

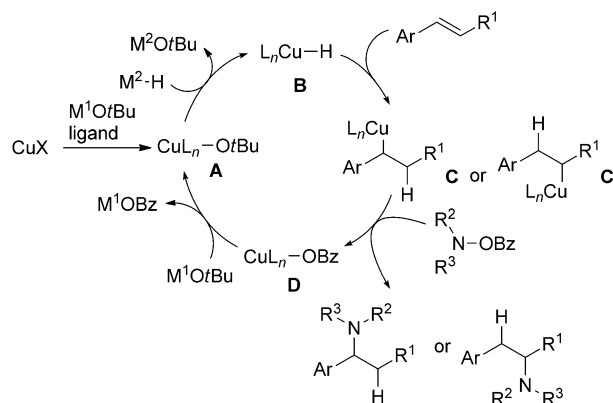
# Copper-Catalyzed Intermolecular Regioselective Hydroamination of Styrenes with Polymethylhydrosiloxane and Hydroxylamines\*\*

Yuya Miki, Koji Hirano,\* Tetsuya Satoh, and Masahiro Miura\*

The catalytic hydroamination reaction of carbon–carbon double bonds has recently received significant attention, as it allows relatively simple starting materials to be readily transformed into alkylamines, which are of great importance in both the fine and chemicals industries. To date, numerous catalytic systems, including various transition-metal catalysts, have been widely developed.<sup>[1]</sup> However, the intermolecular hydroamination of alkenes still remains a challenge, although there are some successful examples with strained alkenes,<sup>[2]</sup> 1,3-dienes,<sup>[3]</sup> allenes,<sup>[4]</sup> styrenes,<sup>[5]</sup> and simple alkenes.<sup>[6]</sup> For example, even in the hydroamination of styrenes,  $\beta$ -substituted substrates are an inaccessible substrate class.<sup>[5]</sup> In addition, most catalytic systems reported were based on precious metals and required elevated temperatures. Thus, further development of the catalytic intermolecular hydroamination of alkenes is strongly desired.

Herein, we report a copper-catalyzed formal intermolecular hydroamination of styrenes with polymethylhydrosiloxane (PMHS) and hydroxylamines, providing hydroaminated products, namely benzylamines, with high regioselectivity.<sup>[7]</sup> The catalytic system consists common, inexpensive, and abundant copper salts, and the reaction proceeds smoothly even at room temperature. This method also accommodates challenging  $\beta$ -substituted styrene derivatives. Moreover, the catalytic asymmetric hydroamination also becomes possible by using an appropriate chiral biphosphine ligand. Although there are many precedents for the preparation of optically active benzylamines, the hydroamination approach to these chiral compounds still remains somewhat challenging, in view of substrate scope and selectivity.<sup>[5a,d,j]</sup> Additionally, to the best of our knowledge, this is the first copper-based catalysis for the enantioselective intermolecular hydroamination of styrenes.

We have recently developed a copper-catalyzed three-component-coupling aminoboration of styrenes with bis(pinacolato)diboron and hydroxylamines.<sup>[8]</sup> In the course of this study, we envisioned our blueprint for the catalytic intermolecular hydroamination with hydrides and hydroxylamines. Our working hypothesis is illustrated in Scheme 1. Initial



Scheme 1. Working hypothesis. Bz = benzoyl, L = ligand.

formation of  $[L_nCuOrBu]$  species **A**<sup>[9]</sup> from a  $CuX$  precursor, ligand, and  $M^1OrBu$ , followed by reaction with an appropriate hydride source, generates an active copper hydride species **B**.<sup>[10]</sup> Subsequent insertion of a styrene derivative into the  $L_nCu-H$  bond of **B** provides alkylcopper intermediates **C** or **C'**.<sup>[11]</sup> Electrophilic amination<sup>[12,13]</sup> with an *O*-benzoylhydroxylamine then occurs to deliver the desired formal hydroamination product, together with a  $[L_nCuOBz]$  complex **D**. Finally, ligand exchange with  $M^1OrBu$  regenerates the starting copper alkoxide **A** to complete the catalytic cycle.<sup>[14]</sup> If the regioselectivity issue in the insertion step was addressed by the proper choice of ligands,<sup>[15]</sup> and a chemoselective reaction of the  $Cu-H$  species toward styrenes over hydroxylamines was feasible, the formal regioselective hydroamination could be achieved.<sup>[16]</sup>

On the basis of the above scenario, we selected styrene (**1a**), *O*-benzoyl-*N,N*-diethylhydroxylamine (**2a**), and triphenylsilane as model substrates, and began optimization studies (Table 1). In an early experiment, treatment of **1a** with **2a** and triphenylsilane in the presence of a  $Cu(OAc)_2/dppbz$  ( $dppbz = 1,2$ -bis(diphenylphosphino)benzene) catalyst and  $LiOrBu$  as the base in THF at room temperature afforded the desired hydroaminated product **3aa** in 41% yield (Table 1, entry 1). Although the yield was moderate, our postulated catalytic cycle could be operating. Moreover, **3aa** was obtained as a single regioisomer. Thus, in the insertion step (Scheme 1, **B** to **C**), the copper species and the hydride can be regioselectively added to the  $\alpha$  and  $\beta$  positions, respectively, of the styrene.<sup>[17]</sup> With this preliminary but promising result in hand, we next screened phosphorous-based ligands (entries 2–7). Some biphosphines promoted the hydroamination; for  $dppbz$  derivatives,  $CF_3$ - $dppbz$  proved to be optimal (entry 7). The origin of the beneficial effects of

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**Table 2:** Copper-catalyzed regioselective hydroamination of styrene derivatives **1** with various *O*-benzoylhydroxylamines **2**.<sup>[a]</sup>

| $\text{Ar}-\text{CH}=\text{CH}-\text{R}^1 + \text{R}^2-\text{N}(\text{R}^3)-\text{OBz} + \text{PMHS} \xrightarrow[\text{LiOtBu, DCE, RT, 4 h}]{\text{Cu(OAc)}_2 (10 \text{ mol}\%), \text{CF}_3\text{-dppbz} (10 \text{ mol}\%)} \text{Ar}-\text{CH}(\text{R}^2)-\text{CH}(\text{R}^3)-\text{R}^1$ |            |   |   |                          |                   |            |   |   |                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|---|---|--------------------------|-------------------|------------|---|---|--------------------------|
| Entry                                                                                                                                                                                                                                                                                              | 1          | 2 | 3 | Yield [%] <sup>[b]</sup> | Entry             | 1          | 2 | 3 | Yield [%] <sup>[b]</sup> |
| 1                                                                                                                                                                                                                                                                                                  |            |   |   | 81                       | 11 <sup>[d]</sup> |            |   |   | 91                       |
| 2 <sup>[c]</sup>                                                                                                                                                                                                                                                                                   | <b>1 a</b> |   |   | 89                       | 12 <sup>[d]</sup> |            |   |   | 91                       |
| 3 <sup>[d]</sup>                                                                                                                                                                                                                                                                                   | <b>1 a</b> |   |   | 72                       | 13                |            |   |   | 72                       |
| 4                                                                                                                                                                                                                                                                                                  | <b>1 a</b> |   |   | 85                       | 14                | <b>1 g</b> |   |   | 63                       |
| 5                                                                                                                                                                                                                                                                                                  | <b>1 a</b> |   |   | 80                       | 15 <sup>[d]</sup> |            |   |   | 85                       |
| 6 <sup>[d]</sup>                                                                                                                                                                                                                                                                                   | <b>1 a</b> |   |   | 78                       | 16                |            |   |   | 50                       |
| 7                                                                                                                                                                                                                                                                                                  | <b>1 a</b> |   |   | 95                       | 17                |            |   |   | 82                       |
| 8                                                                                                                                                                                                                                                                                                  |            |   |   | 97                       | 18                |            |   |   | 87                       |
| 9 <sup>[d]</sup>                                                                                                                                                                                                                                                                                   |            |   |   | > 99                     | 19 <sup>[d]</sup> |            |   |   | 98                       |
| 10                                                                                                                                                                                                                                                                                                 |            |   |   | 83                       | 20 <sup>[d]</sup> |            |   |   | 57                       |

[a] Reaction conditions: Cu(OAc)<sub>2</sub> (0.025 mmol), CF<sub>3</sub>-dppbz (0.025 mmol), LiOtBu (1.0 mmol), **1** (0.30 mmol), **2** (0.25 mmol), PMHS (0.75 mmol), DCE (1.5 mL), N<sub>2</sub>, RT, 4 h. [b] Yield of isolated product. [c] With Ph<sub>3</sub>SiH (0.30 mmol) and LiOtBu (0.60 mmol). [d] With **1** (0.38 mmol). [e] E/Z = 96:4. [f] E/Z = 92:8.

undergo oxidative addition to low valent metal complexes, such as palladium(0). Additionally, in most cases, the hydroaminated products were readily isolated by a simple acid/base workup without purification by column chromatography on silica gel (see the Supporting Information for details).

Finally, we developed an asymmetric variant of this method by using an appropriate optically active ligand.

Pleasingly, good efficiency and enantioselectivity were observed with a combination of CuCl and (*S,S*)-Me-Duphos (**L1**) in THF at room temperature (Scheme 2).<sup>[23]</sup> The copper-catalyzed asymmetric hydroamination of styrene (**1a**) gave optically active benzylamines **3ab–ah** with enantiomeric ratios (e.r.) of 87:13–93:7. With electron-deficient styrenes, (*R,R*)-Ph-BPE (**L2**) gave better enantioselectivities than **L1**

(**3ch**, **3eh**, and **3fh**), whereas electron-rich 4-methoxystyrene (**1b**) and electron-neutral 2-vinylnaphthalene (**1g**) underwent hydroamination with good e.r. values under the same conditions using **L1** (**3bh** and **3gh**). The *trans*  $\beta$ -methylstyrenes **1h** and **1j** were also suitable substrates for this enantioselective reaction (**3hh** and **3jh**). The asymmetric catalyst accommodated more sterically demanding **1k**, which bears an *i*Pr substituent (**3kh**). Moreover, the optically active 1,3-aminoalcohol scaffold **3lh** was readily accessible by the enantioselective hydroamination of cinnamyl ether **1l**.<sup>[24]</sup>

In conclusion, we have developed a copper-catalyzed intermolecular regioselective formal hydroamination of styrenes with PMHS and *O*-benzoylhydroxylamines. The method makes use of common and less expensive copper salts as the metal catalyst and PMHS as the hydride source, and allowed some challenging  $\beta$ -substituted substrates to be successfully hydroaminated. Electrophilic amination with hydroxylamines (umpolung) was the key to success. Moreover, catalytic enantioselective hydroaminations are also possible in the presence of chiral biphosphine-ligated copper complexes. Detailed mechanistic studies on the stereochemical course, expansion of the substrate scope, and further development of related electrophilic aminations are currently underway in our laboratory.

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