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A Modified System for the Synthesis of Enantioenriched *N*-Arylamines through Copper-Catalyzed Hydroamination

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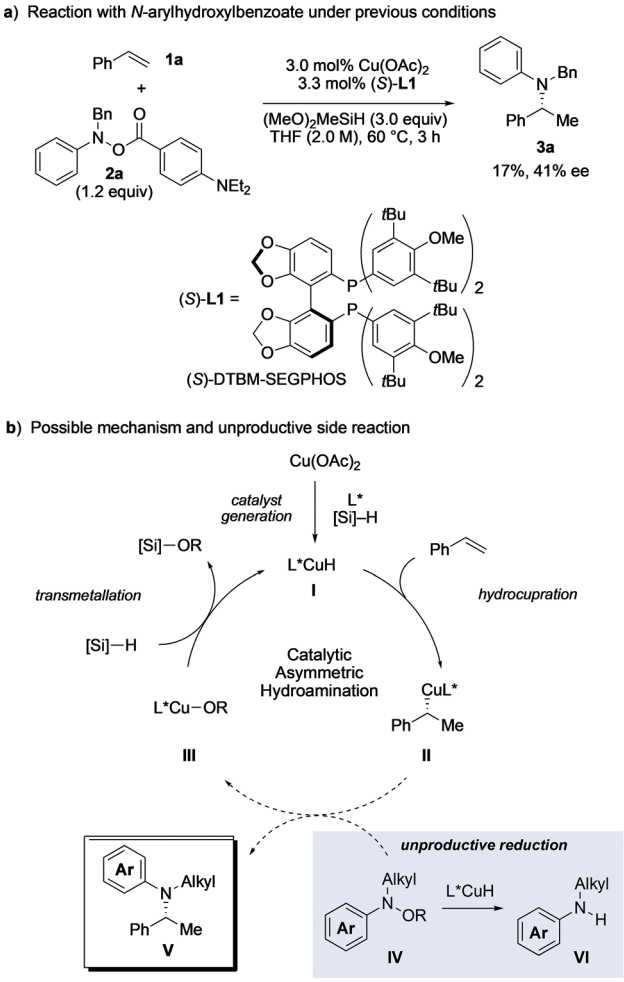
Abstract: *Despite significant recent progress in copper-catalyzed enantioselective hydroamination chemistry, the synthesis of chiral N-arylamines, which are frequently found in natural products and pharmaceuticals, has not been realized. Initial experiments with N-arylhydroxylamine ester electrophiles were unsuccessful and, instead, their reduction in the presence of copper hydride (CuH) catalysts was observed. Herein, we report key modifications to our previously reported hydroamination methods that lead to broadly applicable conditions for the enantioselective net addition of secondary anilines across the double bond of styrenes, 1,1-disubstituted olefins, and terminal alkenes. NMR studies suggest that suppression of the undesired reduction pathway is the basis for the dramatic improvements in yield under the reported method.*

Enantiomerically enriched *N*-arylamines are important synthetic targets in organic chemistry due to their prevalence in a variety of pharmaceuticals, agrochemicals, and functional materials.[1] Consequently, their synthesis has been actively investigated over the past few decades, leading to the development of a number of useful approaches, including the addition of nucleophiles to imines,[2] reductive amination,[3] and late-transition-metal-catalyzed hydroamination.[4] In particular, the enantioselective hydroamination of alkenes and alkynes has received considerable attention due to the conceptual simplicity of this method, although the substrate scope is quite limited.

The use of copper hydride (LCuH) catalysts has recently been demonstrated as a useful approach for the synthesis of chiral secondary and tertiary alkylamines.[5] In reactions using these catalysts, an alkylcopper intermediate, generated through hydrocupration of an alkene, reacts with a *N*-alkylhydroxylamine ester to furnish the amine product. *N*-alkylhydroxylamine esters have previously been employed by several research groups as electrophilic nitrogen sources in transition-metal-catalyzed processes.[6–8] In contrast, to the best of our knowledge, *N*-arylhydroxylamine esters have not been used in these transformations. The extension of the copper-catalyzed asymmetric hydroamination reaction to these electrophilic amine reagents would provide a versatile and flexible approach for the preparation of α-chiral arylamines.

In light of our previous studies,[9] we began our investigation by exploring the reactivity of *N*-arylhydroxylamine esters using styrene as the model substrate, (*S*)-DTBM-SEGPHOS/$Cu(OAc)_2$ as the precatalyst, and $(MeO)_2MeSiH$[10] as the stoichiometric reductant. We chose to employ the 4-diethylaminobenzoate ester of phenylbenzylhydroxylamine (**2a**) as the electrophilic amine source. In the case of aliphatic amines, reagents bearing this modified leaving group were found to possess better stability and enhanced reactivity relative to the benzoate esters (Scheme 1a).[9e,f] Under these conditions, a small amount of the desired product **3a** (17%) was formed in a moderately enantioselective manner (41% *ee*; Scheme 1a). A significant amount of *N*-



Scheme 1. Initial result of the copper-catalyzed hydroamination of styrene **1a** with *N*-arylhydroxylamine ester **2a**.

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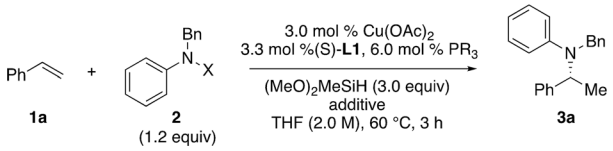
benzylaniline was also formed through reductive cleavage of the N–O bond of **2a** (Scheme 1b).

To improve upon this result, we conducted an extensive evaluation of reaction conditions and additives (Table 1). We found that the addition of a catalytic amount of PPh_3 as a secondary ligand[11] led to a dramatic and unexpected enhancement in yield and enantioselectivity (71% yield, 87% *ee*, entry 1). A non-chiral HCu-PPh_3 species is presumably generated and does not compete with the desired hydroamination catalyzed by the DTBM-SEGPHOS-bound copper species.[11] Further improvements were made by adding a stoichiometric amount of *t*BuOH (1 equiv).[12] In this way, **3a** was obtained in high yield and with a high level of enantiomeric purity (97% yield, 91% *ee*, entry 2). The inclusion of both PPh_3 and *t*BuOH were necessary to achieve these results (entry 3). The use of other phosphines as additives resulted in considerably lower yields and/or enantioselectivity (entries 4–6), while the inclusion of other alcohols lowered the yield of **3a** (entry 7). Alkoxides, such as LiO*t*Bu, were also investigated and were less effective compared to *t*BuOH (entries 8–10). A number of electrophilic amine reagents with different leaving groups also provided the desired product with slightly lower levels of enantioselectivity (entries 11–13).

Table 1: Reaction Optimization.[a,b,c]



Entry	X	PR_3	Additive	Yield [%][b]	*ee* [%][c]
1	$OC(O)C_6H_4NEt_2$	PPh_3	none	71	87
2	$OC(O)C_6H_4NEt_2$	PPh_3	*t*BuOH	97	91
3	$OC(O)C_6H_4NEt_2$	none	*t*BuOH	39	82
4	$OC(O)C_6H_4NEt_2$	PCy_3	*t*BuOH	45	30
5	$OC(O)C_6H_4NEt_2$	$PCyPh_2$	*t*BuOH	81	80
6	$OC(O)C_6H_4NEt_2$	$P(2\text{-anisyl})_2Ph$	*t*BuOH	77	89
7	$OC(O)C_6H_4NEt_2$	PPh_3	*i*PrOH	48	92
8	$OC(O)C_6H_4NEt_2$	PPh_3	LiO*t*Bu	76	87
9	$OC(O)C_6H_4NEt_2$	PPh_3	NaO*t*Bu	19	89
10	$OC(O)C_6H_4NEt_2$	PPh_3	$Mg(OtBu)_2$	62	86
11	OAc	PPh_3	*t*BuOH	88	84
12	OPiv	PPh_3	*t*BuOH	88	84
13	$OC(O)1,3\text{-}OMeC_6H_3$	PPh_3	*t*BuOH	95	88

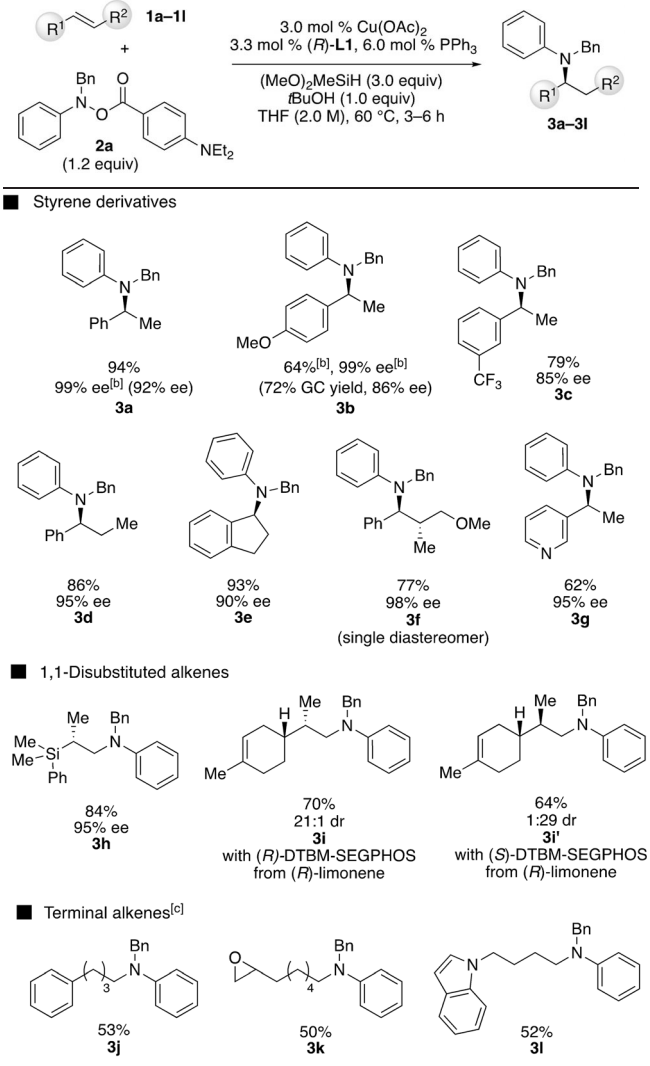
[a] Reaction conditions: 0.2 mmol **1a** (1.0 equiv), **2** (1.2 equiv), $Cu(OAc)_2$ (3.0 mol%), (*S*)-DTBM-SEGPHOS (3.3 mol%), PR_3 (6.0 mol%), additive (1.0 equiv), $(MeO)_2MeSiH$ (3.0 equiv) in THF (0.1 mL) at 60°C; see the Supporting Information for details. [b] The yield was determined by GC analysis using *n*-dodecane as an internal standard. [c] The enantioselectivity was determined by chiral HPLC analysis.

With optimized conditions in hand, we sought to explore the substrate scope of this asymmetric hydroamination process. A variety of olefins could be effectively transformed into the corresponding enantiomerically enriched amines in good to excellent yields (Table 2). Products from styrene (**1a**) as well as from styrenes bearing both electron-donating (**1b**) and electron-withdrawing (**1c**) ring substituents were competent coupling partners using this method. Furthermore, the reaction could be applied to *trans*-β-substituted (**1d**) and *cis*-β-substituted (**1e**) styrenes, hindered β,β-disubstituted styrenes (**1f**), and 1,1-disubstituted alkenes (**1h**). Both *cis*- and *trans*-β-substituted olefins yielded the corresponding products in similar yields and in a stereoselective manner as we previously reported.[9a] Moreover, the reaction with 3-vinylpyridine provided **3g** in an efficient manner. The catalyst system also achieved high levels of diastereoselectivity in the hydroamination of (*R*)-limonene (**3i**, **3i′**). Terminal alkenes (**1j**–**1l**), which are relatively less reactive compared to styrene derivatives, were also competent substrates and gave the desired products in moderate yield under the reaction conditions. This method tolerated terminal alkenes containing a terminal epoxide (**1k**) and an indole (**1l**)

We also surveyed the scope with respect to *N*-arylamine benzoate electrophiles (**2b**–**2j**; Table 3). Electron-poor substituents on the aryl ring of the amine electrophile, including a trifluoromethyl group (**2b**), a fluorine (**2c**), and an ester (**2d**), were compatible with our method. Additionally, those containing an aryl chloride (**2e**) and bromide (**2f**) were suitable substrates for this process. Unfortunately, we were unable to prepare amine electrophiles in which the aryl group of the aniline had electron-donating substituents, such as a methoxy group.[13,14] Substrates bearing heterocycles, including a pyridine (**2c**) and a thiophene (**2g**), were successfully converted into the desired products. Additionally, using arylhydroxylamine esters with primary (**2h**) and cyclic secondary (**2i**) alkyl groups or an allyl group (**2j**) led to good results. We also examined the reaction in the presence of a TIPS-protected propargyl substrate and 1-methyl-1*H*-imidazole. In the former case, the reaction proceeded well, and the latter case, no product was formed (see the Supporting Information for details).

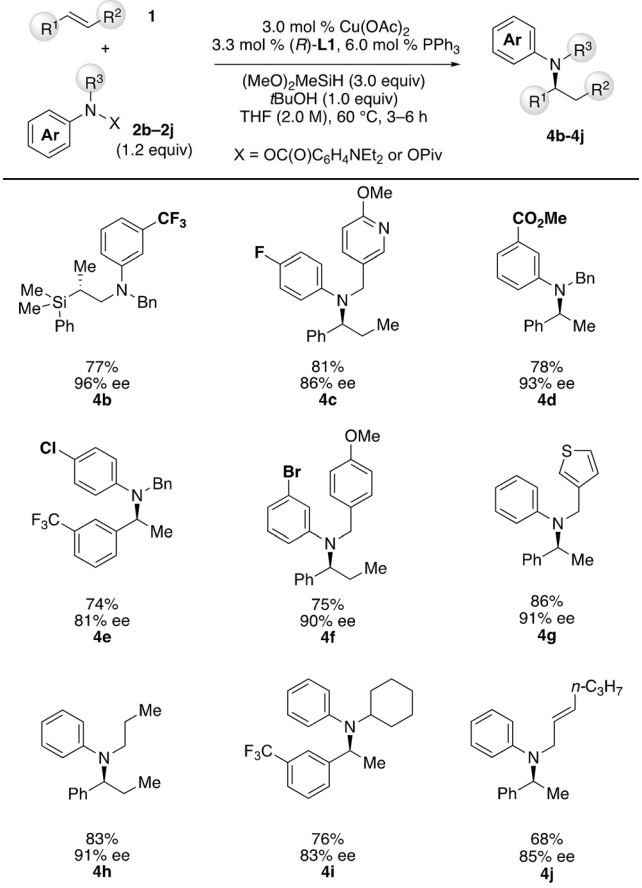
Next, we were interested in ascertaining the origin of the beneficial effect of adding *t*BuOH and PPh_3 to the reaction mixture. We suspected that these additives attenuate the unproductive reduction of the hydroxylamine ester reagent. *N*-arylhydroxylamine ester **2a** was treated with solutions of $(MeO)_2MeSiH$ and copper catalyst in $[D_8]$THF either with or without *t*BuOH/PPh_3, and the consumption of **2a** was monitored by ^1H NMR spectroscopy (Figure 1).[15] We found that if the amount of added PPh_3 was kept constant, the addition of *t*BuOH resulted in significantly slower consumption of **2a**. The same trend was observed when comparing the presence and absence of PPh_3 while the amount of added *t*BuOH was kept constant. We speculate that the degradation pattern in the presence of *t*BuOH without PPh_3 resulted from the fact that *t*BuOH was consumed before the reduction of **2a** proceeded (see the Supporting Information for details). Taken together, these data suggest that both additives play an important role in suppressing the undesired reduction of the hydroxylamine ester, **2**. With both additives, less than 10% of **2** was consumed over 1 hour. In comparison, when

Table 2: Scope with respect to olefins.[a,b]



[a] Reaction conditions: 0.5 mmol olefin (1.0 equiv), **2a** (1.2 equiv), $Cu(OAc)_2$ (3.0 mol%), (*R*)-DTBM-SEGPHOS (3.3 mol%), PPh_3 (6.0 mol%), *t*BuOH (1.0 equiv), $(MeO)_2MeSiH$ (3.0 equiv) in THF (0.25 mL) at 60°C; see the Supporting Information for details. [b] After recrystallization. [c] (±)-DTBM-SEGPHOS was used. Both starting materials were fully converted after the reaction time.

Table 3: Scope with respect to *N*-arylamine benzoate electrophiles.[a,b]



[a] Reaction conditions: 0.5 mmol olefin (1.0 equiv), *N*-arylamine benzoate (1.2 equiv), $Cu(OAc)_2$ (3.0 mol%), (*R*)-DTBM-SEGPHOS (3.3 mol%), PPh_3 (6.0 mol% equiv), *t*BuOH (1.0 equiv), $(MeO)_2MeSiH$ (3.0 equiv) in THF (0.25 mL) at 60°C; see the Supporting Information for details. [b] *N*-arylamine benzoate electrophiles bearing *ortho* substituents on the aryl ring did not give products.

either additive was omitted, less than 10% of the **2** remained after 50 minutes.

Additionally, we monitored the CuH-catalyzed hydroamination of styrene using **2a** in the presence or absence of *t*BuOH/PPh_3 through ^1H NMR spectroscopy. We observed that the reaction rate was also significantly enhanced by the addition of *t*BuOH/PPh_3 (Figure 2), which is consistent with the previously proposed[12,16] role of *t*BuOH and PPh_3 in promoting turnover of the catalyst. It is also possible that PPh_3 prevents the coordination of amine electrophiles to LCuH, thereby helping to suppress its undesired reduction.

In summary, we have developed a copper-catalyzed hydroamination of alkenes with arylamine *O*-benzoates for the preparation of enantioenriched tertiary arylamines. The use of *t*BuOH, in conjunction with a catalytic amount of PPh_3, was critical for enabling the use of *N*-arylhydroxylamine esters as the electrophilic nitrogen source. This method was successfully applied to the synthesis of α- and β-chiral arylamines with a variety of functional groups from a diverse range of olefin substrate classes.

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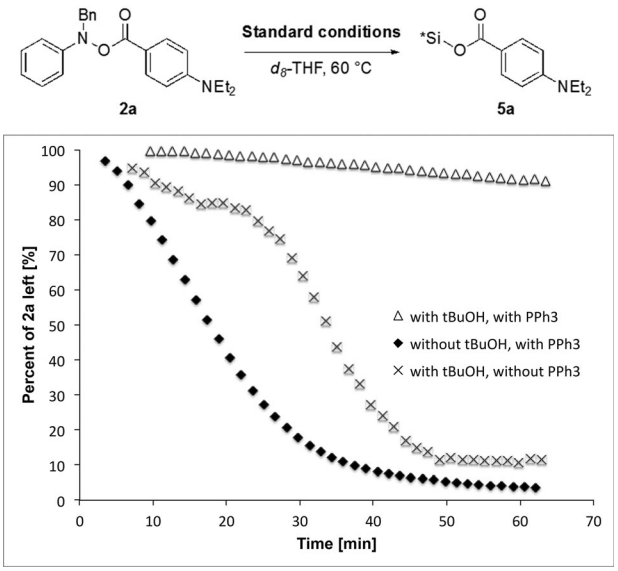

Figure 1. Relative rates of the reactions between LCuH and **2a**. Si* = $Si(OMe)_2Me$. Standard conditions: 0.4 mmol **2a** (1.0 equiv), $Cu(OAc)_2$ (5.0 mol%), (*R*)-DTBM-SEGPHOS (5.5 mol%), PPh_3 (10.0 mol%), *t*BuOH (1.0 equiv), $(MeO)_2MeSiH$ (3.0 equiv), and $[D_8]$THF (0.53 mL). The progress of these reactions was monitored at 60 °C by ^{1}H NMR spectroscopy.

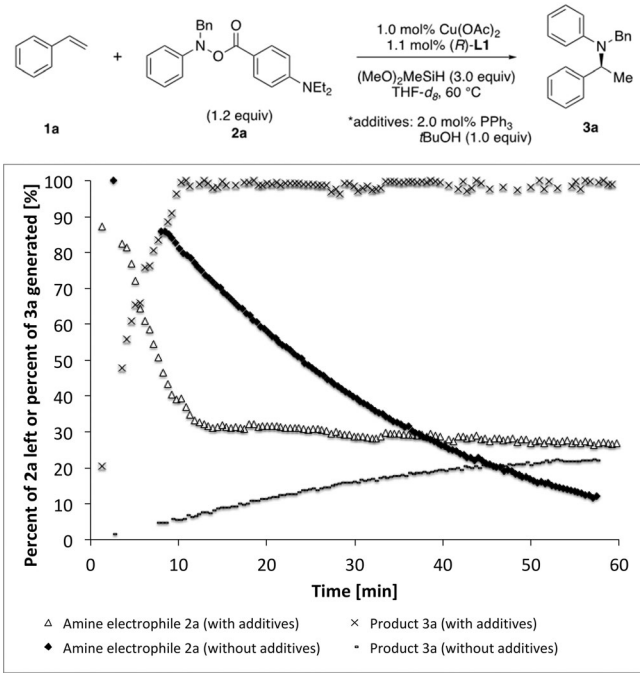

Figure 2. Reaction enhancement by the addition of *t*BuOH and PPh_3.

Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis · copper · homogeneous catalysis · hydroamination · *N*-arylamines

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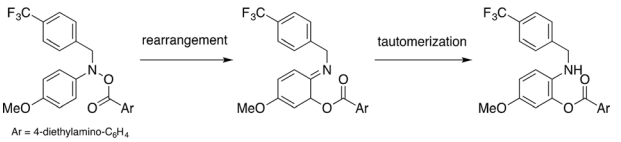
[13] Instead, a rearrangement product was observed, which we speculated was formed through either a [3,3]-sigmatropic rearrangement process or an ion-pair mechanism.



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[15] Formation of PhBnNH and the corresponding silylated benzoyl ester could be detected by GC/MS and ^{1}H NMR spectroscopy.

[16] We speculate that *t*BuOH promoted the catalyst turnover from LCuOR species **III** to LCuH **I** instead of protonating the chiral alkyl copper intermediate **II**, to give the reduced styrene.

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Communications

Asymmetric Catalysis

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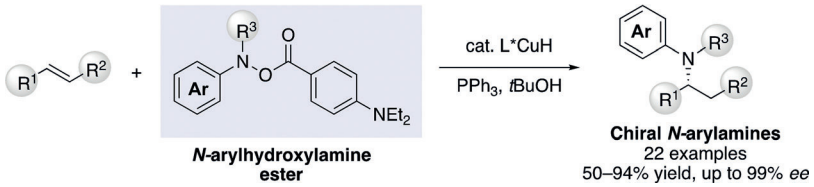
A Modified System for the Synthesis of Enantioenriched *N*-Arylamines through Copper-Catalyzed Hydroamination



Winds of change: An efficient method for the preparation of enantioenriched *N*-arylamines was developed by making key modifications to a previously reported hydroamination. The reaction is mediated by a copper(I)-hydride (CuH) catalyst, and wide range of olefins and *N*-arylhydroxylamines are compatible under the optimized conditions. Key to the successful development of this method was the addition of *t*BuOH and PPh_3 to the reaction mixture.