Hydride

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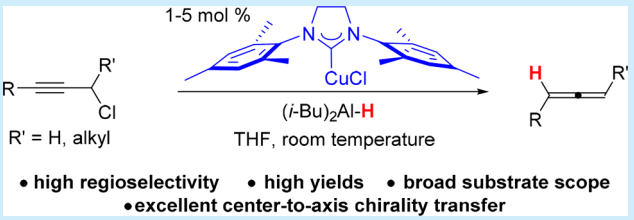
Supporting Information

ABSTRACT: A mild and efficient method for the synthesis of allenes through selective copper-catalyzed hydride addition to propargylic chlorides using commercially available diisobutylaluminum hydride has been developed. This transformation, which is promoted by a readily accessible *N*-heterocyclic carbene−copper complex, provides a wide range of new and versatile functionalized allenes in good to excellent yields with high regio- and stereoselectivities.



Allenes are important structural motifs present in natural products, pharmaceuticals, and molecular materials,[1] and they serve as valuable intermediates in a variety of organic transformations.[2] Therefore, numerous synthetic methodologies for allenes have been studied.[3] Among the routes for the synthesis of allenes, copper-catalyzed selective S_N2' reduction of a propargylic electrophile with a hydride source is one of the most attractive because of the use of low-cost and easy-to-handle copper catalysts, the use of readily available and convenient hydride nucleophiles such as silanes, and the use of easily prepared propargylic substrates.[4]

Copper hydride (CuH)-catalyzed reactions have emerged as an important tool for the formation of carbon−hydrogen bonds. Since Brunner and co-workers developed the first example of using a CuH catalyst for the reduction of acetophenone with silanes,[5] copper hydrides have been utilized in numerous catalytic transformations including selective 1,2-reduction, 1,4-reduction, S_N2' reduction, and hydrogenation.[6,7] In particular, a wide range of alkene and alkyne hydrofunctionalization reactions proceed via the generation of alkyl- or alkenylcopper intermediates derived from the insertion of CuH species into multiple C−C bonds, followed by the reaction of the organocopper intermediates with various electrophiles. These reactions play a crucial role in forming C−H, C−C, C−N, C−Si, and C−B bonds.[8] Stryker, Brummond and co-workers attempted copper-mediated regioselective hydride addition to terminal propargylic acetate moieties using stoichiometric Stryker's reagent ($[(Ph_3P)CuH]_6$),[9] which affored the 1,1′-disubstituted allenes.[10] These results show that the use of copper hydride as a reducing agent in the propargylic reduction reaction could be a new approach for the synthesis of allenes. A catalytic version of the propargylic reduction was first achieved by Krause and co-workers.[4c] They reported that *N*-heterocyclic carbene (NHC)-based copper complexes generated in situ from a mixture of an imidazolium salt, CuCl, and NaO*t*-Bu catalyzed the S_N2' reduction of propargylic oxiranes with polymethylhydrosiloxane (PMHS) to provide various *α*-hydroxyallenes in high regio- and diastereoselectivity. The same researchers applied this methodology to the synthesis of functionalized allenes through NHC-Cu-catalyzed hydride addition to internal propargylic carbonates with PMHS under similar reaction conditions.[4b] In the same year, Ito, Sawamura and co-workers demonstrated that a catalytic system comprising copper acetate and the Xantphos ligand also worked well for the S_N2' reduction of propargylic carbonates with hydrosilanes, affording di- and trisubstituted allenes, including enantiomerically enriched allenes.[4a] These CuH-catalyzed propargylic reduction reactions for allene synthesis are highly regio- and stereoselective and tolerant to various functional groups and proceed under mild reaction conditions. Despite these advances, only three examples of CuH-catalyzed propargylic reduction for synthesizing mainly di- and trisubstituted allenes have been reported, and only hydrosilanes, especially PMHS, have been used as the hydride nucleophile source. Due to the significance and synthetic utilities of functionalized allenes, the development of practical and efficient approaches is still required.

While silanes and boranes are the most commonly used hydride sources in CuH catalysis, the application of aluminum hydride in this field has been rarely studied.[3d] Although a few examples of copper-free propargylic reduction using lithium aluminum hydride or diisobutylaluminum hydride (DIBAL-H) have been reported, there are challenging issues to be solved for the further synthetic applications of these reactions: limited substrate scope, high reaction temperature, and low to moderate yields.[11] In this study, we demonstrate the applicability of DIBAL-H as a new alternative hydride nucleophile for CuH catalysis. The selective hydride addition of DIBAL-H to propargylic chlorides in the presence of 1−5 mol % of an NHC-Cu catalyst proceeds under mild and simple reaction conditions to provide a broad range of new versatile

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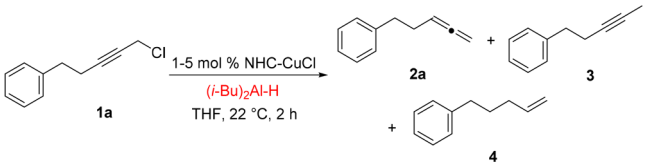
mono- and disubstituted allenes, including chiral allenes, in good to excellent yields with high regio- and stereoselectivities.

We began our investigation by examining the ability of NHC-copper catalysts to promote the regioselective S_N2' reduction of propargylic chloride **1a** using inexpensive and commercially available diisobutylaluminum hydride as a hydride nucleophile, as shown in Table 1. When chloride **1a** was treated with 1.2 equiv of DIBAL-H in the presence of 5 mol % **SIMesCuCl** (Figure 1), the desired terminal allene **2a** was obtained in 83% yield with 94:6 regioselectivity (entry 1). In contrast, there was no transformation of **1a** without using a Cu catalyst (entry 2). As the result in entry 3 describes, CuCl itself did not efficiently or selectively catalyze the S_N2' reduction of **1a** (15% of **2a**, 1:1 = **2a**:**3**), indicating that the NHC ligand may play an important role in stabilizing the copper hydride species[4] and controlling regioselectivity. Based on these results, we postulated that the copper hydride species complexed with an NHC ligand[12] might be generated from the transmetalation of **SIMesCuCl** with DIBAL-H. Similar to the mechanism of Cu-catalyzed propargylic reductions suggested by Krause and co-workers, the in situ generated CuH species presumably undergo S_N2' substitution with the propargylic chloride via the formation of a copper(III) intermediate, followed by reductive elimination, to give the allene product.[4b,13] Phosphine ligands such as dppbz and DPEphos were not effective (entries 4−5). Various NHC ligands were tested, but inferior results in terms of efficiency and selectivities were observed (entries 6−10). Notably, reactions with sterically demanding isopropyl-substituted NHC-CuCl catalysts generate side product **4** derived from the overreduction of allene **2a** (entries 6−7). Therefore, **SIMesCuCl** was selected as the optimal catalyst for the selective and efficient synthesis of allene **2a**. As shown in entry 12 of Table 1, even if 1 mol % of Cu catalyst was used, the hydride addition to **1a** effectively proceeded to complete conversion, affording the desired allene **2a** in 92% yield.

After the optimized reaction conditions were established, the substrate scope of the Cu-catalyzed S_N2' reduction of terminal propargylic chlorides was investigated. All transformations were carried out in the presence of 1−3 mol % **SIMesCuCl** catalyst at ambient temperature, affording a variety of terminal allenes with high regioselectivity and efficiency, as shown in Scheme 1. The copper-catalyzed hydride addition of DIBAL-H to phenethyl-substituted propargylic chlorides **1a**−**1d** bearing a chloro, bromo, or methoxy moiety on the *meta*-position of the phenyl group proceeded to complete conversion within 3 h to provide the desired allenes **2a**−**2d** in excellent yields (82−93%). However, compared to the reactions with **1a**−**1d**, the reaction of substrate **1e** substituted with a chloro group on the *ortho*-position of the phenyl group was less efficient (50% yield of **2e**) owing to steric hindrance. Functional groups such as an ether or chloro moiety on the propargylic substrates were well tolerated in the Cu-catalyzed reductions, affording the corresponding allenes **2f**−**2j** in 74−93% yields. In addition, various alkyl-substituted allenes **2k**−**2m** bearing an *n*-hexyl or sterically demanding cyclohexyl unit were efficiently synthesized in 73−86% yields. Unfortunately, these catalytic S_N2' reduction conditions were not effective in the reaction of an aryl-substituted propargylic chloride. When (3-chloroprop-1-

Table 1. Optimization of the Cu-Catalyzed Propargylic Reduction of 1a[a]



entry	Cu complex	mol % of Cu	equiv of DIBAL-H	conv (%)[b]	yield (%) of **2a**:**3**:**4**[b]
1	SIMes-CuCl	5	1.2	88	83:5:<2
2	no Cu	0	1.2	<2	<2
3	CuCl	5	1.2	30	15:15:<2
4	dppbz + CuCl	5	1.2	33	8:25:<2
5	DPEphos + CuCl	5	1.2	55	25:23:<2
6	IPr-CuCl	5	1.2	74	58:<2:14
7	SIPr-CuCl	5	1.2	60	40:<2:19
8	IMes-CuCl	5	1.2	77	51:26:<2
9	ICy-CuCl	5	1.2	83	26:22:<2
10	Benz-ICy-CuCl	5	1.2	62	28:23:<2
11	SIMes-CuCl	5	1.5	96	83:5:3
12[c]	SIMes-CuCl	1	1.5	>98	92:3:5

[a]Reactions were performed on a 0.30 mmol scale of **1a** in THF (0.2 M) under N_2. Dppbz = 1,2-bis(diphenylphosphino)benzene, DPEphos = bis[(2-diphenylphosphino)phenyl] ether. [b]Determined by ^{1}H NMR or GC analysis using 1,3,5-trimethoxybenzene as an internal standard. [c]Reaction time was 3 h.

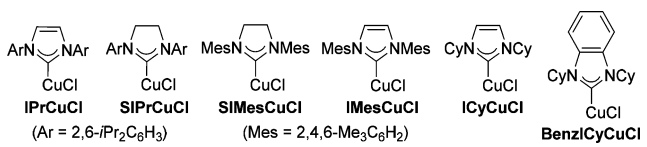
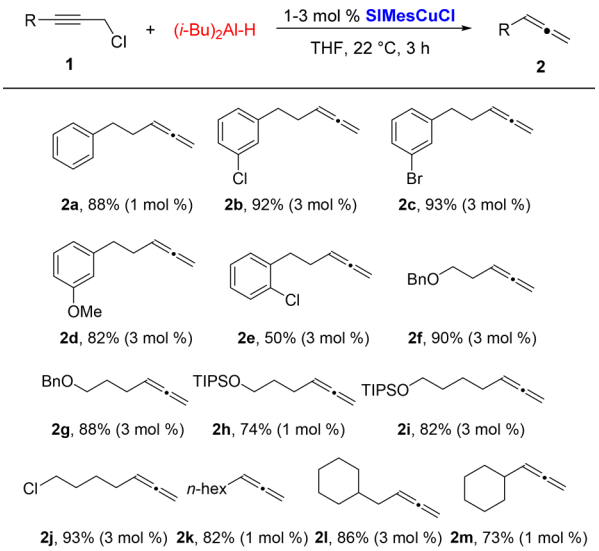


Figure 1. Various NHC-CuCl studied for propargylic reduction reactions.

Scheme 1. Cu-Catalyzed S_N2' Reduction with Various Propargylic Chlorides[a,b]



[a]Reaction conditions: propargylic chloride **1** (0.30 mmol), DIBAL-H (0.45 mmol), **SIMesCuCl** (1−3 mol %), THF (0.2 M) under N_2. In all cases, >95:<5 regioselectivity. [b]Yields of the isolated products.

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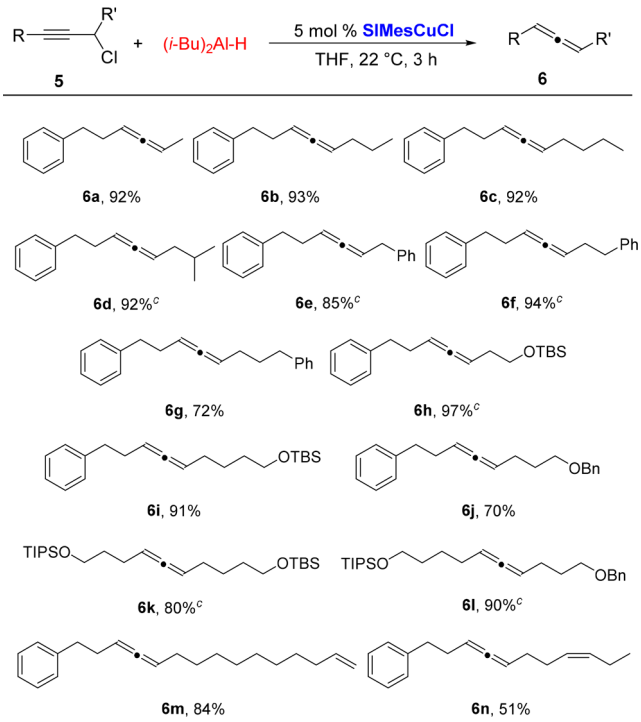
yn-1-yl)benzene was employed with DIBAL-H in the presence of 5 mol % of **SIMesCuCl**, the phenyl-substituted allene product was obtained in <20% yield along with a mixture of byproducts.

Next, we turned our attention to investigating the generality of this catalytic propargylic reduction. As illustrated in Scheme 2, a wide range of internal propargylic chlorides could be utilized in the NHC-Cu-catalyzed hydride addition of DIBAL-H, providing various new functionalized allenes in good to excellent yields with excellent regioselectivity. Substrates **5a**–**5g** substituted with phenethyl and various alkyl functionalities, such as methyl, propyl, butyl, isobutyl, benzyl, phenethyl, and phenylpropyl groups, were successfully converted to the corresponding internal allenes **6a**–**6g** in 72–94% yields. It was found that the reductions of internal propargylic chlorides **5d**–**5f** with a sterically demanding isobutyl or benzyl substituent required longer reaction times (12 h vs 3 h) for improved yields. The catalytic hydride addition was compatible with functional groups such as silyl ethers, benzyl ethers, or alkenes. New and versatile internal allenes **6h**–**6l** including a silyl or benzyl ether group, which could be synthetically valuable intermediates for further transformations, were obtained in 70–97% yields. The alkene substituent present in substrates **5m**–**5n** was not reduced by DIBAL-H under the catalytic reaction conditions, affording alkene-substituted allenes **6m**–**6n** in 51–84% yields. These results demonstrate that the current methodology is a highly efficient and selective route to prepare a broad range of functionalized allenes.

The findings shown in Scheme 3 reveal that, under the present copper catalytic conditions, complete chirality transfer of enantiomerically enriched propargylic chlorides proceeds to provide axially chiral allenes. When propargylic chlorides **7a** and **7b** substituted with a chiral 2,2-dimethyl-1,3-dioxolane group were treated with DIBAL-H, Cu-catalyzed anti-S_N2' substitution occurred to afford the corresponding chiral allenes **8a** and **8b**[14] with the same diastereomeric ratios (dr) of >98:<2 and 5:1, respectively, as the starting materials. In addition, the central chirality of optically pure (*S*)-chloride **9** was transferred to the axial chirality of allene **10**,[15] showing anti-S_N2' stereoselectivity with a >98:<2 enantiomeric ratio (er).[4]

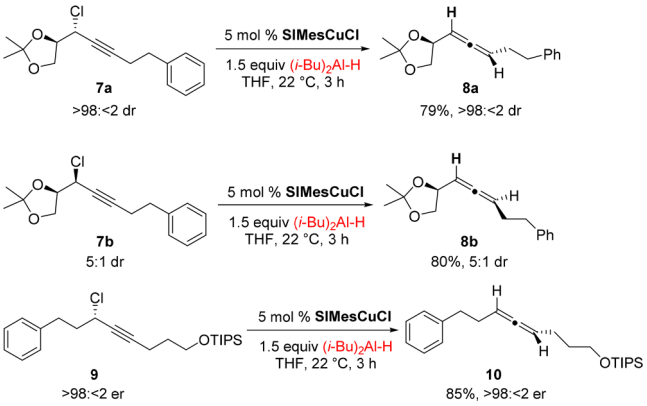
In conclusion, we have described the use of DIBAL-H as a hydride nucleophile in highly regio- and stereoselective Cu-catalyzed S_N2' reductions of propargylic chlorides to synthesize a wide range of new and versatile functionalized allenes in good to excellent yields. The reaction was promoted by an NHC ligand and proceeded with complete chirality transfer to provide optically active allenes. The importance and practicality of this current methodology are highlighted by the high efficiency and stereoselectivity, the simple and mild reaction conditions, the broad substrate scope, the synthetic potential of the functionalized allenes, and the new possibility of readily available and inexpensive DIBAL-H as a substitute for hydrosilanes, which have been the main hydride source used for CuH catalysis. Further study will focus on applying aluminum hydrides to other types of CuH catalysis.

Scheme 2. Cu-Catalyzed Propargylic Reduction with Disubstituted Propargylic Chlorides[a,b]



[a]Reaction conditions: propargylic chloride **5** (0.30 mmol), DIBAL-H (0.45 mmol), **SIMesCuCl** (5 mol %), THF (0.2 M) under N_2. In all cases, >95:<5 regioselectivity. [b]Yields of the isolated products. [c]Reaction time was 12 h.

Scheme 3. Synthesis of Chiral Allenes



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02413.

Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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