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Enantio- and Regioselective CuH-Catalyzed Hydroamination of Alkenes

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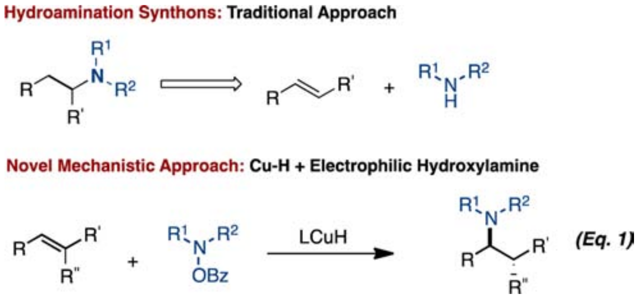
Supporting Information

ABSTRACT: A highly enantio- and regioselective copper-catalyzed hydroamination reaction of alkenes has been developed using diethoxymethylsilane and esters of hydroxylamines. The process tolerates a wide variety of substituted styrenes, including *trans-*, *cis-*, and β,β-disubstituted styrenes, to yield α-branched amines. In addition, aliphatic alkenes coupled to generate exclusively the anti-Markovnikov hydroamination products.

Hydroamination, the direct formation of a C−N bond by the formal addition of an amine to an alkene, is a powerful synthetic procedure with the potential to gain access to amine products which are widely featured in pharmaceutically active compounds.[1] Although great progress has been made in the field of late transition metal-catalyzed hydroamination,[2] several challenges still exist. For example, the intermolecular process requires activated alkenes such as vinyl arenes.[2a,i,h] or acrylic acid derivatives,[2c] while asymmetric variants are limited to the addition of aryl amines to simple β-unsubstituted styrene derivatives and achieve only moderate levels of enantiomeric excess.[2a,3] In addition, there are limited methods available to obtain the anti-Markovnikov product in hydroamination reactions of aliphatic amines.[4] Thus, there remains a need for the development of asymmetric hydroamination reactions that tolerate a wide variety of substitution patterns on the alkene component and proceed with high regio- and enantioselectivity.

Over the past decade, our laboratory has reported several examples of asymmetric reactions involving copper−hydride (CuH) intermediates.[5a−e] We postulated that this CuH strategy could serve as a platform for the hydroamination of alkenes (eq 1). In our approach for asymmetric intermolecular hydroamination, we propose that insertion of an alkene (**1**, **4**) into a chiral ligand-bound LCu(I)H species (**I**) would form an alkylcopper complex (**II**) (Figure 1).[6] Subsequent oxidative addition of an electrophilic amine source, such as a hydroxylamine **2**,[7] followed by reductive elimination, would form the C−N bond enantioselectively. The copper(I) species generated would then undergo transmetalation with an external hydride-transfer reagent to re-form **I**.[10] This mechanism (Figure 1) comes in a straightforward manner from a combination of our previous work in two areas.[5a,11] Herein, we report a mild copper-catalyzed hydroamination strategy using a chiral copper catalyst with a broad substrate scope. We note that toward the end of our work, a paper describing a method similar to the first portion (asymmetric) of this chemistry by Hirano and Miura was reported.[2a]



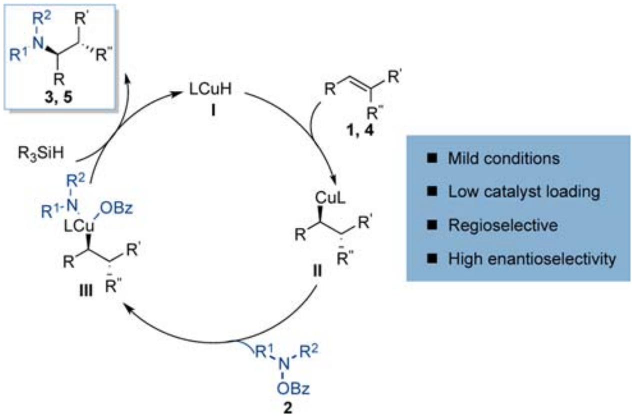


Figure 1. Proposed catalytic cycle for CuH-catalyzed hydroamination of alkenes.

We began our investigation by attempting the hydroamination of styrene (**1a**) using readily available $Cu(OAc)_2$ and easily accessible *O*-benzoylhydroxylamine **2a** (Table 1). Various ligands and hydride-transfer reagents were tested. We were able to achieve the desired cross-coupled products in up to 74% ee using polymethylhydrosiloxane (PMHS) or diethoxymethylsilane (DEMS) in conjunction with the commercially available ligand BINAP (**L1**) (entries 2 and 3). DEMS generated the desired product in the highest yield (entry 3), and thus was chosen as the hydride-transfer reagent of choice in the examination of other chiral ligands (entries 4−8). We were able to realize up to 97% ee when using (*R*)-

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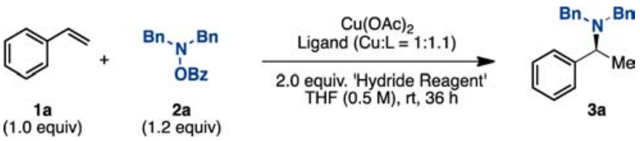
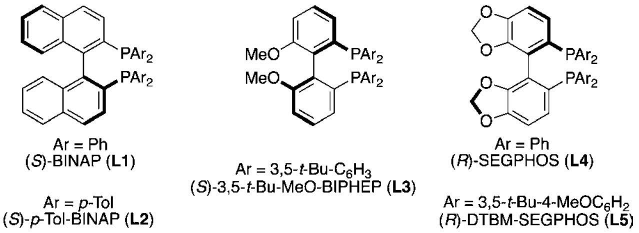
Table 1. Reaction Optimization



entry	Cu(OAc)$_2$ (mol%)	hydride reagent	L	yield 4a[a] (%)	ee (%)
1	10	HBpin	**L1**	2	nd[b]
2	10	PMHS	**L1**	40	−74
3	10	DEMS	**L1**	64	−73
4	10	DEMS	**L2**	83	−65
5	10	DEMS	**L3**	99	−95
6	10	DEMS	**L4**	99	79
7	10	DEMS	**L5**	99	97
8[c]	2	DEMS	**L5**	97	97



[a] GC yields with dodecane as the internal standard. [b] Not determined. [c] Reaction was carried out at 40 °C.

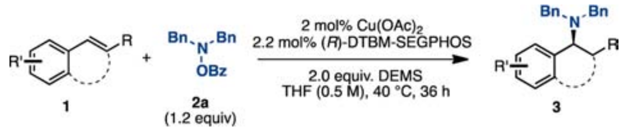
DTBM-SEGPHOS (**L5**) as the ligand (entry 7). Further optimization revealed that the reaction proceeds with low catalyst loading (2 mol%) at 40 °C (entry 8), without diminishing the yield or enantioselectivity. The reaction exclusively generated an α-branched amine, which is consistent with the proposed catalytic cycle (Figure 1) because the hydride migration from the copper catalyst to the alkene would generate the more stable α-bond Cu species.[12]

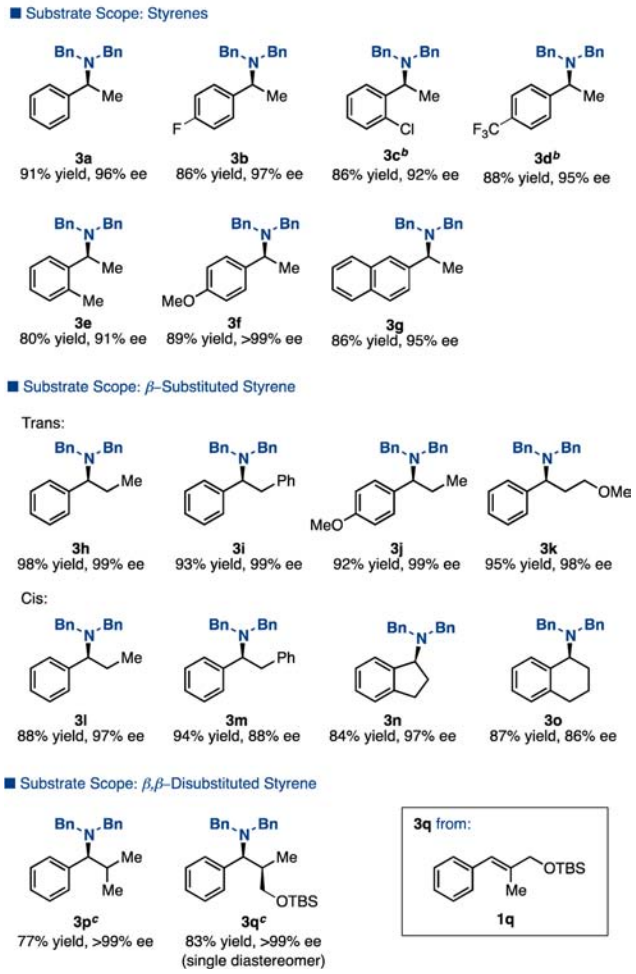
With an optimized protocol in hand, we then explored the substrate scope with respect to the styrene component (Table 2). This hydroamination tolerates a variety of substituents on the aryl ring of styrene (**3b**–**g**). The reaction also works efficiently with both *trans*- and *cis*-β-substituted styrenes (**3h**–**o**). Even hindered β,β-disubstituted styrenes undergo hydroamination in high yield and ee in this reaction (**3p**,**q**). Notably, the hydroamination of β,β-disubstituted styrene **1q** gave the product **3q** as a single diastereomer.

We next explored the use of other amine electrophiles in this reaction. We found that this reaction is applicable to several alkyl- and dialkyl-*N*-OBz amines (Table 3). *N*-(OBz)azepane and other heterocyclic-*N*-OBz amines also furnished the respective hydroamination products in high yields and enantioselectivities.

Since hydroamination of unactivated alkenes remains a challenge, we examined whether the developed protocol would be applicable with aliphatic alkenes.[4b] We found that terminal aliphatic alkenes could be effectively hydroaminated under the same conditions (Tables 4 and 5). In every case, the reaction exclusively produces the anti-Markovnikov products. This protocol tolerated alkenes containing a primary alkyl bromide (**5c**), an epoxide (**5g**), and was compatible with alkenes containing a tosylamine (**5d**), an amide (**5e**), a pyridine (**5f**), a *tert*-butyldimethylsilyl ether (**5i**), and ones with geminal substituents (**5h**,**i**). Additionally, a number of amine electrophiles, including the sterically hindered tetramethylpiperidine *N*-OBz (**5m**), cross-coupled efficiently. Our hypothesis for the

Table 2. Scope of Different Styrene Derivatives[a]





Substrate Scope: Styrenes

- **3a** 91% yield, 96% ee
- **3b** 86% yield, 97% ee
- **3c**[b] 86% yield, 92% ee
- **3d**[b] 88% yield, 95% ee
- **3e** 80% yield, 91% ee
- **3f** 89% yield, >99% ee
- **3g** 86% yield, 95% ee

Substrate Scope: β-Substituted Styrene

Trans:

- **3h** 98% yield, 99% ee
- **3i** 93% yield, 99% ee
- **3j** 92% yield, 99% ee
- **3k** 95% yield, 98% ee

Cis:

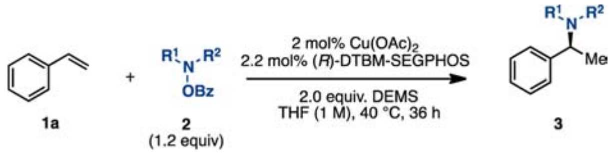
- **3l** 88% yield, 97% ee
- **3m** 94% yield, 88% ee
- **3n** 84% yield, 97% ee
- **3o** 87% yield, 86% ee

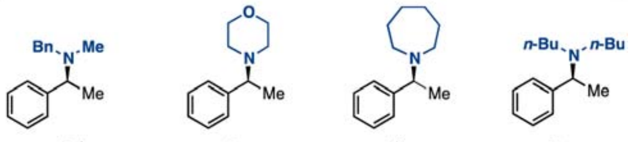
Substrate Scope: β,β-Disubstituted Styrene

- **3p**[c] 77% yield, >99% ee
- **3q**[c] 83% yield, >99% ee (single diastereomer)

[a] Isolated yields (average of two runs). **2** (1 mmol), *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (1.2 mmol), Cu(OAc)$_2$ (2 mol%), (*R*)-DTBM-SEGPHOS (2.2 mol%), DEMS (2 mmol), THF (0.5 M), 40 °C, up to 36 h. [b] Cu(OAc)$_2$ (4 mol%), (*R*)-DTBM-SEGPHOS (4.4 mol%). [c] THF (1 M).

Table 3. Scope of Amine Electrophiles with Styrene[a]

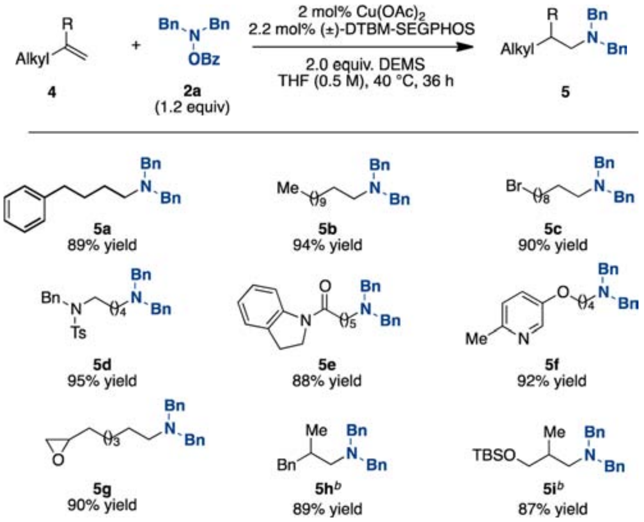




- **3r**[b] 87% yield, 94% ee
- **3s** 87% yield, 95% ee
- **3t** 86% yield, >99% ee
- **3u** 90% yield, 90% ee

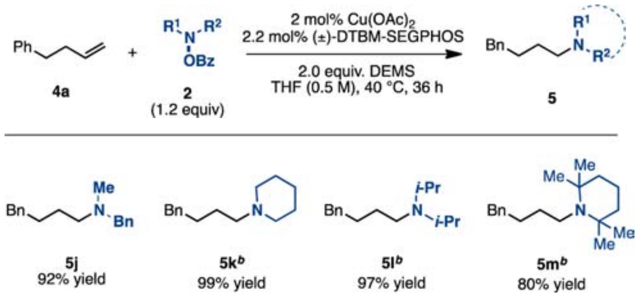
[a] Isolated yields (average of two runs). **2** (1 mmol), hydroxylamine (1.2 mmol), Cu(OAc)$_2$ (2 mol%), (*R*)-DTBM-SEGPHOS (2.2 mol %), DEMS (2 mmol), THF (1 M), 40 °C, up to 36 h. [b] THF (0.5 M).

Table 4. Hydroamination of Terminal Aliphatic Alkenes[a]



[a]Isolated yields (average of two runs). **2** (1 mmol), *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (1.2 mmol), $Cu(OAc)_2$ (2 mol%), (±)-DTBM-SEGPHOS (2.2 mol%), DEMS (2 mmol), THF (0.5 M), 40 °C, up to 36 h. [b]THF (1 M).

Table 5. Scope of Amine Electrophiles with 4-Phenyl-1-butene[a]

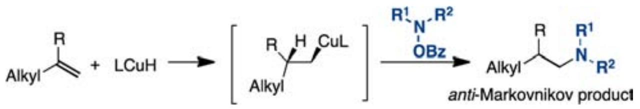


[a]Isolated yields (average of two runs). **2** (1 mmol), hydroxylamine (1.2 mmol), $Cu(OAc)_2$ (2 mol%), (±)-DTBM-SEGPHOS (2.2 mol %), DEMS (2 mmol), THF (0.5 M), 40 °C, up to 36 h. [b]$Cu(OAc)_2$ (4 mol%), (±)-DTBM-SEGPHOS (4.4 mol%) were used.

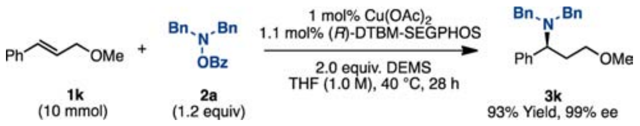
observed selectivity for the anti-Markovnikov products is that the hydride migration from the copper catalyst proceeds to form the less sterically crowded terminal copper intermediate (Scheme 1); here there is no electronic advantage as for styrenes to form the secondary alkyl-Cu intermediate. Oxidative addition of the hydroxylamine and subsequent reductive elimination would generate the unbranched tertiary amines.

As a demonstration of the robustness and practicality of this method, it was carried out at 10 mmol scale (Scheme 2) using the *β*-substituted styrene ((*E*)-(3-methoxyprop-1-en-1-yl)-benzene) as *β*-substituted styrenes are known to be difficult substrates in asymmetric hydroamination reactions.[3] We were able to lower the catalyst loading to 1 mol% with no decrease in the yield or enantioselectivity.

Scheme 1. Anti-Markovnikov Hydroamination of Aliphatic Alkene



Scheme 2. Large-Scale Hydroamination Reaction of *β*-Substituted Styrene



In summary, we have reported a mild method for synthesizing chiral tertiary amines by employing an asymmetric copper-catalyzed hydroamination. Substitution occurs in a regioselective manner to generate a C−N bond at the *α*-position of styrene derivatives. This method has been shown to be compatible with various substituted styrene derivatives, and styrenes with *β*-substitution. Additionally, this method allows the development of copper-catalyzed anti-Markovnikov hydroaminations of terminal aliphatic alkenes. We are currently investigating the asymmetric version of internal aliphatic alkene hydroamination, which will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all 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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