Synthetic Methods

DOI: 10.1002/ange.201304365

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

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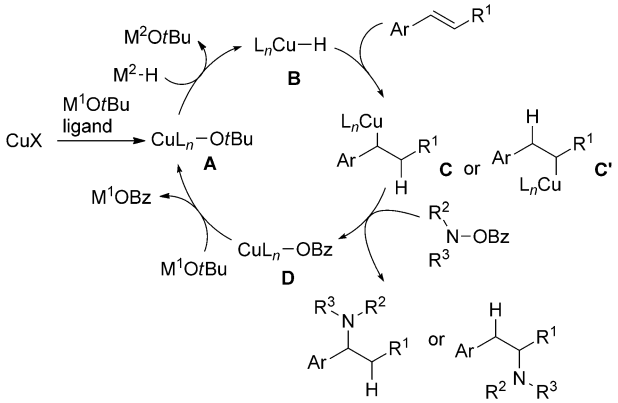
The catalytic hydroamination reaction of carbon–carbon double bonds has recently received significant attention, as it allows relatively simple starting materials to be readily transformed into alkylamines, which are of great importance in both the fine and chemicals industries. To date, numerous catalytic systems, including various transition-metal catalysts, have been widely developed.[1] However, the intermolecular hydroamination of alkenes still remains a challenge, although there are some successful examples with strained alkenes,[2] 1,3-dienes,[3] allenes,[4] styrenes,[5] and simple alkenes.[6] For example, even in the hydroamination of styrenes, β-substituted substrates are an inaccessible substrate class.[5] 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.[7] The catalytic system consists common, inexpensive, and abundant copper salts, and the reaction proceeds smoothly even at room temperature. This method also accommodates challenging β-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.[5a,d,i] 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.[8] 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_nCuO*t*Bu] species **A**[9] from a CuX precursor, ligand, and M¹O*t*Bu, followed by reaction with an appropriate hydride source, generates an active copper hydride species **B**.[10] Subsequent insertion of a styrene derivative into the L_nCu–H bond of **B** provides alkylcopper intermediates **C** or **C′**.[11] Electrophilic amination[12,13] with an *O*-benzoylhydroxylamine then occurs to deliver the desired formal hydroamination product, together with a [L_nCuOBz] complex **D**. Finally, ligand exchange with M¹O*t*Bu regenerates the starting copper alkoxide **A** to complete the catalytic cycle.[14] If the regioselectivity issue in the insertion step was addressed by the proper choice of ligands,[15] and a chemoselective reaction of the Cu–H species toward styrenes over hydroxylamines was feasible, the formal regioselective hydroamination could be achieved.[16]

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 LiO*t*Bu 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 α and β positions, respectively, of the styrene.[17] 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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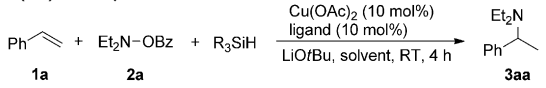
[**] This work was partly supported by Grants-in-Aid from MEXT and JSPS (Japan). K.H. acknowledges The Uehara Memorial Foundation for financial support.

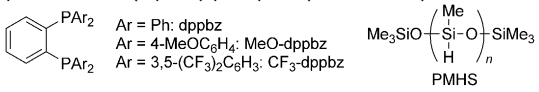
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201304365.

Table 1: Optimization studies for the copper-catalyzed regioselective hydroamination of styrene (**1a**) with *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**2a**) and hydrosilane.[a]



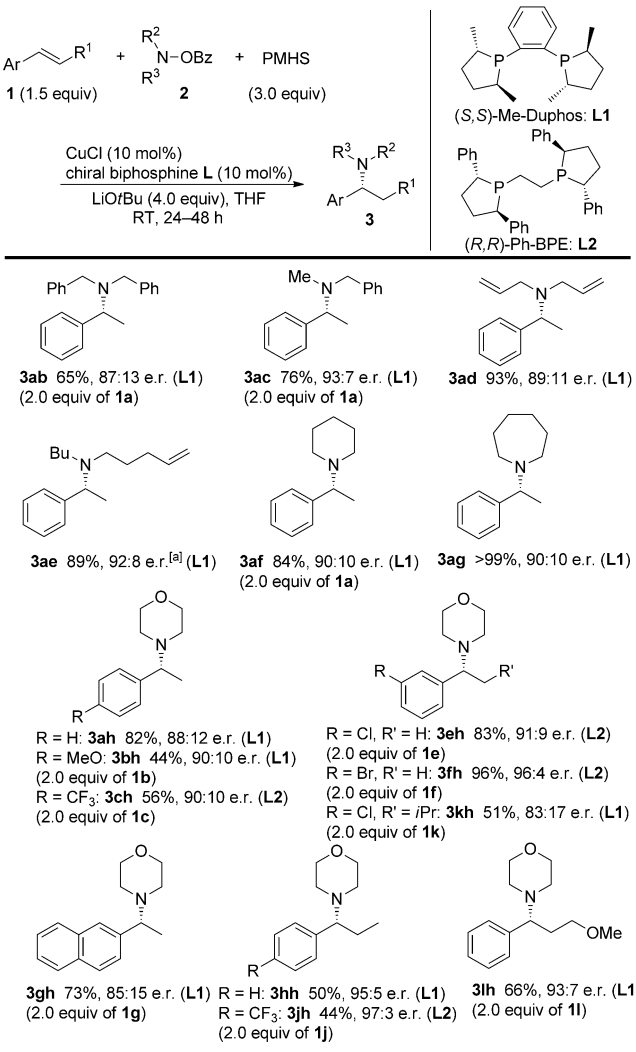
Entry	Ligand	R_3SiH	Solvent	Yield [%][b]
1	dppbz	Ph_3SiH	THF	41
2	PPh_3[c]	Ph_3SiH	THF	0
3	dppe	Ph_3SiH	THF	0
4	dppf	Ph_3SiH	THF	30
5	xantphos	Ph_3SiH	THF	40
6	MeO-dppbz	Ph_3SiH	THF	22
7	CF_3-dppbz	Ph_3SiH	THF	56
8	CF_3-dppbz	Ph_3SiH	toluene	73
9	CF_3-dppbz	Ph_3SiH	DCE	85
10	CF_3-dppbz	Ph_3SiH	DMF	0
11	CF_3-dppbz	Ph_3SiH	DMSO	0
12	CF_3-dppbz	Ph_2MeSiH	DCE	67
13	CF_3-dppbz	$PhMe_2SiH$	DCE	58
14	CF_3-dppbz	PMHS	DCE	53
15[d]	CF_3-dppbz	PMHS	DCE	>99

[a] Reaction conditions: $Cu(OAc)_2$ (0.025 mmol), ligand (0.025 mmol), LiO*t*Bu (0.60 mmol), **1a** (0.25 mmol), **2a** (0.30 mmol), hydrosilane (0.30 mmol), solvent (1.5 mL), N_2, RT, 4 h. [b] Yield estimated by GC analysis with dibenzyl as the internal standard. [c] With PPh_3 (0.050 mmol). [d] With PMHS (0.75 mmol) and LiO*t*Bu (0.75 mmol). dppbz = 1,2-bis(diphenylphosphino)benzene, dppe = 1,2-bis(diphenylphosphino)ethane, dppf = 1,1′-bis(diphenylphosphino)ferrocene, xantphos = 4,5-bis(diphenylphosphino)-9,9′-dimethylxanthene.



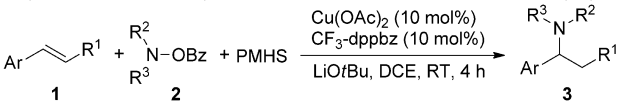
CF_3-dppbz is not clear at present, but its steric bulk and electron-deficient nature may suppress undesirable aggregation of the copper hydride species **B** (Scheme 1). The choice of solvent was also critical for the reaction efficiency (entries 8–11): Less polar toluene and 1,2-dichloroethane (DCE) improved the yield, whereas more polar *N*,*N*-dimethylformamide (DMF) and dimethylsulfoxide (DMSO) completely shut down the reaction. An additional screen of hydride sources revealed that, to our delight, the much less expensive and abundant polymethylhydrosiloxane (PMHS)[18] showed acceptable reactivity (entries 12–14). Finally, we obtained **3aa** in >99% yield (by GC analysis), using $Cu(OAc)_2$/CF_3-dppbz (10 mol%), PMHS (3.0 equiv), and LiO*t*Bu (entry 15). On the other hand, other bases such as LiOMe, NaO*t*Bu, and LiF did not form **3aa** at all (data not shown).[19]

Based on the optimization studies (Table 1), we evaluated the scope of the amine coupling partners with styrene (**1a**; Table 2). With hydroxylamines other than **2a**, a slight excess of styrene and 4.0 equivalents of LiO*t*Bu generally gave better results. Acyclic amines that bear *N*,*N*-dibenzyl, *N*-benzyl-*N*-methyl, and *N*,*N*-diallyl substituents participated in the reaction (entries 1–3). The resultant benzyl and allyl moieties can be a useful synthetic handle for further manipulation after a selective deprotection.[20] The reaction with **2e**, which contains a pendant olefin moiety, gave the usual hydroaminated product exclusively, and no cyclic products arising from a 5-*exo* radical cyclization were detected (entry 4). Thus, an aminyl radical pathway is less likely.[21] Moreover, the cyclic hydroxylamines of piperizine, azepane, and morpholine could be employed for the catalytic hydroamination (entries 5–7). A variety of styrene derivatives could also be employed.[22] Not only electron-rich **1b**, but also electron-deficient **1c** and **1d** reacted smoothly with **2h**, to form the corresponding hydroaminated products **3bh–dh** in high yields (entries 8–10). Notably, the copper catalyst was compatible with aryl chloride and bromide functional groups (entries 11 and 12), providing additional opportunities for further transformations with palladium catalysts. The fused naphthalene system could also be employed (entries 13 and 14). This process accommodated β-substituted styrenes **1h–k** (entries 15–18), which were an inaccessible substrate class under the previously reported palladium-catalyzed conditions.[5] In particular, the challenging substrates cinnamyl methyl ether (**1l**) and cinnamyl acetate (**1m**) could be successfully hydroaminated; their allylic moieties tend to

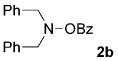
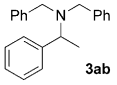
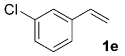
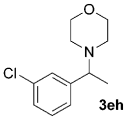
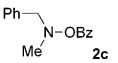
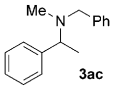
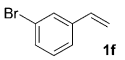
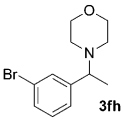
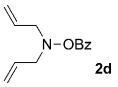
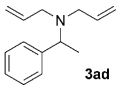
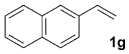
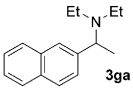
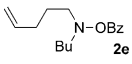
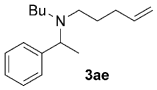
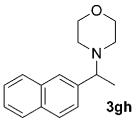
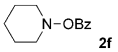
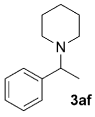
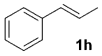
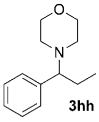
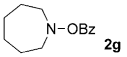
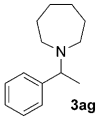
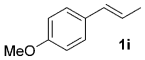
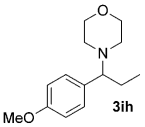
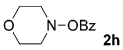
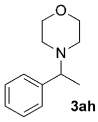
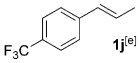
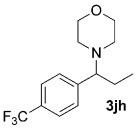
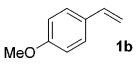
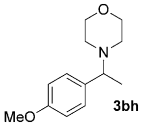
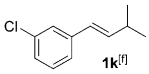
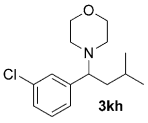
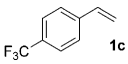
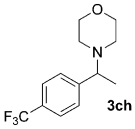
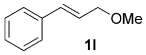
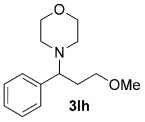
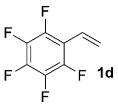
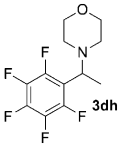
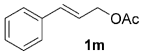


Scheme 2. Catalytic asymmetric hydroamination. The chiral biphosphine employed is given in parentheses. [a] ±5%.

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



1 **2** **3**

Entry	1	2	3	Yield [%][b]	Entry	1	2	3	Yield [%][b]
1	 **1a**	 **2b**	 **3ab**	81	11[d]	 **1e**	**2h**	 **3eh**	91
2[c]	**1a**	 **2c**	 **3ac**	89	12[d]	 **1f**	**2h**	 **3fh**	91
3[d]	**1a**	 **2d**	 **3ad**	72	13	 **1g**	**2a**	 **3ga**	72
4	**1a**	 **2e**	 **3ae**	85	14	**1g**	**2h**	 **3gh**	63
5	**1a**	 **2f**	 **3af**	80	15[d]	 **1h**	**2h**	 **3hh**	85
6[d]	**1a**	 **2g**	 **3ag**	78	16	 **1i**	**2h**	 **3ih**	50
7	**1a**	 **2h**	 **3ah**	95	17	 **1j**[e]	**2h**	 **3jh**	82
8	 **1b**	**2h**	 **3bh**	97	18	 **1k**[f]	**2h**	 **3kh**	87
9[d]	 **1c**	**2h**	 **3ch**	>99	19[d]	 **1l**	**2h**	 **3lh**	98
10	 **1d**	**2h**	 **3dh**	83	20[d]	 **1m**	**2b**	**3mb**	57

[a] Reaction conditions: $Cu(OAc)_2$ (0.025 mmol), CF_3-dppbz (0.025 mmol), LiO*t*Bu (1.0 mmol), **1** (0.30 mmol), **2** (0.25 mmol), PMHS (0.75 mmol), DCE (1.5 mL), N_2, RT, 4 h. [b] Yield of isolated product. [c] With Ph_3SiH (0.30 mmol) and LiO*t*Bu (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).[23] 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* β-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**.[24]

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 β-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.

Received: May 21, 2013
Revised: July 5, 2013
Published online: August 22, 2013

Keywords: amines · copper · hydroamination · synthetic methods · umpolung

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