

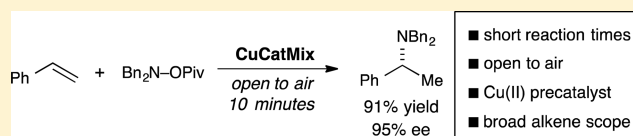
Mechanistic Studies Lead to Dramatically Improved Reaction Conditions for the Cu-Catalyzed Asymmetric Hydroamination of Olefins

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S Supporting Information

ABSTRACT: Enantioselective copper(I) hydride (CuH)-catalyzed hydroamination has undergone significant development over the past several years. To gain a general understanding of the factors governing these reactions, kinetic and spectroscopic studies were performed on the CuH-catalyzed hydroamination of styrene. Reaction profile analysis, rate order assessment, and Hammett studies indicate that the turnover-limiting step is regeneration of the CuH catalyst by reaction with a silane, with a phosphine-ligated copper(I) benzoate as the catalyst resting state. Spectroscopic, electrospray ionization mass spectrometry, and nonlinear effect studies are consistent with a monomeric active catalyst. With this insight, targeted reagent optimization led to the development of an operationally simple setup (ligated copper(II) precatalyst, open to air) and short reaction times (<30 min). This improved protocol is amenable to a diverse range of alkene and alkyne substrate classes.



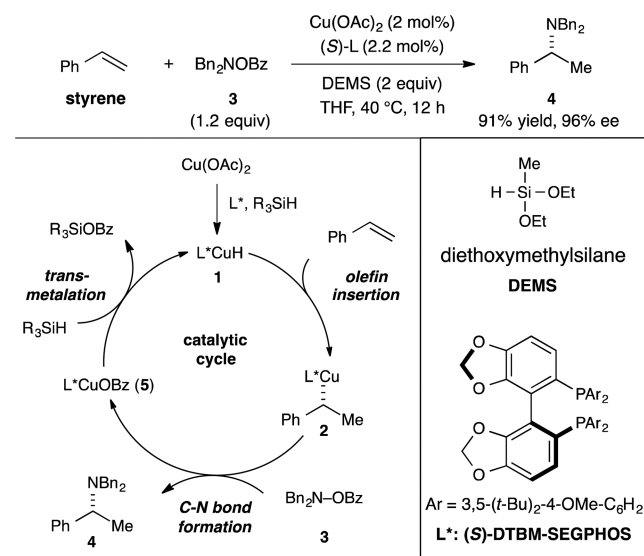
- short reaction times
- open to air
- Cu(II) precatalyst
- broad alkene scope

INTRODUCTION

Due to their importance and ubiquity, significant efforts have been made toward the construction of enantioenriched amines.¹ Hydroamination, the formal addition of a nitrogen and hydrogen atom across a carbon–carbon π -bond, represents a particularly attractive and direct method for appending amino groups onto a molecule. Although significant progress has been achieved in this regard using late transition metal catalysis, a number of drawbacks have limited the utilization of these methodologies.² In the context of intermolecular hydroamination, these methods furnish products with moderate stereoselectivity and rely on the use of activated alkenes, such as vinyl arenes and acrylate derivatives, while unactivated alkenes typically fail to react. Similarly, lanthanide and early transition metal catalysts have shown promise as hydroamination systems although further developments are needed to address the generally limited substrate scope.³ The development of a general approach for regio- and enantioselective hydroamination of a broad range of alkene classes remains an important challenge.⁴ In 2013, Miura's⁵ and our lab⁶ disclosed contemporaneous reports describing a new method of styrene hydroamination that involves a copper(I) hydride (CuH) catalyst and amine electrophiles to generate α -chiral amines in excellent yields and enantioselectivities. Since then, CuH-catalyzed hydroamination has been extended to a wide scope of substrate classes, including vinyl silanes, terminal alkenes, internal unactivated alkenes, alkynes, and strained cyclic alkenes.^{7,8}

A general catalytic cycle for the hydroamination of styrene is shown in Scheme 1. Formation of the phosphine-ligated CuH catalyst (L^*CuH , **1**) occurs from the combination of $\text{Cu}(\text{OAc})_2$, a phosphine ligand, and silane. Olefin insertion

Scheme 1. Proposed Catalytic Cycle for CuH-Catalyzed Hydroamination of Styrene



into L^*CuH **1** presumably forms copper(I) alkyl species **2**. Interception of **2** by amine electrophile **3** generates chiral amine **4** and phosphine-ligated copper(I) benzoate (L^*CuOBz , **5**). Regeneration of L^*CuH **1** from L^*CuOBz complex **5** closes the catalytic cycle.

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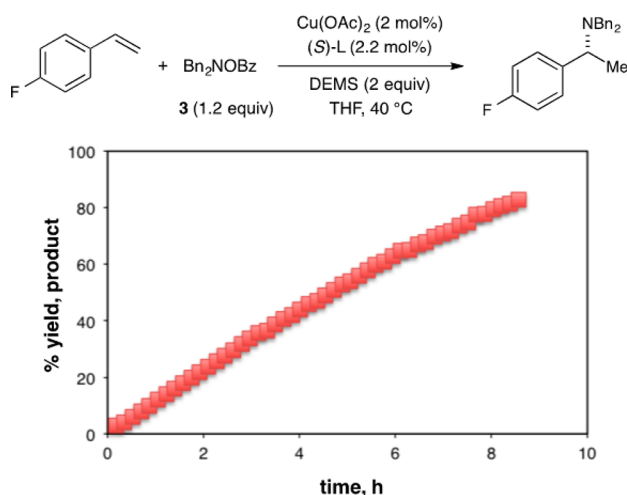
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Given that this CuH-catalyzed hydroamination strategy has undergone rapid development in terms of substrate scope, we felt a general understanding and improvement of these processes would be welcomed. In particular, identification of the turnover-limiting step and resting state of the copper catalyst might provide a foundation for the development of a more efficient and practical protocol. Herein, we report detailed kinetic and spectroscopic studies of the CuH-catalyzed hydroamination of styrene. These studies have provided evidence that the phosphine-ligated CuOBz complex **5** is the resting state of the catalyst and the turnover-limiting step entails regeneration of the CuH catalyst via its reaction with a silane reagent. Through this mechanistic insight, rational optimization of several parameters has led to short reaction times (<30 min) and operational simplicity (simple copper(II) precatalyst and open to air) for an array of olefin and alkene substrates. Similarly, a separate modified protocol is amenable to the use of low loadings of the chiral ligand (0.1–0.2 mol%). This is important as it is the most expensive component of this catalyst system.

RESULTS AND DISCUSSION

Mechanistic Studies of the CuH-Catalyzed Hydroamination of Styrene. The hydroamination of styrenes was chosen as the model system for our detailed kinetic studies. To begin, the reaction profile for the hydroamination of 4-fluorostyrene was studied. In our initial report, we detailed a reaction time of 36 h to give the desired product in 86% yield and 97% ee.⁶ Using *in situ* ¹⁹F NMR spectroscopy, the reaction, under the previously reported conditions, was found to be complete in approximately 9 h. Moreover, the process appeared to be overall zero-order in substrate (Scheme 2).⁹ Same-excess

Scheme 2. Reaction Progress Monitored by *in Situ* ¹⁹F NMR^a



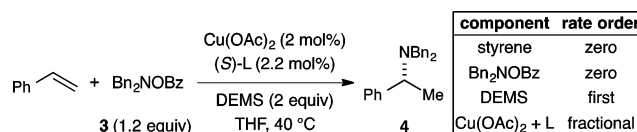
^aL = DTBM-SEGPHOS; 1 equiv of 1-fluoronaphthalene added as internal standard.

experiments¹⁰ were also conducted and displayed a similar reaction profile, indicating that catalyst deactivation and product inhibition were not significant in this system (see Supporting Information for details).

Initial rate experiments were next performed with styrene and amine electrophile **3** to gather more detailed information about the catalytic cycle of this hydroamination process

(Scheme 3). Corroborating our full kinetic analysis, initial-rate kinetics demonstrated that the reaction was zero-order in

Scheme 3. Model System Used for Initial-Rate Kinetics Determined by GC Analysis and the Observed Rate Orders^a



^aL = DTBM-SEGPHOS.

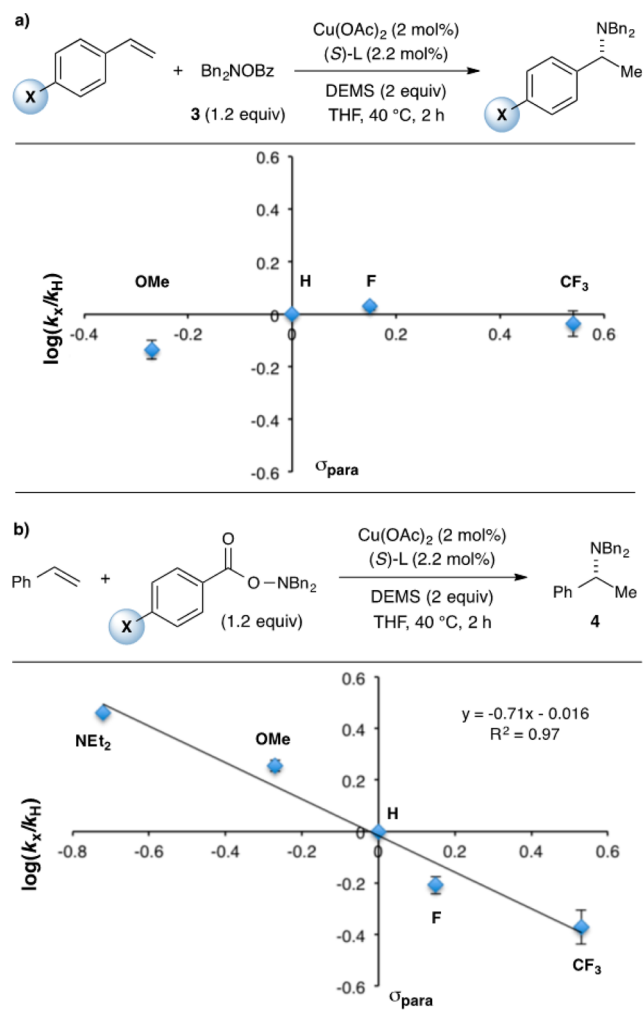
styrene and amine electrophile **3** across a range of concentrations for each component. In addition, a clear first-order dependence was observed for diethoxymethylsilane (DEMS) and an apparent fractional-order¹¹ was observed while simultaneously changing the concentration of Cu(OAc)₂ and DTBM-SEGPHOS.

Hammett studies were conducted to determine the impact that electronic variation of the styrene and the amine electrophile components had on the rate of hydroamination.¹² In the first Hammett study, a series of *para*-substituted styrenes reacted with amine electrophile **3** at similar rates (Scheme 4a), implying that the olefin is most likely not involved in the turnover-limiting step of this process. A second Hammett study showed that electronic variation of the amine electrophile had a significant impact on the rate of styrene hydroamination (Scheme 4b). A linear correlation was observed with σ_{para} Hammett constants ($\rho = -0.71$, $R^2 = 0.97$) indicating more electron rich amine-*O*-benzoates led to increased reaction rates.¹³

The observations described above suggested that regeneration of the CuH catalyst **1** from the presumed ligated CuOBz complex **5** and silane is the turnover-limiting step of the CuH-catalyzed hydroamination process (Scheme 1).¹⁴ This interpretation is supported by (a) the zero-order dependence on styrene and amine electrophile; (b) the first-order dependence on the silane, DEMS; and (c) the linear free energy relationship between the Hammett electronic parameter of the amine electrophile benzoate and the initial rate. The enhanced initial rates observed with more electron-rich benzoates is consistent with a faster transmetalation of phosphine-ligated CuOBz complex **5** with silane. Interestingly, independent initial-rate measurements collected with diphenylsilane and deuterio-diphenylsilane (Ph₂SiD₂) of the model reaction did not show a measurable kinetic isotope effect (KIE) ($k_{\text{H}}/k_{\text{D}} = 1.06 \pm 0.10$).¹⁵

The fractional order dependence observed while manipulating [Cu(OAc)₂] and [DTBM-SEGPHOS] inspired a closer examination of the active catalytic species. A series of studies were employed to investigate the possible nature of the copper catalyst in the CuH-catalyzed hydroamination of styrene. Historically, CuH complexes with sterically unencumbered ligands have been isolated as higher-order species and aggregates.^{16–19} Our initial ³¹P NMR studies on the CuH catalyst solution (Cu(OAc)₂, (S)-DTBM-SEGPHOS, and DEMS in THF)²⁰ did not allow identification of a distinct CuH species. However, the major new species observed in the spectrum does have a similar ³¹P NMR shift and peak shape attributed to phosphine-ligated CuH clusters reported in the literature.²¹ When this CuH solution was subjected to the model hydroamination reaction, ³¹P NMR showed that a new

Scheme 4. (a) Hammett Study with Para-Substituted Styrenes; (b) Hammett Study with Para-Substituted Amine-O-benzoates^a



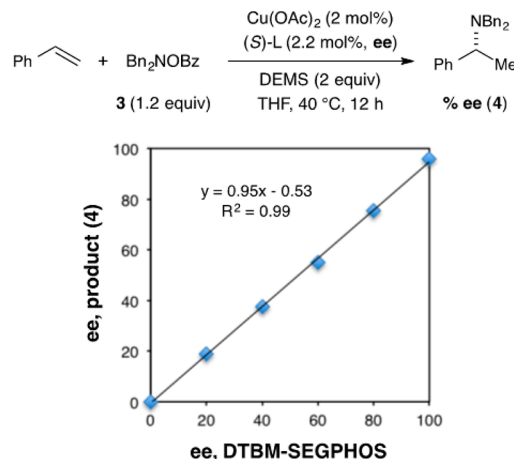
^aEach data point is the average of two experiments with standard deviations included as error bars; L = DTBM-SEGPHOS.

species attributed to LCuOBz **5** accounts for the majority of the ligated species observed. The assignment of LCuOBz **5** is supported by its independent preparation. These observations are consistent with intermediate **5** acting as the catalyst resting state prior to the turnover-limiting step of the hydroamination reaction. Surprisingly, approximately 50% of the DTBM-SEGPHOS ligand remains unbound throughout the course of the reaction. Additional details and a discussion of these experiments are provided in the [Supporting Information](#). Efforts toward isolation and characterization of discrete copper(I) intermediates are ongoing.

Electrospray ionization mass spectrometric (ESI-MS) analysis of aliquots taken from the purported CuH mixture gave major peaks that are attributed to a monomeric DTBM-SEGPHOS-bound copper(I) species and the unbound DTBM-SEGPHOS ligand (see [Supporting Information](#) for details). A CuH cluster or copper aggregate could readily decompose on ionization and cannot be ruled out with these experiments. Nonlinear effect studies on the enantiomeric composition of the chiral ligand and amine product indicated a linear relationship (see [Scheme 5](#)). These results are consistent with

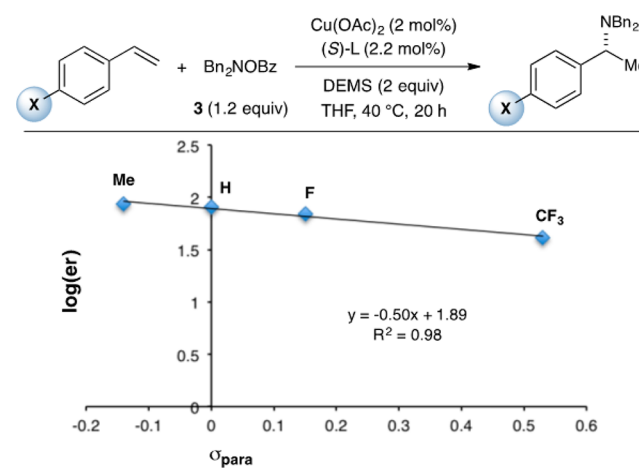
an active catalyst being of a monomeric nature; however, we cannot exclude the possibility that higher order species are involved.^{22–24}

Scheme 5. Nonlinear Effect Study on the Enantiomeric Composition of DTBM-SEGPHOS and Amine Product **4**



We next sought to identify the enantioselectivity-determining step (EDS) of the styrene hydroamination reaction. To this end, we searched for linear free energy relationships (LFERs) between substrate Hammett electronic parameters and the observed enantioselectivities for a variety of para-substituted styrenes.^{25,26} A linear relationship was observed with para-substituted styrenes as enantioselectivity decreased with the introduction of electron-withdrawing substituents ($\rho = -0.50$, $R^2 = 0.98$, [Scheme 6](#)): 98% ee and 95% ee were observed for 4-

Scheme 6. Hammett Plot for the Enantiomeric Ratio of Hydroamination Products Using Para-Substituted Styrenes^a



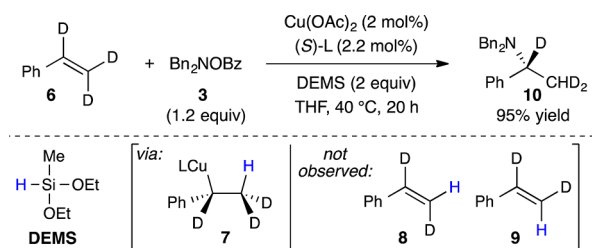
^aer = enantiomeric ratio; L = DTBM-SEGPHOS.

methylstyrene ($\sigma_p = -0.14$) and 4-(trifluoromethyl)styrene ($\sigma_p = 0.53$), respectively.^{13,27} In contrast, a linear free energy relationship was not observed between the electronic nature of the amine electrophile (varying the para-substituent of the benzoate of the amine-O-benzoate) and the enantioselectivity of the product (see [Supporting Information](#) for details). Additionally, the identity of the silane did not appear to affect the enantioselectivity of the process. Taken together, these

results indicate that hydrocupration is most likely the enantio-determining step.

We expected hydrocupration to be irreversible since it appears to be the enantio-determining step and occurs before the rate-determining step.²⁸ To provide further support that hydrocupration is enantiodetermining, styrene- α,β,β - d_3 (**6**) was subjected to the standard hydroamination conditions using DEMS as the hydride source. If hydrocupration is reversible due to β -hydride elimination of copper(I) alkyl **7**, then isotopic isomers **8** and **9** should be observed throughout the reaction due to potential β -deuteride elimination.²⁹ The reaction was monitored by ^1H NMR spectroscopy and no signals attributable to olefinic protons were observed throughout the course of the reaction, indicating that β -deuteride elimination did not occur. Further, we would expect to see some proportion of **10** containing only two deuteria. In fact, a single isotopic product **10** was isolated from the crude reaction mixture (Scheme 7). Taken together, these results strongly

Scheme 7. Hydroamination of Styrene- α,β,β - d_3 (**6**) under Standard Reaction Conditions^a



^aReaction monitored by ^1H NMR spectroscopy. L = DTBM-SEGPHOS.

support the notion that hydrocupration is irreversible.³⁰ In addition, these results are consistent with previous reports that β -hydride elimination most likely does not occur during the CuH-catalyzed hydrosilylation of ketones.^{11,31}

Rational Optimization of Hydroamination Reagents.

With a good understanding of the factors controlling the rate and selectivity of this CuH-catalyzed hydroamination process, we next turned our attention to improving the overall efficiency of the reaction. We focused our efforts on the identity of the silane and amine electrophile components since these appear to be directly involved in the rate-determining step. Importantly, we expected to be able to increase the overall rate of hydroamination without significantly diminishing the enantio-selectivity of the reaction since the rate- and enantio-determining steps are presumed to be separate processes. The independent and rational optimization of these components is described below.³²

Table 1 shows the observed initial rates of hydroamination using a variety of readily available silanes. Most notably, with the use of dimethoxymethylsilane (DMMS), a 3-fold initial-rate enhancement was observed relative to DEMS (entries 1 and 2). Employing other siloxanes, such as 1,1,2,2-tetramethyldisiloxane and PMHS, resulted in lower reaction rates (entries 3 and 4). The use of diphenylsilane provided product, whereas trialkylsilanes, such as triethylsilane, were ineffective hydride sources (entries 5 and 6). Due to safety concerns, trialkoxysilanes were not investigated.³³ In terms of performance and practicality, DMMS was chosen as the optimal silane among those that we examined.³⁴

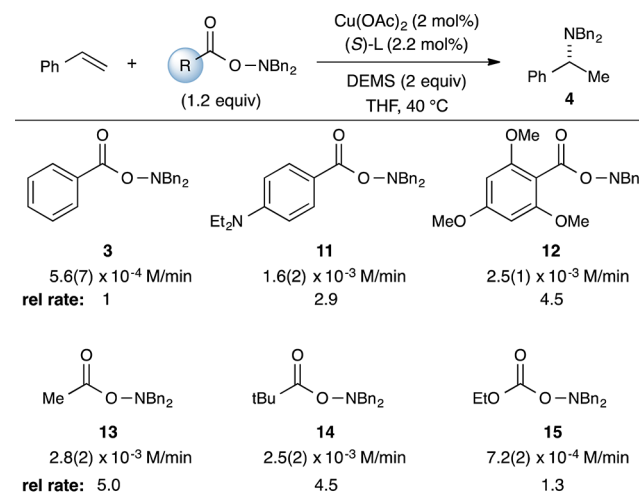
Table 1. Effect of Silane on Initial-Rate Measurements^a

entry	silane	rate (M/min)	rel rate
1	HSiMe(OEt) ₂	$5.6(3) \times 10^{-4}$	1
2	HSiMe(OMe) ₂	$1.8(1) \times 10^{-3}$	3.1
3	(HMe ₂ Si) ₂ O	$3.1(4) \times 10^{-4}$	0.6
4	PMHS	$1.9(1) \times 10^{-4}$	0.3
5	Ph ₂ SiH ₂	$1.3(4) \times 10^{-3}$	2.3
6	Et ₃ SiH	nr ^b	—

^aL = DTBM-SEGPHOS. ^bNo reaction.

As noted earlier, the electronic nature of the amine electrophile dramatically affected the initial rate of the hydroamination reaction, which is believed to influence the regeneration of the CuH catalyst from copper(I) benzoate intermediate **5** (Scheme 4b). For example, use of amine electrophile **11**, bearing a 4-diethylaminobenzoate group, led to a 3-fold rate enhancement compared to amine **3** with an unsubstituted benzoate group (Scheme 8). This rate enhance-

Scheme 8. Effect of Amine Electrophile on Initial-Rate Kinetics^a



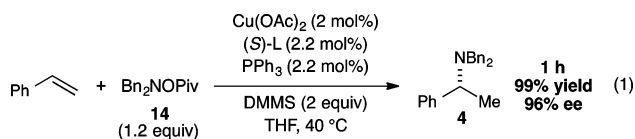
^aL = DTBM-SEGPHOS.

ment could be increased further by using 2,4,6-trimethoxybenzoate (**12**), acetate (**13**) or pivalate (**14**) bearing amine electrophiles (initial-rates $(2.5\text{--}2.8) \times 10^{-3}$ M/min). We selected the pivalate-appended oxidant (**14**) as the optimal amine electrophile due to its accessibility and long-term stability.³⁵ An amine electrophile featuring a carbonate (**15**), which could potentially decarboxylate to access a copper alkoxide intermediate, was found to provide a comparable rate of reaction to amine electrophile **3**.

Lipshutz has reported that secondary ligands, such as PPh₃, can be employed in CuH catalysis to lower catalyst loadings and improve overall reactivity for certain systems.³⁶ Addition of 2.2 mol % PPh₃ to our model system did indeed result in a slight rate enhancement (1.2-fold increase), but higher loadings of PPh₃ did not result in any further increase in reaction rate. Testing the addition of other achiral phosphine additives led

only to slightly increased reaction rates and variable levels of enantioselectivity (see [Supporting Information](#) for details).

By employing the optimized reagents, *N,N*-dibenzyl-*O*-pivaloylhydroxylamine (**14**), DMMS, and PPh₃ additive, the hydroamination of styrene was complete in 1 h at 40 °C with a high yield and enantioselectivity (eq 1, 99% yield, 96% ee). For



comparison, our previous report detailed reaction times at 36 h at this temperature, while we found (see above) that the reaction actually required 9 h to proceed to completion. The greatly reduced reaction time suggests that the increased reaction rates observed while optimizing these reagents independently are indeed additive. Final optimization of the hydroamination protocol is described in the following section.

Optimized Protocol for a Range of Substrate Classes.

At the outset of this study, our ultimate goal was to improve the efficiency and practicality of our previously reported asymmetric hydroamination methodologies. We specifically sought to decrease the relatively long reported reaction times (24–36 h), enable lower catalyst loadings, and make reaction setup more robust and user-friendly.

To these ends, we first prepared a precomplexed copper catalyst mixture that contained Cu(OAc)₂, (*S*)-DTBM-SEGPHOS, and PPh₃ (1:1.1:1.1 ratio) that was used throughout this section (see [Supporting Information](#) for details of the preparation of this precatalyst).³⁷ This air-stable free-flowing powder rapidly dissolves in a variety of organic solvents and enables quick reaction setup. In our previous reports, the preparation of the active CuH catalyst was performed in a separate reaction flask than the one that the hydroamination reaction was carried out in and required up to 30 min for activation due to the slow complexation of Cu(OAc)₂ with DTBM-SEGPHOS ligand and subsequent reaction with DEMS. We have found that this two-pot procedure is unnecessary and instead are able to perform a simple one-pot operation in which the silane is added once all the other reagents are in solution. Traditionally, reactions that proceed through copper(I) alkyl intermediates are performed under an inert atmosphere due to their incompatibility with oxygen and moisture.³⁸ We wished to remove this constraint for as many hydroamination reactions as possible, and the reaction setups described below are carried out fully open-to-air unless otherwise noted.³⁹

After optimizing temperature and concentration parameters, we found that the CuH-catalyzed hydroamination of styrene could be completed in 10 min at 60 °C while open to the atmosphere, delivering the chiral amine product **4** in 90% isolated yield and 95% ee (entry 1, [Table 2](#)). It is worth noting that this reaction is complete in a third of the time previously required to prepare the active CuH solution and only a fraction of the 36 h total reaction time originally reported.⁶

At this point in our study, all of the hydroamination reactions described have involved unsubstituted styrenes, a relatively unhindered and reactive class of alkene. We wanted to see whether this optimized protocol would be amenable to other classes of alkenes and alkynes. [Table 2](#) highlights the broad scope of this hydroamination protocol. *Trans*- β -substituted styrenes, vinylsilanes, alkynes, and terminal alkenes all under-

Table 2. Hydroamination of Various Substrates under Optimized Protocol^a

Conditions: Bn ₂ NOpiv (1.2 equiv), CuCatMix (2 mol%), DMMS (2 equiv), THF, 60 °C, air			
Entry	Substrate	Product	
1			10 min 91% yield 95% ee
2			20 min 89% yield 98% ee
3 ^b			2 h 83% yield 96% ee
4			20 min 91% yield
5 ^b			3 h 95% yield 95% ee
6			15 min 88% yield 99% ee
7			15 min 91% yield ^c

^aCuCatMix = Cu(OAc)₂, (*S*)-DTBM-SEGPHOS, PPh₃ (1:1.1:1.1 ratio, precomplexed). ^bReaction performed under argon atmosphere. ^c¹H NMR yield.

went hydroamination in high yield in short reaction times (entries 2, 4, 6, and 7, 88%–91% yield, 98%–99% ee, 15–20 min). These results suggest that regeneration of the CuH catalyst is likely rate limiting for the hydroamination of these substrate classes. *Cis*- β -substituted styrenes and 1,1-disubstituted terminal alkenes proved to be less reactive. However, by performing the hydroamination of these substrates under an inert atmosphere, we were able to significantly decrease the previously reported reaction times of 36 h to under 4 h (entries 3 and 5).^{6,7a}

As a final demonstration of the improvements made by the new hydroamination protocol, [Table 3](#) shows that high yields

Table 3. Hydroamination of Styrene and 4-Phenyl-1-butene Using Low Loadings of (*S*)-DTBM-SEGPHOS

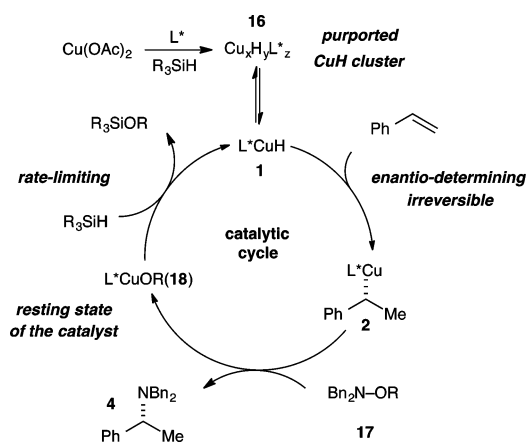
Conditions: Bn ₂ NOpiv (1.2 equiv), Cu(OAc) ₂ (2 mol%), PPh ₃ (2 mol%), DMMS (2 equiv), THF, 60 °C, N ₂ , 24 h			
Entry	(<i>S</i>)-DTBM-SEGPHOS	Substrate	Product
1	0.1 mol%		 88% yield 92% ee
2	0.2 mol%		 85% yield

were obtained when using just 0.1–0.2 mol % (*S*)-DTBM-SEGPHOS ligand in the hydroamination of styrene and 4-phenyl-1-butene. Reactions that employ low ligand loadings are more air-sensitive and require setup in an inert atmosphere glovebox with longer reaction times (24 h).

CONCLUSION

A modified and more detailed mechanistic picture is presented in [Scheme 9](#). Spectroscopic studies suggest a phosphine-ligated

Scheme 9. Modified Catalytic Cycle for the CuH-Catalyzed Hydroamination of Styrene



CuH cluster **16** is formed when $\text{Cu}(\text{OAc})_2$ is treated with silane and DTBM-SEGPHOS (**L**), although our current view is that the active catalyst is of a monomeric nature. Linear free energy relationship studies indicate that hydrocupration to form aliphatic copper(I) species **2** is the enantio-determining step in this catalytic cycle, and deuterium-labeling studies show that this step is likely irreversible. Interception of this species with amine electrophile **17** produces chiral amine **4** and phosphine-ligated copper(I) carboxylate **18**, which is the resting state of the catalyst, as shown through ESI-MS and ^{31}P NMR studies. The turnover-limiting step is regeneration of the CuH catalyst **1** from the phosphine-bound CuOR **18**.

Rate enhancement is observed with judicious choice of silane, amine electrophile, and secondary phosphine ligand additive. We have developed an efficient and optimized protocol for the hydroamination of a variety of olefins and alkynes that is insensitive to air and uses a simple copper precatalyst that incorporates DTBM-SEGPHOS, PPh_3 , and $\text{Cu}(\text{OAc})_2$. Further mechanistic work, in particular stoichiometric studies and computational investigations for the mechanism of the C–N bond formation step in this process, is in progress.⁴⁰ Last, new avenues for asymmetric olefin functionalization through CuH catalysis are also under development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10219.

Experimental procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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